VA/DoD CLINICAL PRACTICE GUIDELINE FOR SCREENING AND MANAGEMENT OF OVERWEIGHT AND OBESITY

Department of Veterans Affairs
Department of Defense

QUALIFYING STATEMENTS

The Department of Veterans Affairs and the Department of Defense guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision-making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

This Clinical Practice Guideline is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendations.

Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

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Prepared by:

The Management of Overweight and Obesity Working Group

With support from:

The Office of Quality, Safety and Value, VA, Washington, DC
&
Clinical Performance Assurance Directorate, United States Army MEDCOM

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Executive Summary

Obesity and associated chronic health conditions cause significant morbidity and negatively impact military readiness. Sixty-one to 83% of Department of Defense (DoD) beneficiaries and 78% of Veterans are overweight or obese, and excess weight is estimated to cost at least $370 per patient per year in additional medical and non-medical costs. Treatment of both overweight and obesity is consistent with the priorities outlined by the leadership of the Department of Veterans Affairs as a part of personalized, proactive Veteran-driven care. Similarly, it is consistent with the DoD's priority for a fit fighting force and embodied in the US Army's Performance Triad of Nutrition, Physical Activity, and Sleep. Moreover, screening, treatment, and follow-up of overweight and obesity can be successfully managed in the primary care setting with an interdisciplinary approach.

Overweight and obesity are typically identified through screening or as a result of presentation for obesity-associated chronic health conditions. Routine screening should include measurement of height and weight to calculate body mass index (BMI) in all patients. Normal adult weight is defined by a BMI of 18.5-24.9 kg/m^2. Overweight is defined by a BMI between 25.0 and 29.9 kg/m^2. Obesity is defined by a BMI $\geq$ 30.0 kg/m^2 and can be sub-classified as Stage 1 (BMI 30.0 to 34.9 kg/m^2), Stage 2 (BMI 35.0 to 39.9 kg/m^2), or Stage 3 (BMI $\geq$ 40 kg/m^2). Measurement of waist circumference may also be useful to predict risk in overweight and obese patients as it is considered a comorbidity equivalent. In these patients, the presence of obesity-associated chronic health conditions should be identified. Normal weight and overweight patients without obesity-associated chronic health conditions may be offered education, information, and counseling about a healthy lifestyle and maintaining or achieving a healthy weight. Comprehensive lifestyle intervention for weight loss should be offered to all obese patients and overweight patients with obesity-associated chronic health conditions.

Comprehensive lifestyle intervention is the foundation of treatment for overweight and obesity and should include at least 12 contacts over a year of an intervention that combines dietary, physical activity and behavioral components. Diet and physical activity together must create an energy deficit of 500-1000 kcal/day for effective weight loss. Adherence to any particular calorie-deficit diet is more important than choice of a specific diet. Physical activity, through short bursts of activity or a single longer episode, typically must accumulate to at least 150 minutes per week. On average, weight loss will occur at the rate of 0.5 to 2 pounds per week, plateauing between three and six months. After a plateau is reached, reassessment for weight maintenance or additional weight loss is required.

A shared decision-making model should be employed to reach a mutual understanding of risks and benefits of treatment, to explore patient priorities, and to determine if a patient is willing to commit to an intervention. For a patient who is unwilling, a motivational intervention should be used and reassessment should be undertaken at least biannually. For a patient who is willing to participate in an intervention, an individualized plan should be formulated, tangible intermediate and long-term weight loss goals must be identified, and frequent reassessment should be arranged.

Continued treatment should be guided by a patient's intermediate weight loss goals. Patients who are meeting goals should continue current treatment until long-term weight loss goals are achieved. For

patients not meeting intermediate goals, the treatment plan should be modified to address any barriers to treatment adherence. When no further amelioration of barriers is possible and weight loss has plateaued, adjunctive interventions such as pharmacotherapy or referral for bariatric surgery may be considered in select patients. Patients who do not complete intensive treatment should be offered a motivational intervention and reassessed at least biannually. All patients reaching their long-term goals should be offered a maintenance program, ongoing support, and periodic reassessment.

Weight loss treatment for overweight and obesity can be effectively delivered through an interdisciplinary approach in a primary care setting. Comprehensive lifestyle intervention alone and comprehensive lifestyle intervention with adjunctive pharmacotherapy or bariatric surgery are effective for many. Though providing these interventions will require upfront resources from health-care systems, they have the potential to reduce lifetime medical costs. Through effective management, morbidity from obesity-associated chronic health conditions can be reduced and military readiness improved.

Background

The epidemic of overweight and obesity is one of the most significant problems facing the US health care system today. The Centers for Disease Control and Prevention (CDC) defines overweight and obesity using body mass index (BMI). Having a BMI of 25-29.9 kg/m^2 is considered overweight, while a BMI of 30 kg/m^2 or higher is considered obese. [1] According to the Office of the US Surgeon General, the prevalence of obesity in the US more than doubled (from 15% to 34%) among adults and more than tripled (from 5% to 17%) among children and adolescents from 1980 to 2008. [2] Based on data reported for 2009-2010 from the National Health and Nutrition Examination Surveys, the prevalence rate for overweight or obesity is 68%. [3] Moreover, about 1 in 20 Americans has a BMI of >40 kg/m^2, defined as more severe, class III obesity. [3]

The active military and Veteran populations have been similarly affected by the obesity epidemic. Self-reported overweight or obesity among active duty military is 61%. [4] The Army Obesity Study, conducted in 2012, evaluated 430,497 active duty Soldiers with a BMI recorded in the outpatient electronic medical record. Preliminary data found that 49.3% were overweight and 19.4% were obese. Among 261,028 adult non-active duty beneficiaries and 108,604 retirees, 63.0% and 86% were overweight or obese, respectively. [5] Among 4,869,451 Veterans, aged 18-100, who had an outpatient or inpatient visit in fiscal year 2013 and a height and weight available, 77.8 % were overweight or obese and 40.7% were obese. [6]

Additionally, the Armed Forces Health Surveillance Center (AFHSC) reported that from 1998-2010, the number and prevalence of active duty members who received at least one overweight/obesity-related diagnosis more than tripled, from 25,766 active members and a prevalence rate of 1.6% in 1998, to 86,186 members and a prevalence rate of 5.3% in 2010. [7] In 2008, an estimated 23% and 16% of Service members diagnosed with overweight or obesity had at least one medical encounter for a joint or back disorder, respectively, within the prior year. [8] Also, according to the AFHSC, joint and back disorders are among the most frequent conditions to co-occur with overweight/obesity among affected military members. [7]

The evidence clearly links overweight and obesity with an increased risk of chronic health conditions and reduced quality of life, as well as earlier mortality among those with class II and III obesity. Overweight and obesity are associated with increased prevalence and worsening of several obesity-associated conditions, including type 2 diabetes, hypertension, dyslipidemia, metabolic syndrome, osteoarthritis, and obstructive sleep apnea. [9] The CDC estimates that 9 out of 10 people diagnosed with type 2 diabetes are overweight or obese. Furthermore, as a result of the obesity epidemic, the lifetime risk of developing type 2 diabetes for an individual born in 2000 is 33%. [10] The development or worsening of type 2 diabetes, hypertension, and dyslipidemia is particularly hazardous due to the independent effects on risk for coronary artery disease and stroke.

In addition to the aforementioned obesity-associated conditions, excess body weight is the most important risk factor for the development of non-alcoholic fatty liver disease (NAFLD) which has recently emerged as a major health problem in the western world. The exact prevalence in the general adult

population is unknown, but ranges from 10 to 46%. [11,12] It is now the most common form of liver disease in the US. [13] One study estimates that approximately 40% of NAFLD will progress to nonalcoholic steatohepatitis. [14] NAFLD has surpassed alcohol as a reason for liver transplants in the US and will likely become the leading condition necessitating liver transplants (ahead of hepatitis C) within 10-20 years. [13,15]

Relative to normal weight, overweight is associated with lower all-cause mortality. [16] This seeming contradiction has been termed the "obesity paradox." However, it is clear that obesity overall is also associated with increased all-cause mortality, which in turn results in increased direct and indirect healthcare costs. A 2004 estimate found that obesity accounted for $190 billion annually or 21% of the overall US healthcare costs. [17] The CDC cites another study that estimates health costs attributed to overweight and obesity may be upwards of $78.5 billion. [18] Regarding the VA and DoD populations, the estimated direct medical costs of obesity among TRICARE Prime enrolled beneficiaries was $1.1 billion in 2006. [19]

Overweight and obesity together constitute a complex and chronic disease that develops from an interaction between the individual's genotype, dietary and physical activity behaviors, and the environment. Effective treatment produces substantial health benefits with even modest weight reduction in overweight and obese individuals. Substantial weight loss induced by bariatric surgery may even reduce mortality. (See Bariatric Surgery section for further discussion.)

Currently, many healthcare professionals do not aggressively address excess weight with their patients, perhaps due to the complicated etiology of the condition and limited availability of the multi-component resources needed for treatment. Although many individuals successfully lose weight via diet modification and physical activity, the major barrier to sustained weight loss is adherence to necessary long-term behavioral changes. The complex nature of this condition requires a thorough investigation into the benefits and risks of various therapeutic approaches and the identification of best practices for the provider community.

About This Clinical Practice Guideline

The Veterans Affairs (VA) and Department of Defense (DoD) Evidence-Based Practice Working Group (EBPWG) was established and first chartered in 2004, with a mission to advise the "…Health Executive Council on the use of clinical and epidemiological evidence to improve the health of the population across the Veterans Health Administration (VHA) and Military Health System," by facilitating the development of clinical practice guidelines for the VA and DoD populations. [20] This Clinical Practice Guideline (CPG) is intended to provide primary care clinicians with a framework by which to evaluate the individual needs and preferences of overweight and obese patients, leading to improved clinical outcomes.

In 2006, the VA and DoD published a CPG for the Screening and Management of Overweight and Obesity (2006 CPG), which was based on evidence reviewed through February 2005. [21] Since the release of

that guideline, a growing body of research has expanded the general knowledge and understanding of overweight and obesity, including new findings regarding weight loss and weight loss maintenance strategies and their effects on associated comorbidities. Recognition of the epidemic of overweight and obesity has led to the development of new drugs approved by the Food and Drug Administration (FDA) for weight loss, better understanding of dietary and physical activity behaviors and strategies that promote weight loss as well as weight loss maintenance, more information on associated risk factors/comorbidities, and more data on weight loss outcomes such as major adverse cardiovascular events and mortality.

Consequently, a recommendation to update the 2006 CPG was initiated in November 2012, and this updated CPG will be referred to in this text as the "2014 CPG." The updated CPG includes objective, evidence-based information on the patient-centered approach to weight loss, the benefits and harms of pharmacologic and non-pharmacologic therapies, the management of comorbid conditions, best practices for care delivery, and emerging innovations in clinical research and care.

Key Elements of Weight Loss and Management

The key elements of weight loss and weight management that are addressed by this guideline include:

- Obesity is a chronic disease requiring lifelong commitment to treatment and long-term maintenance
- Obesity may not be the chief complaint in a patient encounter, yet it requires foremost attention
- The primary care team plays an integral role in weight management
- Screening, documentation, and regular assessment are critical to weight management
- Assessment for obesity-associated chronic health conditions is an essential component of treatment decisions
- Shared decision-making and assessment of patient motivation are fundamental to weight management
- Comprehensive lifestyle intervention is central to successful and sustained weight loss
- Tangible intermediate and long-term weight loss goals are critical to weight loss success
- Energy deficit should be achieved through decreased caloric intake and increased physical activity
- Pharmacotherapy and bariatric surgery may be considered as adjuncts to comprehensive lifestyle intervention

Methods

The methodology used in developing the 2014 CPG follows the "Guideline for Guidelines," an internal document of the Veterans Affairs (VA) and Department of Defense (DoD) Evidence-Based Practice Working Group (EBPWG). This document provides information regarding the process of developing guidelines, including the identification and assembly of the Guideline Champions (Champions) and other

subject matter experts from within the VA and DoD, known as the Work Group, and ultimately, the submission of an updated obesity CPG.

The Champions and Work Group for this CPG were charged with developing evidence-based clinical practice recommendations and publishing a guideline document to be used by providers within the VA/DoD healthcare system. Specifically, the Champions for this guideline were responsible for identifying the key questions of greatest clinical relevance, importance, and interest for the management and treatment of overweight and obesity. In addition, the Champions assisted in:

1. Conducting the evidence review, including providing direction on inclusion and exclusion criteria;
2. Assessing the level and quality of the evidence;
3. Identifying appropriate disciplines to be included as part of the Work Group;
4. Directing and coordinating the Work Group; and
5. Participating throughout the guideline development and review processes.

The VA Office of Quality, Safety and Value, in collaboration with the Medical Command of the DoD, identified two clinical leaders, Dr. Michael Goldstein from VA and Dr. Y. Sammy Choi from DoD, as Champions for the 2014 CPG.

The Lewin Group (Lewin), contracted by VA and DoD to support the development of this CPG and conduct the evidence review, held the first conference call in November 2012, with participation from the contracting officer's representatives (COR), leaders from the VA and DoD evidence-based guideline development program, and the Champions. During this call, the project team discussed the scope of the guideline initiative, the roles and responsibilities of the Champions, the project timeline, and the approach for developing specific research questions on which to base a systematic review about the management and treatment of overweight and obesity. The team also identified a list, from which the Work Group members were recruited, of clinical specialties and areas of expertise that are important and relevant to the treatment and management of overweight and obesity. The specialties and areas included were Clinical Dietetics, Family Medicine, Healthcare Systems Management and Policy, Internal Medicine, Nursing, Pharmacy Benefit Management, Physical Therapy, Psychiatry, Psychology and Surgery.

The evidence review and synthesis portion of the guideline development process for the 2014 CPG consisted of the following steps:

- Formulating evidence questions (key questions)
- Conducting the systematic review
- Convening a two and a half day face-to-face meeting with the CPG Champions and Work Group members
- Drafting and submitting a final CPG on the screening and management of overweight and obesity to the VA/DoD EBPWG

Appendix A provides a detailed description of each of these tasks.

Evidence Tables

The Champions and a smaller subset of the Work Group, known as the editorial team, developed a comprehensive evidence table for this CPG, shown in Appendix C, which provides detailed information on each recommendation, the grade of each recommendation, and the literature supporting each recommendation, including the certainty of evidence and magnitude of net benefit. If a recommendation was also included in the 2006 version of this CPG, the assigned grades from both 2006 and 2014 are specified. If a recommendation is new and was not addressed in the 2006 version, a N/A is marked in the 2006 grade column.

In some cases, a recommendation was assigned a grade of "I" for insufficient evidence. In such cases, the quality of the evidence base or the certainty of the evidence is deemed low, either due to a lack of evidence to address the question or because there is conflicting evidence as to the balance of benefits and harms.

In other cases, a recommendation was assigned a grade of "EO" for expert opinion. A recommendation may have an "EO" when the certainty of the evidence is low or insufficient, but, based on expert opinion, the potential magnitude of the net benefit (benefits minus harms) might be substantial enough for providers to consider offering the recommendation. In these cases, the panel used position statements or consensus building comments from major organizations, where available, to craft and support the recommendation.

Limitations

It is important to note that due to resource limitations, the Work Group could not formally update all aspects of the 2006 CPG. The key questions chosen for this CPG are those of highest priority that would be supported by a comprehensive evidence review. For instance, though vitally important, an evidence synthesis was not performed for the direct effects of diet and physical activity on weight loss. This is because the authors/editors felt that the principle of creating an energy deficit applies to all forms of dietary and physical activity interventions and therefore new research in this area would not likely substantially change recommendations regarding their effects on weight loss. [22]

Additionally, the systematic review conducted for this CPG examined literature that was published up to February 1, 2013. The Work Group recognizes that several new studies have been published since that time. Consequently, the group reviewed and incorporated new evidence in developing and refining the recommendations, as long as the studies met all *a priori* inclusion criteria for the systematic review.

Reconciling 2006 Recommendations

The 2006 CPG recommendations and topics that were not subject to the 2013 evidence review were directly carried over into the 2014 CPG, without revisions to the statements or their associated grade (strength of recommendation). These "carryover" recommendations are identified in the evidence table by an arrow pointed from the 2006 grade column to the 2014 grade column. Recommendations from the 2006 CPG were only carried over into the 2014 CPG if the core intent of the original recommendation remained the same and without any substantial revisions to the wording of the

recommendation. The authors of this CPG also note that in some cases, there exists additional evidence since 2006 supporting those recommendations and grades that were carried over, which simply strengthens the evidence base. This information is noted in the evidence tables under "Additional Supporting Literature." Any topic not addressed by the 2013 evidence review, which the authors felt warranted a change or addition to the 2006 recommendation addressing that topic, was noted as part of the discussion section and included the relevant new information (although not systematically reviewed).

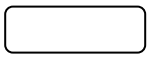
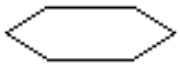
Algorithm Format

This clinical practice guideline includes an algorithm, which is designed to maximally facilitate clinical decision-making for the management overweight and obese patients. The use of the algorithm format was chosen based on the understanding that such a format can diagnostic and therapeutic decision-making, and has the potential to change patterns of resource use.

The algorithmic format allows the provider to follow a linear approach to critical information needed at the major decision points in the clinical process, and includes:

- An ordered sequence of steps of care
- Recommended observations
- Decisions to be considered
- Actions to be taken

A clinical algorithm diagrams a guideline into a step-by-step decision tree. Standardized symbols are used to display each step in the algorithm, [23] and arrows connect the numbered boxes indicating the order in which the steps should be followed.

	Rounded rectangles represent a clinical state or condition.
	Hexagons represent a decision point in the guideline, formulated as a question that can be answered Yes or No.
	Rectangles represent an action in the process of care.
	Ovals represent a link to another section within the guideline.

Guideline Working Group

Guideline Working Group*	
VA	**DOD**
Michael Goldstein, MD **Co-Chair**	**Y. Sammy Choi, MD** **Co-Chair**
Ariana Aoun, MS, RD, CSR, LD	**Raymond Batz, DO, MPH**
Edwin Earl Gaar, MD	Ronny Bigham, PA
Navjit Goraya, MD	Elmer Combs, PhD, RN**
Gwen Hampton, RN	Pennie Lou Pearson Hoofman, PhD
Sophia Hurley, MSPT	Elizabeth Liebner, PT
Kenneth Jones, PhD	Belinda Millner, RN
Todd Semla, MS, PharmD	Theresa Newlin, FNP, FPC-BC
Carol Volante, ARNP	Connie Scott, MSM, RD
	James Sebesta, MD
	Robert Selvester, MD
	Maime Shell, RN-BC
	Leilani Siaki, PhD, FNP-BC
	Darrell Zaugg, DO
Staff Support Carla Cassidy, MSN, ANP **M. Eric Rodgers, PhD, FNP, BC**	**Staff Support** **Ernest Degenhardt, MSN, FNP** **Marjory Waterman, MN, RN**
Lewin Group	
Cliff Goodman, PhD **Erin Gardner** Josie Idoko-Pean **Anjali Jain, MD** **Hillary Kleiner** **Sneha Rangarao** Paul Wallace, MD	

* Bolded names are members of the core editing panel. Additional contributor contact information is available in Appendix L.

** Left the Work Group following the first face-to-face meeting.

Scope and Definitions

This Clinical Practice Guideline (CPG) is designed to assist primary care providers in treating and managing overweight and/or obese patients. This CPG addresses the following elements.

Population

The patient population of interest for this CPG is adults (men and women who are > 18 years old) that are eligible for care in the Veterans Health Administration (VHA) or the Department of Defense (DoD) healthcare delivery system. This CPG does not provide recommendations for the treatment of children, adolescents, or pregnant/lactating women.

Interventions

This CPG provides information on both pharmacologic and non-pharmacologic therapies for overweight and obesity. Pharmacologic therapies are limited to available Food and Drug Administration (FDA) approved medications that are specifically indicated for use in treating overweight and/or obesity. These include lorcaserin, orlistat, or the combination phentermine/topiramate extended-release (P/T ER). Non-pharmacologic interventions include lifestyle (i.e., diet and exercise) and behavioral interventions (i.e., counseling).

In this guideline, overweight and obesity are defined according to the 1998 National Heart, Lung, and Blood Institute (NHLBI) classification **(Table 1)** that relies on body mass index (BMI) and, in some cases, waist circumference. The classification is based primarily on the associations between BMI, chronic disease, and mortality. The relation between BMI and disease risk varies among individuals and among different populations. For example, individuals who are short in stature or who have a relatively high muscular mass may fall into the overweight category by BMI but may not have increased adipose tissue and thus may not be at increased risk of obesity-associated conditions. Therefore, this classification must be viewed as generally corresponding to disease risk but with some exceptions.

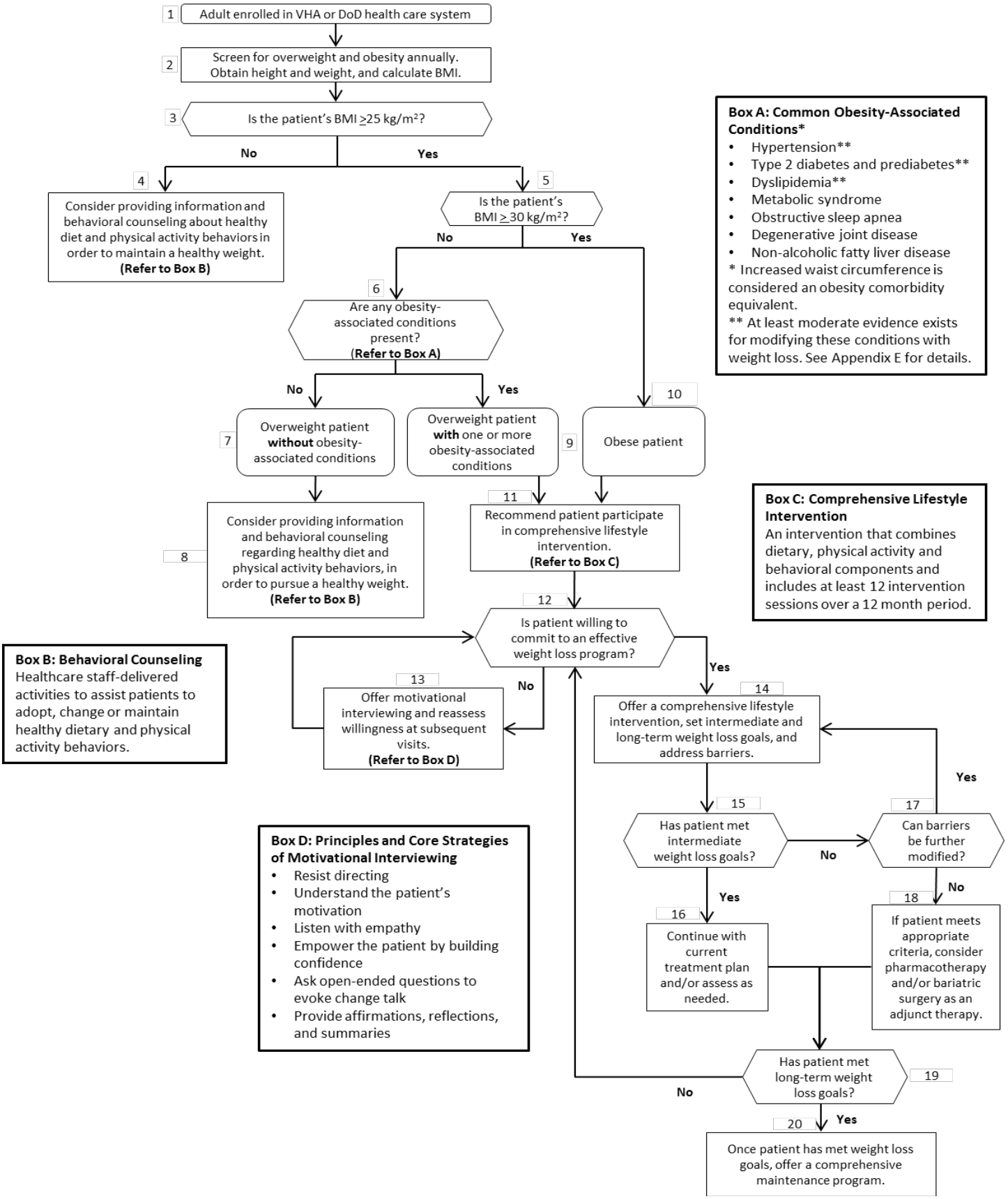
Table 1: Classification of Overweight and Obesity by BMI and Associated Disease Risk* [24]

Classification	BMI (kg/m^2)	Disease Risk with Normal Waist Circumference	Disease Risk with Excessive Waist Circumference
Underweight	< 18.5	–	–
Normal	18.5 – 24.9	–	–
Overweight	25.0 – 29.9	Increased	Moderate
Obese I	30.0 – 34.9	Moderate	Severe
Obese II	35.0 – 39.9	Severe	Very Severe
Obese III	≥ 40.0	Very Severe	Very Severe

** Disease risk for obesity-associated conditions*

See Appendix D for the BMI calculation chart. Additional BMI calculators and tables can be accessed at: http://www.cdc.gov/nccdphp/dnpa/bmi/

Algorithm


1 Adult enrolled in VHA or DoD health care system
2 Screen for overweight and obesity annually. Obtain height and weight, and calculate BMI.
3 Is the patient's BMI ≥25 kg/m²?
No
Yes
4 Consider providing information and behavioral counseling about healthy diet and physical activity behaviors in order to maintain a healthy weight. (Refer to Box B)
5 Is the patient's BMI ≥30 kg/m²?
No
Yes
6 Are any obesity-associated conditions present? (Refer to Box A)
No
Yes
7 Overweight patient without obesity-associated conditions
Overweight patient with one or more obesity-associated conditions 9
10 Obese patient
8 Consider providing information and behavioral counseling regarding healthy diet and physical activity behaviors, in order to pursue a healthy weight. (Refer to Box B)
11 Recommend patient participate in comprehensive lifestyle intervention. (Refer to Box C)
12 Is patient willing to commit to an effective weight loss program?
No
13 Offer motivational interviewing and reassess willingness at subsequent visits. (Refer to Box D)
Yes
14 Offer a comprehensive lifestyle intervention, set intermediate and long-term weight loss goals, and address barriers.
15 Has patient met intermediate weight loss goals?
No
17 Can barriers be further modified?
Yes
No
Yes
16 Continue with current treatment plan and/or assess as needed.
18 If patient meets appropriate criteria, consider pharmacotherapy and/or bariatric surgery as an adjunct therapy.
Has patient met long-term weight loss goals? 19
No
Yes
20 Once patient has met weight loss goals, offer a comprehensive maintenance program.
Box A: Common Obesity-Associated Conditions*
• Hypertension**
• Type 2 diabetes and prediabetes**
• Dyslipidemia**
• Metabolic syndrome
• Obstructive sleep apnea
• Degenerative joint disease
• Non-alcoholic fatty liver disease
* Increased waist circumference is considered an obesity comorbidity equivalent.
** At least moderate evidence exists for modifying these conditions with weight loss. See Appendix E for details.
Box B: Behavioral Counseling
Healthcare staff-delivered activities to assist patients to adopt, change or maintain healthy dietary and physical activity behaviors.
Box C: Comprehensive Lifestyle Intervention
An intervention that combines dietary, physical activity and behavioral components and includes at least 12 intervention sessions over a 12 month period.
Box D: Principles and Core Strategies of Motivational Interviewing
• Resist directing
• Understand the patient's motivation
• Listen with empathy
• Empower the patient by building confidence
• Ask open-ended questions to evoke change talk
• Provide affirmations, reflections, and summaries

Recommendations

Recommendation	GRADE
Screening and Assessment	
1. Screen adult patients to establish a diagnosis of overweight or obesity by calculating body mass index (BMI), and document the presence of overweight or obesity in the medical record.	B
2. Screen for overweight and obesity at least annually.	EO
3. Assess for the presence of obesity-associated conditions among overweight patients or patients with increased waist circumference.	B
4. Perform a targeted assessment on overweight and obese patients. In addition to the basic medical history and physical examination, assess for factors contributing to obesity.	EO
Normal Weight Patients	
5. Consider providing normal weight patients with information and behavioral counseling regarding healthy diet and physical activity behaviors, in order to maintain a healthy weight.	C
Overweight Patients Without Obesity-Associated Condition(s)	
6. Consider providing overweight patients without obesity-associated conditions with information and behavioral counseling regarding healthy diet and physical activity behaviors, in order to pursue a healthy weight.	C
Overweight Patients With Obesity-Associated Condition(s)	
7. Offer comprehensive lifestyle intervention to achieve weight loss and to improve blood pressure and/or glucose control in overweight patients.	A
8. Offer comprehensive lifestyle intervention to overweight patients with dyslipidemia for weight loss and to improve lipid levels.	B
9. Current evidence is insufficient to recommend for or against offering comprehensive lifestyle intervention for weight loss to overweight patients with degenerative joint disease, non-alcoholic fatty liver disease, and/or obstructive sleep apnea to reduce harms of these conditions.	I
Obese Patients	
10. Offer obese patients comprehensive lifestyle intervention for weight loss to improve lipid levels, blood pressure, and/or glucose control.	A
11. Offer obese patients comprehensive lifestyle intervention for weight loss to reduce harms of obstructive sleep apnea.	B
12. Consider offering obese patients comprehensive lifestyle intervention for weight loss to reduce harms of degenerative joint disease.	C
13. Current evidence is insufficient to support weight loss through comprehensive lifestyle intervention for reducing harms of non-alcoholic fatty liver disease.	I
Shared Decision-Making	
14. Reach a shared understanding with overweight and obese patients about the risks of overweight and obesity, and the benefits of weight management.	EO
General Treatment Principles of Weight Loss	
15. Perform an in-depth clinical assessment in order to assess the risks and benefits of different weight management treatments and to develop a weight management plan.	EO
16. Use motivational interviewing techniques to evoke patient motivation to accept and participate in weight loss treatments.	EO

Recommendation	GRADE
17. Convey the importance of weight loss and maintenance as a lifelong commitment rather than a brief episode of treatment.	EO
18. Offer patients at least 12 contacts within 12 months of a comprehensive lifestyle intervention that combines dietary, physical activity and behavioral strategies.	B
19. Plan a net deficit of 500 to 1,000 kcal/day addressing both diet and physical activity to achieve a weight loss of 0.5 to 2 pounds per week, resulting in a 5-10% reduction in body weight over 6 months.	A
20. Assess adherence to the weight loss program one-to-two times per month by measuring the patient's weight and providing feedback and ongoing support.	EO
21. Re-evaluate the treatment plan for patients who have lost an average of less than 0.5 pound per week.	EO
22. Offer patients who have met their weight loss goals a comprehensive maintenance program consisting of behavioral components and ongoing support.	B
Behavioral and Lifestyle Approaches	
23. Offer comprehensive lifestyle interventions for weight loss, in either individual or group setting.	B
24. Offer telephone-based comprehensive lifestyle intervention for weight loss, either as an alternative or an adjunct to face-to-face intervention.	B
25. There is insufficient evidence for or against offering internet-based comprehensive lifestyle intervention for weight loss, as an alternate or adjunct to face-to-face intervention.	I
Dietary Approaches	
26. Offer any of several diets that produce a caloric deficit and have evidence for weight loss efficacy and safety (e.g., low-carbohydrate, Dietary Approaches to Stop Hypertension (DASH), low-fat).	A
27. Offer very-low-calorie diets for weight loss, but only for short durations (12-16 weeks) and under close medical supervision.	B
28. Offer meal replacements to achieve low-calorie or very low-calorie diets.	A
Physical Activity Approaches	
29. Offer physical activity elements (e.g., home fitness, lifestyle, or structured/supervised physical activities) that can be combined to produce a caloric deficit leading to weight loss.	A
30. Offer physical activity options that include short intermittent bursts (at least 10 minutes) as well as longer continuous exercise.	A
31. Offer, as part of a comprehensive lifestyle intervention, moderate-intensity physical activity performed for at least 150 minutes/week to result in weight loss.	A
32. Offer, as part of comprehensive lifestyle intervention, moderate-intensity physical activity performed for 200-300 minutes per week to prevent weight regain after initial weight loss.	EO
Pharmacotherapy	
33. Offer pharmacotherapy with the combination phentermine/topiramate extended-release to patients with a body mass index (BMI) ≥30 kg/m^2 and to those with a BMI ≥27 kg/m^2 who also have obesity-associated conditions, as an adjunct to comprehensive lifestyle intervention, when lifestyle interventions alone do not produce the desired weight loss.	A

Recommendation	GRADE
34. Offer pharmacotherapy with orlistat or lorcaserin to patients with a body mass index (BMI) ≥30 kg/m^2 and to those with a BMI ≥27 kg/m^2 who also have obesity-associated conditions, as an adjunct to comprehensive lifestyle intervention, when lifestyle interventions alone do not produce the desired weight loss.	B
35. Offer pharmacotherapy (i.e., orlistat, lorcaserin, combination phentermine/topiramate extended-release) as an adjunct to comprehensive lifestyle intervention, to patients with obesity-associated conditions, for its beneficial effects on type 2 diabetes, hypertension, and/or dyslipidemia.	B
36. Offer patients who achieve their weight loss goal a program that includes continued use of medication for weight maintenance.	B
Bariatric Surgery	
37. Offer bariatric surgery, as an adjunct to comprehensive lifestyle intervention, for weight loss in adult patients with a body mass index (BMI) >40 kg/m^2 or those with BMI 35.0-39.9 kg/m^2 with one or more obesity-associated conditions.	A
38. Offer bariatric surgery, as an adjunct to comprehensive lifestyle intervention, to improve some obesity-associated conditions in adult patients with a body mass index (BMI) ≥35.0 kg/m^2.	A
39. Current evidence is insufficient to assess the balance of benefits and harms of offering bariatric surgery as an adjunct to comprehensive lifestyle intervention, for weight loss or to improve some obesity-associated conditions, to patients over age 65 or with a body mass index (BMI) <35 kg/m^2.	I
40. Engage all patients who are candidates for bariatric surgery in a general discussion of the benefits and potential risks. If more detailed information is requested by the patient to assist in the decision-making process, a consultation with a bariatric surgical team should occur.	EO
41. Provide lifelong follow-up after bariatric surgery to monitor adverse effects and complications, dietary restrictions, adherence to weight management behaviors and psychological health.	EO

Screening and Assessment for Overweight and Obesity

Recommendations

1. Screen adult patients to establish a diagnosis of overweight or obesity by calculating body mass index (BMI), and document the presence of overweight or obesity in the medical record. [B]
2. Screen for overweight and obesity at least annually. [EO]
3. Assess for the presence of obesity-associated conditions among overweight patients or patients with increased waist circumference. [B]
4. Perform a targeted assessment on overweight and obese patients. In addition to the basic medical history and physical examination, assess for factors contributing to obesity. [EO]

Discussion

Body Mass Index (BMI) is recommended as a practical screening tool to determine overweight and obesity in adult populations. The BMI is easily calculated, reliable and is the basis for mortality risk estimates. [25] BMI is defined as a person's weight in kilograms divided by the square of the person's height in meters (kg/m^2). When weight is measured in pounds and inches, the BMI is calculated as [weight (in pounds)/height (in inches)^2]x 703.

The optimal frequency for calculating BMI in the clinical setting has not been evaluated and is a matter of clinical discretion. [26] However, overweight and obesity pose substantial health risks in both Veterans and Service members. This increases the importance of regular screening, particularly among patients who have obesity-associated chronic health conditions or are at risk for conditions that may be exacerbated by overweight or obesity. Moreover, the harms of screening are minimal and the cost of screening is relatively low. [26] Screening at least annually provides an opportunity for patients and clinicians not only to identify overweight and obesity, but also to engage in productive discussions about the benefits of maintaining a healthy weight.

Although BMI is commonly used to identify obesity, there are questions regarding its accuracy in distinguishing between some obese and non-obese individuals. For example, the optimal BMI for those over 65 may be slightly higher than for younger people. [27] Additionally, use of BMI as an indicator for bariatric surgery has been questioned and the Swedish Obesity Study (SOS) showed the reduction in cardiovascular events in those receiving bariatric surgery was not related to baseline weight. [28,29]

Box 1: Common Obesity-Associated Conditions*

- Hypertension**
- Type 2 diabetes and pre-diabetes**
- Dyslipidemia**
- Metabolic syndrome
- Obstructive sleep apnea
- Degenerative joint disease
- Non-alcoholic fatty liver disease

*Increased waist circumference is considered an obesity comorbidity equivalent

** At least moderate evidence exists for modifying these conditions with weight loss. See Appendix E for details.

Measurement of body fat has been suggested as an alternative to BMI for screening for obesity. Frankenfield found that obesity based on body fat was always present in subjects with a BMI of at least 30 kg/m^2. [30] However, 30% of men and 46% of women with a BMI below 30 kg/m^2 also had obesity levels of body fat. [30] Additionally, truncal obesity may be a more important indicator of risk, especially in people with a BMI below 30 kg/m^2. [30]

Waist circumference (WC) is the most practical and reproducible anthropometric measurement for assessing a patient's level of abdominal fat and is an indicator of increased disease risk for overweight patients. [31] Though there are several other ways to estimate body fat, (e.g., skin-fold calipers, hydrodensitometry, dual energy x-ray absorptiometry, and bioelectrical impedance) most methods are not readily available or convenient in the clinical setting. Gender-specific WC cut-offs (i.e., greater than 40 inches for a man; greater than 35 inches for a non-pregnant woman) may be used in conjunction with BMI to identify increased disease risk associated with abdominal or truncal obesity. It should be noted that waist-to-height ratio may be the best predictor of cardiometabolic risk. [32] The waist circumference measurement should be made with a tape measure placed around the bare abdomen just above the iliac crest. The tape should be snug but should not compress the skin and the measurement should be obtained while the patient is standing at the end of normal exhalation. [33]

Obesity is clearly associated with several chronic health conditions, as shown in **Box 1**. While increased BMI is not required for these conditions, it is a risk factor for them. The Work Group chose to focus on the particular conditions listed in **Box 1**. However, it is well known that obesity is a health hazard for many other conditions, such as venous thrombosis, many types of cancer, stroke, and several psychiatric disorders. [31] See Appendix E for a detailed discussion regarding those conditions listed in **Box 1**.

An assessment of a patient's health history **(Box 2)** identifies the clinical, social, and behavioral factors that may affect their weight. In addition to the basic medical history and physical examination, patients should be assessed for factors contributing to obesity, including medications, co-morbid conditions, dietary and physical activity behaviors and the patient's motivation and readiness for change. Review of current medications and

Box 2: Elements of Medical Assessment of Overweight or Obesity

- History of overweight/obesity and previous weight loss attempts
- Current motivation for, and barriers to, weight loss
- Current and past psychiatric history
- Over-the-counter and prescription medication use
- Alternative and complementary therapy use
- Dietary and physical activity behaviors or limitations
- Tobacco and alcohol use
- Family history and obesity in family members
- Comorbidities and other conditions which may contribute to obesity
- Social history including support systems

Physical examination of the overweight and obese patient includes:

- Height and weight
- Calculated BMI
- Measurement of waist circumference
- Blood pressure

Laboratory tests may be obtained as clinically appropriate based on medical history and physical examination. These may include:

- Lipid profile
- ALT/AST
- Fasting blood glucose/A1C

health conditions may identify those that may induce weight gain or interfere with weight loss. Information obtained from the assessment may also be useful when counseling the patient regarding healthy behaviors and engaging in shared decision-making regarding weight management options.

Normal Weight Patients

Recommendations

5. Consider providing normal weight patients with information and behavioral counseling regarding healthy diet and physical activity behaviors, in order to maintain a healthy weight. [C]

Discussion

In 2012, based on a systematic review of trials of physical activity or dietary counseling to prevent cardiovascular disease (CVD), [34] the United States Preventive Services Task Force (USPSTF) issued a C recommendation regarding offering behavioral counseling interventions to promote a healthful diet and physical activity for cardiovascular disease prevention in adults. [35] Behavioral counseling interventions in clinical care are those activities delivered by primary care clinicians and related healthcare staff to assist patients in adopting, changing, or maintaining health behaviors. [36] The USPSTF panel concluded with moderate certainty, that medium- or high-intensity behavioral counseling interventions in the primary care setting to promote a healthful diet and physical activity have a small net benefit in adult patients without CVD, hypertension, hyperlipidemia, or diabetes. [34,35] Medium-intensity behavioral counseling interventions are at least 30 minutes per session, usually involve multiple sessions, and are often delivered by health educators or nurses, counselors or psychologists, dietitians or nutritionists, or exercise instructors or physiologists, rather than primary care providers themselves. Therefore, clinicians may choose to selectively counsel patients, or consider referring patients for counseling services available within the health care setting or the community. The clinician may take the following into consideration when choosing whether to provide or refer for behavioral counseling interventions: risk factors for CVD, a patient's readiness for change, social support and community resources that support behavioral change, and other health care and preventive service priorities. [35]

Normal weight patients may be educated about the health benefits of maintaining a healthy weight, praised for current healthy eating and physical activity behaviors, advised to balance caloric intake and energy expenditure, and encouraged to maintain a healthy weight. Patient education may also include recommending a diet balanced in fruits, vegetables, lean protein, whole grains, and low-fat dairy products.[1] In addition, moderate intensity daily physical activity (≥30 min/day, five of more days per week) should be encouraged.[2] [37]

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[1] see MyPlate at http://www.choosemyplate.gov or VHA's Eat Wisely and Strive for a Healthy Weight Healthy Living messages at http://www.prevention.va.gov/Healthy_Living/Nine_Healthy_Living_Messages.asp

[2] see VHA's Be Physically Active Healthy Living message at http://www.prevention.va.gov/Healthy_Living/Nine_Healthy_Living_Messages.asp

Overweight Patients Without Obesity-Associated Condition(s)

Recommendations

6. Consider providing overweight patients without obesity-associated conditions with information and behavioral counseling regarding healthy diet and physical activity behaviors, in order to pursue a healthy weight. [C]

Discussion

There is no evidence that weight loss interventions reduce mortality or morbidity from chronic disease among overweight/non-obese patients. However, adults who are overweight may still be at increased risk for developing chronic conditions (e.g., hypertension, diabetes, dyslipidemia, and cardiovascular disease). Furthermore, as body weight tends to increase with age, young adults who are overweight are at increased risk for gaining weight over time and becoming obese.

As noted in the section on normal weight patients, the United States Preventive Services Task Force (USPSTF) concluded that, for adult patients without cardiovascular disease (CVD) or CVD risk factors, there is adequate evidence that the benefits of medium-to-high intensity behavioral counseling interventions to improve diet and increase physical activity have a small net benefit. [34,35] See the section on normal weight patients for the USPSTF definition of a behavioral counseling intervention and the criteria used to specify medium-intensity behavioral counseling interventions. Clinicians may decide to selectively provide medium-to-high intensity behavioral counseling interventions to overweight patients without obesity-associated conditions, or refer these patients for behavioral counseling services taking the following into consideration: other risk factors for CVD, a patient's readiness for change, social support and community resources that support behavioral change, and other health care and preventive service priorities. [35]

Offering information about the benefits of healthy eating, physical activity, and achieving a healthy weight may also be valuable. See the section on normal weight patients for examples of content and resources for offering educational information regarding these topics.

For those overweight patients without obesity-associated conditions who request help to lose weight, establishing reasonable weight management goals, setting realistic expectations, and developing a plan to meet healthy eating, physical activity and weight management goals may be valuable.

Overweight Patients With Obesity-Associated Condition(s)

Recommendations

7. Offer comprehensive lifestyle intervention to achieve weight loss and to improve blood pressure and/or glucose control in overweight patients. [A]
8. Offer comprehensive lifestyle intervention to overweight patients with dyslipidemia for weight loss and to improve lipid levels. [B]

9. Current evidence is insufficient to recommend for or against offering comprehensive lifestyle intervention for weight loss to overweight patients with degenerative joint disease, non-alcoholic fatty liver disease and/or obstructive sleep apnea to reduce harms of these conditions. [I]

Discussion

The ultimate goal of weight loss is to reduce or prevent major adverse cardiovascular events (MACE) i.e., myocardial infarction, stroke, or cardiovascular mortality and to reduce all-cause mortality. High quality evidence in the form of randomized controlled trials have not shown, or are not available, to demonstrate prevention of MACE outcomes from weight loss intervention in those who are overweight. For instance, the Look AHEAD trial was halted after nearly 10 years of follow-up based on a futility analysis when the intervention condition failed to reduce MACE in patients with type 2 diabetes. [38]

While MACE may not be affected, there is good evidence that some of the obesity-associated conditions can be favorably modified by weight loss. This discussion focuses on some of the more common obesity-associated conditions listed in **Box 1**.

There is strong evidence that weight loss resulting from comprehensive lifestyle interventions significantly impacts hypertension, [38-44] type 2 diabetes, [31,39,45-48] and pre-diabetes [39,46] in the overweight population. There is also moderate evidence that weight loss has beneficial effects for dyslipidemia. [31,39,46,49] In this guideline, we define comprehensive lifestyle interventions for weight loss as interventions that combine dietary, physical activity and behavioral components, and include at least 12 intervention sessions over a 12 month period. See recommendation 18 in General Treatment Principles for additional discussion regarding the evidence supporting this definition of comprehensive lifestyle intervention.

Because prevention of MACE generally requires many years of follow-up, it is hoped that weight loss induced improvements in cardiovascular risk factors (i.e., hypertension, type 2 diabetes, and dyslipidemia) will ultimately result in improved cardiovascular morbidity and mortality.

Currently, there is insufficient evidence to show that weight loss in overweight patients improves health outcomes related to osteoarthritis or obstructive sleep apnea or improves quality of life. Additionally, few weight loss studies specifically measured all components of the metabolic syndrome though it is expected that this condition would improve from the positive benefits of weight loss on blood pressure, glucose control, and lipids.

Non-alcoholic fatty liver disease (NAFLD), though not mentioned in the 2006 CPG, is increasing in prevalence and warrants discussion. NAFLD encompasses a broad range of conditions from simple fatty liver to advanced cirrhosis. The inflammatory state of NAFLD is known as non-alcoholic steatohepatitis (NASH). NAFLD is the most common form of liver disease in the US and its prevalence is estimated to be 10-46%. [11,12] One study estimates that approximately 40% of NAFLD will progress to NASH. [14] NAFLD has surpassed alcohol as a primary cause for liver transplants in the US and will likely become the leading cause of liver transplant ahead of hepatitis C within 10-20 years. [13] Though lifestyle

interventions for weight loss may be promising for NAFLD and NASH, lack of sufficient data and high risk of bias in published studies preclude any firm recommendations.

For a more detailed discussion of obesity-associated conditions and quality of life, see Appendix E.

Obese Patients

Recommendations

10. Offer obese patients comprehensive lifestyle intervention for weight loss to improve lipid levels, blood pressure, and/or glucose control. [A]
11. Offer obese patients comprehensive lifestyle intervention for weight loss to reduce harms of obstructive sleep apnea. [B]
12. Consider offering obese patients comprehensive lifestyle intervention for weight loss to reduce harms of degenerative joint disease. [C]
13. Current evidence is insufficient to support weight loss through comprehensive lifestyle intervention for reducing harms of non-alcoholic fatty liver disease. [I]

Discussion

The data previously cited for overweight patients show strong net benefit for weight loss when hypertension, type 2 diabetes, pre-diabetes and/or dyslipidemia are present. Comprehensive lifestyle intervention has also been shown to produce these strong benefits for obese patients. [31,38-49] Weight loss from comprehensive lifestyle intervention in the obese produces benefit for those with obstructive sleep apnea and this benefit is comparable to that seen with the more dramatic weight loss associated with bariatric surgery. [50] The improvement is primarily seen through measurement of the apnea-hypopnea index (AHI) rather than daytime sleepiness or quality of life. [51,52] In the Sleep AHEAD study, 13.6% of subjects had a decrease in AHI from a mean of 23.2 to less than 5 events per hour, which was considered a clinical cure. [53]

The evidence for benefit from weight loss in osteoarthritis is somewhat less. A meta-analysis of four studies showed the reduction in self-reported disability and pain, though statistically significant, was weak; there was no clinical effect via the global osteoarthritis disease index. [54]

There is insufficient evidence to recommend lifestyle interventions for weight loss to benefit non-alcoholic fatty liver disease (NAFLD) or quality of life. See discussion above in the section on overweight patients for more on the benefits to NAFLD. Additionally, few studies specifically measured all components of the metabolic syndrome, though it is expected that this condition would improve from the positive benefits of weight loss on blood pressure, glucose control, and lipids.

For a more detailed discussion of obesity-associated conditions and quality of life, see Appendix E.

Shared Decision-Making

Recommendations

14. Reach a shared understanding with overweight and obese patients about the risks of overweight and obesity and the benefits of weight management. [EO]

Discussion

The clinical team and the patient should reach a shared understanding of the risks and benefits related to an individual's present weight and overall health status, and the potential risks and benefits of treatments for overweight and obesity. Achieving shared understanding of the patient's health status and conditions is an important step in the process of helping the patient consider self-management strategies and make informed decisions about the treatment approach. [55] The recommended process for achieving shared understanding is based on evidence-based principles of health education, [56] health behavior counseling [36,57] shared decision-making [55] and motivational interviewing. [58,59] It is useful to begin by asking permission to discuss weight in order to ensure that patients are receptive. Asking permission supports patient autonomy and is consistent with the principles of motivational interviewing, an evidence-based clinical method for building motivation for behavior change. [59] Specific techniques for effectively reaching shared understanding are specified in **Box 3**. [56-60]

Box 3: Methods for Reaching Shared Understanding

- Ask permission to discuss weight-related health risks and the potential benefits and risks of weight loss and weight management
- Explore the patient's understanding, beliefs, experience and values regarding the health risks associated with their weight and the impact of weight management on their health and wellbeing, and tailor information accordingly
- Share information about potential health risks based on the patient's BMI and current health status and the presence of weight-associated conditions
- Emphasize, if needed, the value of viewing obesity as a chronic disease condition that requires ongoing attention and weight management
- Provide small amounts of information in a manner that is easy to understand
- Use a "teach-back" method to confirm shared-understanding

Reaching a shared understanding with a patient includes presenting objective data obtained from the patient's history, examination and laboratory testing, as well as information about risks associated with the patient's current weight, particularly when obesity-associated conditions are present. However, the process is more than simply informing or educating a patient about their conditions and the benefits of weight loss interventions. It requires engaging in a dialogue with patients that begins with exploring their knowledge about the links between excess weight and their health conditions and risks. It is often useful to review the patient's prior experience with weight management, their beliefs and values about the benefits of weight loss, as well as the influences of relatives and friends. Exploring such issues helps the health care team to tailor information and advice, align recommendations with values (e.g., "preventing complications of diabetes will help you to be available to your family, which you said is very important to you"), respect preferences, build motivation and work collaboratively with the patient to plan the next step in weight management.

General Treatment Principles

Recommendations

15. Perform an in-depth clinical assessment in order to assess the risks and benefits of different weight management treatments and to develop a weight management plan. [EO]
16. Use motivational interviewing techniques to evoke patient motivation to accept and participate in weight loss treatments. [EO]
17. Convey the importance of weight loss and maintenance as a lifelong commitment rather than a brief episode of treatment. [EO]

Discussion

Choice among weight management options builds upon the initial targeted assessment discussed previously and includes a more thorough assessment of previous experience with weight loss and response to treatments, presence of conditions or factors that increase risk of untoward reactions to elements of treatments (e.g., previous adverse effects from weight loss pharmacotherapy, surgical risks), as well as patient preferences. Ultimately, patient preference will determine choice of treatment. Obesity can also be induced or exacerbated by health conditions and by certain medications. Therefore, it is important to identify these potential contributors to obesity before initiating treatment.

For a patient who is willing to commit to a weight loss intervention, a thorough assessment of the patient's dietary and physical activity behaviors is an essential element of effective behavioral intervention programs for obesity (see also: recommendation 18 and associated discussion). It is useful to assess current levels of physical activity (including activity type, frequency, duration, and intensity) and the presence of sedentary behaviors (e.g., prolonged television watching). Dietary evaluation may include an assessment of problem eating behaviors (e.g., excessive snacking, frequent high caloric fast foods), while weight and dieting history may include the number and types of diets and attempts at weight loss, possible triggers of weight gains and losses, and the range of weight changes. Social and psychological assessment should include exploration of motivation to change dietary, physical activity and monitoring behaviors. Assessment may identify barriers as well as strengths and resources that may impact patient participation in weight loss programs.

If an initial assessment of the patient's motivation indicates that the patient is not ready to commit to recommended treatment, an intervention based on motivational interviewing may be considered. Though there is considerable evidence that using motivational interviewing increases the likelihood that a patient will follow through with treatment recommendations across a wide range of health behaviors, there is only limited evidence for the impact of motivational interviewing on follow through with weight management treatment. [59,61-69] Principles and core

Box 4: Principles and Core Strategies of Motivational Interviewing

1. Resist directing
2. Understand the patient's motivation
3. Listen with empathy
4. Empower the patient by building confidence
5. Ask open-ended questions to evoke change talk
6. Provide affirmations, reflections, and summaries

strategies of motivational interviewing are listed in **Box 4**. For a more detailed discussion of motivational interviewing, please see Appendix F.

Once a patient is engaged in treatment, weight loss and maintenance should be conceptualized as a lifelong commitment rather than a brief episode of treatment. Patient participation in each element of the plan should be stressed at initiation of treatment and periodically over the duration of treatment, particularly if lapses occur. Building a collaborative relationship with the patient is central to establishing trust and is associated with improved patient attendance and participation in treatment activities and adherence to behavioral elements of intervention. [70] Building a strong collaborative provider-patient relationship is accomplished through the use of effective patient-centered communication strategies, including open-ended questions, reflective listening, empathy, support of patient autonomy, and affirmation of effective coping and self-care strategies. [70]

Recommendations

18. Offer patients at least 12 contacts within 12 months of a comprehensive lifestyle intervention that combines dietary, physical activity, and behavioral strategies. [B]

Discussion

In this guideline, we define "comprehensive lifestyle interventions" for weight loss as interventions that combine three critical "lifestyle" components (i.e., dietary, physical activity and behavioral components) and include at least 12 intervention sessions over a 12 month period. This definition is based on the 2011 Agency for Health Research and Quality (AHRQ) evidence synthesis that found that intensive (12 or more sessions in 12 months) multicomponent lifestyle interventions were associated with significantly greater weight loss than less intensive interventions. High intensity lifestyle interventions (12 or more sessions) achieved a total weight loss of 4-7 kg in intervention groups compared to 1.5-4 kg of weight loss in less intensive interventions. [31,71]

The AHRQ evidence-based synthesis found that the behavioral component of the comprehensive lifestyle intervention usually included the following elements: setting weight loss diet and physical activity goals, addressing barriers to change, self-monitoring, and strategizing how to maintain lifestyle changes. [26,71] These elements are also emphasized in other reviews of comprehensive lifestyle intervention for weight loss. [72,73] Evidence suggests that no single type of behavioral strategy is superior to the others and that multimodal strategies appear to work better than one strategy alone. [9,71,73]

These findings led to the 2012 United States Preventive Services Task Force (USPSTF) recommendation that patients with a BMI of 30 kg/m^2 or higher should be offered or referred to intensive, multicomponent behavioral interventions. This recommendation received a B Grade, indicating that the USPSTF found there is high certainty that the net benefit is moderate. [26] As noted above, we prefer to use the term comprehensive lifestyle intervention to refer to the effective intervention elements, an approach favored in other recent reviews [73] and in the American Heart Association/American College

of Cardiology/The Obesity Society Guideline for the Management of Overweight and Obesity in Adults. [74]

Three recently completed high quality trials tested comprehensive lifestyle interventions delivered in primary care settings. [75-77] All of the active intervention arms across the three studies provided two years of intervention and more than 12 intervention contacts during the first year, delivered by trained counselors/coaches either in-person in the primary care setting, via telephone, or via a web-based interface. All three studies reported that the intensive intervention arms, which included dietary, physical activity, behavioral and supportive components, produced significantly greater weight loss than usual care conditions. Taken together, these three trials demonstrate the effectiveness and impact of delivering comprehensive lifestyle interventions in real-world primary care settings. Other recent research in primary care settings suggest that interventions that are delivered by non-physician staff or include referral to evidence-based commercial programs (with primary care clinician follow-up and support) are more likely to lead to clinically significant weight loss than interventions delivered by physicians alone. [73,78]

See Appendix G for more background on the evidence for the effectiveness of comprehensive lifestyle interventions on weight loss outcomes.

Recommendations

19. Plan a net deficit of 500 to 1,000 kcal/day addressing both diet and physical activity to achieve a weight loss of 0.5 to 2 pounds per week, resulting in a 5-10% reduction in body weight over 6 months. [A]

Discussion

The centerpiece of any weight loss program is the creation of an energy deficit which, regardless of any co-existing metabolic condition, results in weight loss. [73] While it is true that one pound of weight loss occurs whenever the net energy deficit equals 3500 kcal, it is difficult to predict the actual amount of weight loss due to alterations in energy requirements as a result of changing body mass. [79] Hence, even when the levels of physical activity and caloric intake that led to initial weight loss are unchanged, the magnitude of weight loss will not be sustained. With this in mind, an energy deficit is created by either increasing energy expenditure or decreasing energy intake and it is preferable to have a combination of both. Hence, as noted previously, a balanced comprehensive lifestyle approach that includes increased physical activity, reduced caloric intake, and use of behavioral strategies to promote self-monitoring and achievement of dietary and behavioral goals is recommended. [9,26,73] This approach is also consistent with the American Heart Association/American College of Cardiology/The Obesity Society Guideline for the Management of Overweight and Obesity in Adults. [74] See the section on Dietary Approaches for additional dietary recommendations and discussion.

Setting appropriate, specific, and realistic weight loss goals is critical to successful weight management. [9,80] Achieving 5-10% weight loss after 6 months is a reasonable initial treatment goal that can produce clinically significant benefits, especially for patients with obesity-associated conditions.

[9,26,71,73] A short-term initial weight loss goal of 0.5-2.0 pounds per week is achievable with a net caloric deficit of 500-1,000 kcal/day. This short-term weight loss goal, along with specific dietary, physical activity and self-monitoring goals can serve as benchmarks for assessing progress during initial treatment.

Recommendations

20. Assess adherence to the weight loss program one-to-two times per month by measuring the patient's weight and providing feedback and ongoing support. [EO]
21. Re-evaluate the treatment plan for patients who have lost an average of less than 0.5 pound per week. [EO]

Discussion

As previously noted, weight loss is enhanced when patients participate in a comprehensive lifestyle intervention that includes at least 12 visits over 12 months. This level of intensity of intervention provides opportunities for patients to address the challenges of adopting the dietary, physical activity and other behavioral strategies that are required to achieve weight loss goals.

Frequent treatment contacts also provide opportunities to review the patient's progress and assess the patient's experience in making desired changes in dietary, physical activity and other self-management behaviors. Measuring weight at these visits is critical to tracking progress, as is identifying barriers to treatment plan adherence. [73,74] If motivation is waning, or the patient is having difficulty meeting behavioral goals, specific attention to these elements of treatment is warranted. [68,73] If, despite increased attention to these barriers, the patient continues to struggle to meet short-term weight loss goals, consideration should be given to increasing the intensity of treatment. Considerations for intensification include: increasing the intensity or frequency of the comprehensive lifestyle intervention, adding a recommended pharmacotherapeutic agent for weight loss, and referral to a bariatric surgical team. See the algorithm as well as recommendations regarding pharmacotherapy and bariatric surgery for further guidance.

Recommendations

22. Offer patients who have met their weight loss goals a comprehensive maintenance program consisting of behavioral components and ongoing support. [B]

Discussion

Once long-term weight loss goals have been achieved, the focus of weight management shifts to preventing weight regain, a goal that requires maintenance of dietary and physical activity behaviors and many of the other self-management behaviors that contributed to successful weight loss. [81] Evidence demonstrates that the majority of people who lose weight regain much of that weight over a period of one to five years in the absence of continued intervention. [73,81,82] Data from the National Weight Control Registry (NWCR) indicate that approximately 20% of individuals who achieve a 10% reduction in body weight maintain the loss for at least one year. [81] The NWCR data indicate that those

who maintain their weight loss for more than five years report eating a low-calorie, low-fat diet; eating breakfast regularly; engaging in high levels of physical activity (approximately 1 hour per day); self-monitoring weight on a nearly daily basis; and maintaining a consistent eating pattern across weekdays and weekends. There is also evidence from controlled trials that offering a comprehensive maintenance intervention that includes dietary, physical activity and behavioral components plus ongoing support reduces the likelihood of weight regain. [71,73,83,84]

For example, Perri and colleagues compared groups that underwent a 20-week comprehensive lifestyle intervention with no follow-up to four forms of follow-up contact, each with a different emphasis. [85] The participants in the four continued contact groups maintained 82.7% of the mean post-treatment weight loss, compared with 33.3% in the no follow-up contact group. Perri and colleagues also compared two extended follow-up groups to a no follow-up contact group following a 20-week treatment program. Both the completed only and the intention-to-treat analysis found that those groups who were given extended contact maintained a significantly greater percentage of their initial weight loss at the 12-month post-treatment point. [86]

More research is needed in the area of weight loss maintenance particularly regarding duration of the maintenance intervention and the frequency and mode of contact (e.g., face-to-face, telephone, text message, or email).

Because the rates of regain after weight loss are high, it is vitally important to continue to measure weight in those achieving weight loss goals at each routine health visit or at least twice per year.

Behavioral and Lifestyle Approaches

Recommendations

23. Offer comprehensive lifestyle interventions for weight loss, in either individual or group setting. [B]
24. Offer telephone-based comprehensive lifestyle intervention for weight loss, either as an alternative or an adjunct to face-to-face intervention. [B]
25. There is insufficient evidence for or against offering internet-based comprehensive lifestyle intervention for weight loss, as an alternate or adjunct to face-to-face intervention. [I]

Discussion

As discussed in the General Treatment Principles section, comprehensive lifestyle interventions for weight loss that feature behavioral, dietary and physical activity components are highly effective for producing weight loss. [26,31,71,73] Behavioral approaches and strategies help overweight and obese individuals modify eating, activity and related thinking behaviors that contribute to their excess weight. [73] The Agency for Health Research and Quality (AHRQ) evidence synthesis identified the following behavioral strategies as common to successful interventions: setting weight loss diet and physical activity goals, addressing barriers to change, self-monitoring, and strategizing how to maintain lifestyle changes. [26,31,71] Other common behavioral strategies include stimulus control, positive

reinforcement, stress management, problem solving, and cognitive restructuring activities. Evidence suggests that no single type of behavioral strategy is superior to the others and that multimodal strategies appear to work better than one strategy alone. [9,31,73] As discussed in the General Treatment Principles section, higher intensity comprehensive lifestyle intervention that includes behavioral strategies is more effective than lower intensity interventions. [26,31,71,73] Further description of specific behavioral strategies can be found in the Appendix G.

Recommendations 24 and 25 address the format for delivering comprehensive lifestyle intervention. Though comprehensive lifestyle interventions are often delivered in group programs, treatments utilizing either group or individual face-to-face formats are effective. [26,31,71,73] Though a single randomized controlled trial found that a group format produced significantly greater weight loss (about two kilograms) than individual care [87], no firm conclusions can be made about the comparative effectiveness of group versus individual formats of comprehensive lifestyle interventions. [71,74] Several studies have demonstrated that telephone-based comprehensive lifestyle interventions are effective for achieving weight loss. [73,88] Thus, delivering comprehensive lifestyle intervention by telephone is an alternative for those who cannot participate in face-to-face interventions or as a supplement to face-to-face sessions. Evidence regarding the comparative effectiveness of telephone versus face-to-face comprehensive interventions is lacking. [71]

The internet or other electronic health (e-health) delivery systems offer alternatives to person-to-person treatment programs. Though e-health interventions offer the opportunity for asynchronous intervention that increase accessibility to an intervention and trained interventionists, several studies indicate that in-person comprehensive lifestyle intervention is superior to internet-based adaptations. [89-91] There is limited evidence that electronic formats may be effective for delivering maintenance interventions. [92] However, there is currently insufficient evidence to recommend for or against providing internet or other electronic comprehensive weight loss interventions as an alternative or adjunct to face-to-face interventions.

Dietary Approaches

Recommendations

26. Offer any of several diets that produce a caloric deficit and have evidence for weight loss efficacy and safety (e.g., low-carbohydrate, Dietary Approaches to Stop Hypertension (DASH), or low-fat). [A]
27. Offer very-low-calorie diets for weight loss, but only for short durations (12-16 weeks) and under close medical supervision. [B]
28. Offer meal replacements to achieve low-calorie or very low-calorie diets. [A]

Discussion

Diet is one of the three pillars of the comprehensive lifestyle intervention and a referral to a registered dietitian should be made as part of a comprehensive lifestyle approach to weight loss. A 10% weight loss

over six months is an achievable weight loss goal. Together with physical activity, a total calorie deficit of 500-1000 kcal/day is required to achieve weight loss of 1-2 lbs per week for the first 12-16 weeks. Because dietary restriction is measurable and predictable, it is frequently the hallmark of achieving this negative energy balance. It is more difficult to achieve a comparable calorie deficit through physical activity alone—it may take 225-420 minutes of moderate-intensity aerobic exercise per week (e.g. walking 35 miles per week) to lose one pound per week. [9,73]

From the standpoint of creating a calorie deficit, the choice of a specific diet is less important; rather it is the attainment of caloric deficit that is the key to weight loss. [73,93-98] Any nutritionally balanced diet can be recommended (See **Box 5** and **Table 2** for examples). [73,91,99-101] The focus should be on adherence to a diet that is individualized for medical and metabolic conditions and ease of long-term maintenance and adherence. [22,73,74]

Box 5: Categories of Fat and Macronutrient Composition of Diets

- High-fat (55 to 65 percent), low-carbohydrates (100 grams of carbohydrates per day), high-protein diets
- Moderate-fat (20 to 30 percent), balanced nutrient reduction diets, high in carbohydrates and moderate in protein
- Low-fat (11 percent to 19 percent) and very-low-fat (VLF) (10 percent), very high-carbohydrates, moderate-protein diets

The Dietary Approaches to Stop Hypertension (DASH) diet is endorsed by the US Department of Health and Human Services while the MyPlate Food Guidance System is endorsed by the US Department of Agriculture. The Academy of Nutrition and Dietetics recommends portion control with total daily calories split over four to five meals per day. [98] Nutritionally complete very-low-calorie diets (<800 kcal/day) may be considered under close supervision for 12-16 weeks, but post-diet maintenance is crucial for maintaining the substantial weight loss that is possible. High-fat, low carbohydrate diets demonstrate better-than-average weight loss up to six months, [101] but weight loss beyond one year mirrors other macronutrient diet plans. [39,46,102]

The use of commercial programs with proven track records of successful weight loss may be effective for some patients. See Appendix H for a discussion of this and other select dietary models, e.g., Mediterranean, low-carbohydrate, and low-glycemic index.

Table 2: Definitions of Common Diets

Diet approach	Content (% of total calories)		
	Fat	Carbohydrates	Protein
Very-low carbohydrates (High-fat)	55-65	<20 (<100g)	25-30
Low carbohydrates (Moderate-fat)	20-30	30-40	25-30
Moderate-fat, balanced nutrient reduction (Low-calorie)	20-30	55-60	15-20
Low-fat	11-19	>65	10-20

Physical Activity Approaches

Recommendations

29. Offer physical activity elements (e.g., home fitness, lifestyle, or structured/supervised physical activities) that can be combined to produce a caloric deficit leading to weight loss. [A]
30. Offer physical activity options that include short intermittent bursts (at least 10 minutes) as well as longer continuous exercise. [A]
31. Offer, as part of a comprehensive lifestyle intervention, moderate-intensity physical activity performed for at least 150 minutes/week to result in weight loss. [A]
32. Offer, as part of comprehensive lifestyle intervention, moderate-intensity physical activity performed for 200-300 minutes per week to prevent weight regain after initial weight loss. [EO]

Discussion

The Surgeon General's Vision for a Healthy and Fit Nation 2010, [103] the American College of Sports Medicine (ACSM) and others recommend at least 150 minutes of moderate-intensity physical activity per week for general health benefits. [99] Two large randomized controlled trials of lifestyle intervention have shown the benefit of this level of exercise for producing weight loss and cardiovascular risk reduction. [39,46]

However, physical activity may be an ineffective way to lose weight if unaccompanied by caloric restriction. [99,104] In Miller's meta-analysis of interventional trials employing diet and/or exercise, the mean weight loss at 15.6 weeks for exercise alone vs. exercise with diet was -2.9 kg and -11.0 kg, respectively. [105] One of the reasons may be the amount of effort needed through activity alone to produce the energy deficit required for any level of weight loss. In a study conducted by Ross et al., subjects with no change in caloric intake, exercised on average of one hour per day at 77% of maximal predicted heart rate in order to lose approximately 1.4 lbs per week for a total of 16.5 pounds at 12 weeks. [106] To lose one pound per week, it may take walking 35 miles per week. [73] Since weight loss is contingent on the principle of energy deficit, a dose-response exists, i.e., greater duration and intensity will result in more weight loss. When physical activity is a component of a comprehensive lifestyle intervention (CLI), lesser amounts of activity may be needed to achieve weight loss. The American Heart Association/American College of Cardiology/The Obesity Society (AHA/ACC/TOS) Obesity CPG recommends that CLI include at least 150 minutes/week of aerobic physical activity such as brisk walking. [74] Participants in the Diabetes Prevention Program targeted at least 150 minutes of physical activity per week as part of CLI and lost over 6 kg at 6 months. [46] Similarly, participants in the Look AHEAD trial targeted at least 175 minutes of physical activity per week as part of CLI and lost over 8 kg at 12 months. [38]

Physical activity is particularly crucial for weight maintenance after weight loss. The actual level of physical activity required for weight maintenance has not been determined as there is a lack of high quality randomized controlled trials. [99,107] For instance, controlled studies showed no difference [108-113] or mixed results [114] in weight in those randomized to the increased physical activity group. Secondary analysis of trials has shown that longer duration (>200 minutes per week) [107,108] or higher

intensity (>2500 kcal/week) [110] physical activity is associated with improved weight maintenance. Additionally, observational studies indicate that higher levels of physical activity are associated with greater weight maintenance after weight loss. [115] For instance, those in the National Weight Control Registry who were able to maintain a weight loss of 30 pounds for five years averaged approximately one hour per day of moderate-intensity activity such as brisk walking. [81] Given the available literature, the ACSM advocates a "more is better" approach and recommends approximately 60 minutes of walking per day at moderate intensity (approximately four miles per hour) to maintain weight after initial weight loss. [99] The AHA/ACC/TOS CPG recommends high levels of physical activity, i.e., 200-300 minutes/week, for weight loss maintenance. [74]

The benefits of physical activity extend beyond weight loss. Epidemiological studies show that those who walk regularly have a reduced risk of cardiovascular disease. [116,117] Furthermore, randomized control trials have clearly demonstrated reduction in cardiovascular risk factors with physical activity, particularly when combined with an overall lifestyle approach. [39,46,73,99]

Physical activity should be initiated after the patient and provider have developed a plan that includes activity type, intensity, duration, and frequency. A detailed physical activity prescription is more likely to be adhered to if factors such as patient preference, progress, target weight loss, and physical abilities are considered. Simply increasing activity by approximately 30 minutes per day above baseline by walking or taking stairs instead of elevators may be all that it takes for some to achieve modest weight loss. [118] Such home-based lifestyle interventions can be just as effective as formal structured and supervised exercise programs and may actually result in greater adherence over the long-term. [106,116] Furthermore, short intermittent bursts of exercise are just as effective as longer duration exercise if the total estimated calorie expenditure is the same. [118,119] Due to difficulty maintaining longer duration exercise, it is typically not any more effective or may be less effective than shorter duration exercise for the maintenance of weight loss. [114]

As alluded to above, several organizations have made recommendations on the amount of physical activity to engage in and there is general agreement that the intensity of exercise should be moderate and carried out at least 30 minutes per day to achieve improved health outcomes. [9,37,99,103] The intensity of an activity is quantified by a metabolic equivalent (MET). A single MET is defined as 3.5 ml of oxygen consumption per kg per minute (3.5 ml O^2/kg/min), which is also equivalent to 1 kcal/kg/hr of energy use. Activity of light intensity is defined as 1.1-2.9 METS, moderate-intensity as 3.0-5.9 METS and vigorous activity as $\geq$ 6 METS. One MET or 1 kcal/kg/hr represents the typical metabolic rate or energy cost of sitting quietly at rest. A 2.0 MET activity, such as driving a car, requires twice the energy required to sit quietly. Walking slowly requires 3.0 METs. A typical moderate intensity walking pace is four miles per hour. Appendix I lists the MET equivalent for various types of physical activity. Additionally, the Compendium of Physical Activities was developed to provide consistency in scoring physical activity questionnaires and provides METs associated with common physical activities in 21 general categories. [120] It can be accessed at https://sites.google.com/site/compendiumofphysicalactivities/. It should be noted that the compendium does not account for adjustments in MET values based on individual weights. Thus, these MET values may be incorrect, depending on the weight, fitness level, and age of the patient and should not be used as a way to calculate precise caloric expenditure.

The estimated kcal energy expenditure associated with any physical activity can be calculated as follows:

kcal per week = METs x number of sessions per week x hours per session x body weight in kg

Some examples of physical activity and exercise are available in Appendix I.

Pharmacotherapy

Recommendations

33. Offer pharmacotherapy with the combination phentermine/topiramate extended-release to patients with a body mass index (BMI) ≥30 kg/m^2 and to those with a BMI ≥27 kg/m^2 who also have obesity-associated conditions, as an adjunct to comprehensive lifestyle intervention, when lifestyle interventions alone do not produce the desired weight loss. [A]
34. Offer pharmacotherapy with orlistat or lorcaserin to patients with a body mass index (BMI) ≥30 kg/m^2 and to those with a BMI ≥27 kg/m^2 who also have obesity-associated conditions, as an adjunct to comprehensive lifestyle intervention, when lifestyle interventions alone do not produce the desired weight loss. [B]
35. Offer pharmacotherapy (i.e., orlistat, lorcaserin, combination phentermine/topiramate extended-release), as an adjunct to comprehensive lifestyle intervention, to patients with obesity-associated conditions, for its beneficial effects on type 2 diabetes, hypertension, and/or dyslipidemia. [B]
36. Offer patients who achieve their weight loss goal, a program that includes continued medication use for weight maintenance. [B]

Discussion

Although lifestyle changes alone can result in weight loss for some, many overweight and obese patients need additional interventions for weight reduction. The use of pharmacologic treatment for obesity has increased in response to the increasing prevalence of obesity. A number of medications have been approved for short-term use e.g., diethylpropion and phentermine, but data on their effectiveness or safety following long-term exposure is lacking. [121] The evidence of efficacy beyond one year of treatment is limited to orlistat, lorcaserin, and to the combination phentermine/topiramate extended-release (P/T ER) that have all been approved by the Food and Drug Administration (FDA) for treating obesity among people with body mass index (BMI) greater than 30 kg/m^2 or BMI $\geq$27 kg/m^2 with obesity-associated conditions. However, side effects are common and continual assessment by the provider for both efficacy and safety is necessary. No combination of orlistat, lorcaserin, or P/T ER should be used, as there are no data for the efficacy and safety of these drugs when used together. The use of weight loss drugs during pregnancy is contraindicated.

A comprehensive lifestyle intervention (CLI) consisting of a reduced-calorie diet, increased physical activity, and behavioral modification provides the safest and most successful therapy for weight loss and weight maintenance. Systematic reviews, meta-analyses and subsequent randomized controlled trials

provide good evidence that the use of medications (orlistat, combination P/T ER, or lorcaserin) combined with CLI result in weight loss in obese adults when used for six months to one year and can also lessen weight regain as a part of a weight maintenance program. [121-131] CLI should be continued when pharmacotherapy is initiated. After one year, and under these conditions, orlistat and lorcaserin result in an approximate mean weight loss of 3 kg greater than placebo. Patients taking the combination P/T ER averaged a 6.7 to 8.8 kg greater weight loss compared to placebo. A ≥5% loss from baseline weight was achieved by 21%, 37% to 47%, and 62% to 70% of persons taking orlistat, lorcaserin, and combination P/T ER, respectively. [121,122,125-131]

Controversy exists around the optimal *timing* of introducing pharmacotherapy into a weight loss program. Some providers favor prescribing these agents only after CLI has failed to produce weight loss consistent with goals. Others offer these agents earlier in treatment to assist in the initiation of weight loss, boost patient self-confidence, and expedite the reduction in risk for obesity-associated conditions. Regardless of when pharmacotherapy is introduced, it should always be in combination with a reduced calorie diet and other lifestyle changes.

Note: In clinical trials, pharmacotherapy was started simultaneously with comprehensive lifestyle interventions. Introduction of drugs very early in treatment is not suggested in clinical practice. Hence, the initial weight loss may be less than demonstrated in studies when pharmacotherapy is started after comprehensive lifestyle interventions.

For drug information please see Appendix J, which discusses efficacy for weight loss, secondary outcomes, adverse effects and weight maintenance.

Off-Label Pharmacotherapy

Weight loss is a noted side effect of many drugs. Several of these drugs have been studied and are at times prescribed to promote weight loss. Such off-label use is often limited by dose-related weight loss and side effects (e.g., topiramate), modest or inconsistent effect (e.g., metformin), or safety concerns (e.g., hormone therapies, amphetamines). For this reason, the off-label use of drugs to promote weight loss, whether monotherapy or combination therapy, cannot be endorsed. For additional information see Appendix J on pharmacotherapy.

Bariatric surgery

Recommendations

37. Offer bariatric surgery, as an adjunct to comprehensive lifestyle intervention, for weight loss in adult patients with a BMI >40 kg/m^2 or those with BMI 35.0-39.9 kg/m^2 with one or more obesity-associated conditions. [A]
38. Offer bariatric surgery, as an adjunct to comprehensive lifestyle intervention, to improve some obesity-associated conditions in adult patients with BMI ≥ 35.0 kg/m^2. [A]

39. Current evidence is insufficient to assess the balance of benefits and harms of offering bariatric surgery as an adjunct to comprehensive lifestyle intervention, for weight loss or to improve some obesity-associated conditions, to patients over age 65 or with a BMI<35 kg/m^2. [I]

Discussion

Obese patients often do not achieve substantial weight loss as a result of lifestyle modifications and drug therapy. Only bariatric surgery has been demonstrated to consistently result in profound and sustained weight loss. [132] For instance, one randomized controlled trial (RCT) reported a two year weight loss of 20% of initial weight vs. 1.4% in the control group or -21.1 kg vs. -1.5 kg, respectively. [50] Baseline body mass index (BMI) (kg/m^2) decreased from 36.9 to 29.5 vs. 37.1 to 36.6 in the surgery and controls groups, respectively. [50] Another RCT reported a two year difference in weight of 15.5 kg in the surgery vs. control groups. [133] The Swedish Obesity Study (SOS) reported a 10 and 20 year weight change of -17% and -18% vs. 1% and -1% in the surgery vs. control groups, respectively. [134]

While hypertension, type 2 diabetes, and dyslipidemia substantially improve with bariatric surgery in those with BMI increasingly above 35 kg/m^2, little is known for those with lesser degrees of obesity. [132,135-140] An Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review evaluated this question for diabetes or impaired glucose tolerance and found that weight loss and improvement in hemoglobin A1C levels was substantial short-term, but there was low strength of evidence for short-term harms and no long-term data was available. [141] Overall, there is insufficient evidence to recommend for or against bariatric surgery for BMI categories < 35 kg/m^2.

Only one study reported on the benefit of bariatric surgery in patients with obstructive sleep apnea. No difference in apnea-hypopnea index was found in the surgical vs. lifestyle group in spite of a markedly increased weight loss with surgery. [50] There were no studies that evaluated the outcomes of osteoarthritis with bariatric surgery.

For non-alcoholic fatty liver disease (NAFLD), two reviews have shown improvement in histologic scores such as steatosis. [142,143] However, out of 18 studies reviewed, fibrosis improved in only six studies and worsened in four studies, which were typically larger and followed patients for a longer time. [143] As worsening fibrosis is a strong predictor of advanced NAFLD, no definitive recommendation can be made for or against surgery.

In addition to improvement of obesity-associated conditions (OAC), bariatric surgery may have improvement in short-term quality of life (QoL). Livingston summarized 11 studies (all but one short-term) and concluded that QoL improved significantly enough to outweigh harms. [144] More recently, Colquitt reported on one RCT and one cohort study showing short-term benefit; another cohort study did not. [132] At 10 years, the benefit shown in the cohort study was not significantly different from the control group. The prospective Utah study showed benefits in the health related QoL Short Form-36 (SF-36) physical component and total QoL but not mental component scores at six years. [136]

While the evidence for modifying some obesity-associated conditions via comprehensive lifestyle intervention, pharmacotherapy and/or bariatric surgery is substantial and rigorous, the evidence is

significantly less rigorous for improvement in major adverse cardiovascular events (MACE). Lifestyle or pharmacotherapy has not been shown to reduce MACE. Recently, the Look AHEAD trial was halted after nearly 10 years of follow-up based on a futility analysis when it failed to reduce MACE. [38]

Several non-randomized controlled trials of bariatric surgery have been conducted evaluating MACE. Pontiroli's meta-analysis of eight studies showed a reduction in cardiovascular and overall mortality. Of the 14,052 total patients that had surgery, 21% were men. The mean BMI was 47.0 kg/m^2 and the duration of follow-up was 7.5 years. [145] Six of these studies either did not use gastric bypass (the most frequent procedure performed in the US) as the primary procedure or did not have optimal controls. [146-151]

In terms of cardiovascular morbidity, Christou's observational cohort study (79% received gastric bypass) showed a reduction in the development of cardiovascular disorders in the surgical group compared to controls (mean follow-up 5.3 years). [152] A sub-study of the SOS (16% received gastric bypass) showed a reduction in myocardial infarction incidence but not stroke incidence compared to controls. [29]

While encouraging data exists, more research is needed to better define the outcome of bariatric surgery on cardiovascular morbidity/mortality and all-cause mortality. [153]

Finally, a significant portion of the Veterans Affairs (VA) and Department of Defense (DoD) beneficiary population is over 65 years of age. Among Veterans, the prevalence of overweight or obesity is estimated to be 78%. For the DoD retiree beneficiary population, 46% are obese and 86% are overweight or obese. [5] There are currently no controlled trials to assess the benefit vs. risks/harms of bariatric surgery in individuals over 65 years of age.

Recommendations

40. Engage all patients who are candidates for bariatric surgery in a general discussion of the benefits and potential risks. If more detailed information is requested by the patient to assist in the decision-making process, a consultation with a bariatric surgical team should occur. [EO]
41. Provide lifelong follow-up after bariatric surgery to monitor adverse effects and complications, dietary restrictions, adherence to weight management behaviors, and psychological health. [EO]

Discussion

Surgery may be considered for patients with a body mass index (BMI) >40 kg/m^2 or >35 kg/m^2 with one or more obesity-associated conditions. [74,132,154] There are several surgical options for qualified patients. Bariatric operations can be broadly categorized into two types: restrictive and malabsorptive. Restrictive procedures include gastric banding, adjustable gastric banding, and lateral sleeve gastrectomy. Malabsorptive procedures include biliopancreatic diversion and biliopancreatic diversion with duodenal switch. The Roux-en-Y gastric bypass combines both restrictive and malabsorptive techniques. (See Appendix K) In the US, Roux-en-Y gastric bypass is the most commonly performed procedure. Due to the limited evidence and overall quality of the trials, comparative safety and effectiveness between types of bariatric procedures could not be evaluated. [132]

While the Lap-Band® has a Food and Drug Administration (FDA) indication for patients with a BMI >35 kg/m^2 or patients with BMI >30 kg/m^2 with obesity-associated conditions, there is insufficient evidence to routinely recommend this procedure in those with a BMI <35 kg/m^2. [155]

All these operations are associated with some degree of morbidity and mortality and require good adherence to medical follow-up. Laparoscopic approaches are currently available for most bariatric procedures and are associated with lower morbidity and mortality compared to open approaches. Any patient being considered for bariatric surgery should be carefully evaluated. Patients who are older than age 65, who weigh more than 400 pounds, or who have severe comorbidity, may be at greater risk for complications. The decision regarding surgery should be an individualized, shared decision-making process between the patient and the surgeon, weighing both the benefits and risks. For a more detailed discussion regarding bariatric surgery to include risks and follow-up care, see Appendix K.

Future Research

Despite the progress that has been made in identifying effective interventions to assess and treat overweight and obese adults since the initial publication of the 2006 Clinical Practice Guideline, many important gaps remain, particularly regarding the impact of screening and weight management interventions on long-term outcomes, including quality of life, nonalcoholic fatty liver disease, cardiovascular morbidity (e.g., myocardial infarction and ischemic stroke) and all-cause mortality. Moreover, the vast majority of reviewed research studies were conducted in academic settings, among non-active duty and non-Veteran populations that also included individuals who were predominantly women, white, young or middle aged, and motivated to participate in a weight management trial. There is a need for more research evaluating screening and weight management intervention in Veterans and Service members, particularly men and among older adults, and in those with mental illness. Gaps also remain regarding the efficacy of alternative modalities of lifestyle intervention (e.g., internet, phone, phone apps, and secure messaging), the efficacy and comparative effectiveness of various interventions for maintaining weight loss, and the efficacy and comparative effectiveness of intermediate intensity lifestyle interventions (e.g., 4 - 11 sessions/year), particularly when integrated within primary care settings and/or paired with pharmacotherapy. There is also a need for research that evaluates the cost effectiveness of screening and comparative cost effectiveness among weight management interventions.

The panel also recommends research that addresses the following specific questions:

- What is the best method for screening for overweight and obesity and risk stratification (e.g., waist circumference, waist–hip ratio, body mass index (BMI)) in Veterans and active duty Service members?
- Are there individual differences that predict response to comprehensive lifestyle intervention, a specific pharmacotherapy, or a specific bariatric procedure?
- How should a clinician prioritize choice of intervention based on presence of specific obesity-associated conditions?

- What are the essential elements of comprehensive lifestyle intervention?
- What are the benefits and harms of weight loss or weight management in patients who are overweight with or without obesity-associated conditions?
- What are the benefits and harms of surgical intervention for obesity for patients with a BMI of 30 - 35?
- What are the benefits and harms of surgical intervention for osteoarthritis?

Appendix A: Evidence Review Methodology

Formulating Evidence Questions

The Clinical Practice Guideline (CPG) Champions were tasked with identifying key evidence questions to guide the systematic review of the literature on overweight and obesity. These questions, which were developed in consultation with the Lewin Group's evidence review team, addressed clinical topics of the highest priority for the Veterans Affairs (VA) and Department of Defense (DoD) populations, including the benefits and harms of various pharmacologic and non-pharmacologic therapies on weight loss and other comorbidities. The key questions follow the population, intervention, comparison, outcome, timing and setting (PICOTS) framework for evidence questions, as established by the Agency for Healthcare Research and Quality (AHRQ). **Table A-1** provides a brief overview of the PICOTS typology.

Table A-1: PICOTS [156]

P	Patients, Population or Problem	A description of the patients of interest. It includes the condition(s), populations or sub-populations, disease severity or stage, co-morbidities, and other patient characteristics or demographics.
I	Intervention or Exposure	Refers to the specific treatments or approaches used with the patient or population. It includes doses, frequency, methods of administering treatments, etc.
C	Comparison	Describes the interventions or care that is being compared with the intervention(s) of interest described above. It includes alternatives such as placebo, drugs, surgery, lifestyle changes, standard of care, etc.
O	Outcome	Describes the specific results of interest. Outcomes can include short, intermediate, and long-term outcomes, or specific results such as quality of life, complications, mortality, morbidity, etc.
(T)	Timing, if applicable	Describes the duration of time that is of interest for the particular patient intervention and outcome, benefit, or harm to occur (or not occur).
(S)	Setting, of applicable	Describes the setting or context of interest. Setting can be a location (such as primary, specialty, or inpatient care).

The Champions and evidence review team carried out several iterations of this process, each time narrowing the scope of the CPG and the literature review by prioritizing the topics of interest. **Table A-2** contains the final set of key questions used to guide the systematic review for this CPG. **Table A-3** provides a detailed chart which outlines some of the decisions that the Champions made in prioritizing the key questions.

Table A-2: Key Questions Used in the Systematic Review

Key Question	Review date parameters
KQ1 What is the impact of the quality (e.g., type) and quantity (e.g., intensity) of behavioral treatments (i.e., anything that enhances adherence to diet or exercise, but not diet and exercise themselves) on weight loss outcomes?	September 9, 2010 – February 1, 2013
KQ2 What is the relative comparative effectiveness of medications approved by the FDA for weight loss among overweight and obese individuals?	September 9, 2010 – February 1, 2013
KQ3a Which population would benefit most from non-lifestyle interventions, i.e., drug therapy and surgery? a. Obese vs. overweight	September 9, 2010 – February 1, 2013
KQ3b Which population would benefit most from non-lifestyle interventions, i.e., drug therapy and surgery? b. Younger vs. older	September 9, 2010 – February 1, 2013
KQ3c Which population would benefit most from non-lifestyle interventions, i.e., drug therapy and surgery? c. Returning from combat	March 1, 2005 – February 1, 2013
KQ3d Which population would benefit most from non-lifestyle interventions, i.e., drug therapy and surgery? d. With psychiatric co-morbidity	March 1, 2005 – February 1, 2013
KQ4a What is the impact of weight loss itself (independent of method) on major adverse cardiovascular events (e.g., acute myocardial infarction, ischemic stroke, and death)?	March 1, 2005 – February 1, 2013
KQ4b What is the impact of weight loss itself (independent of method) on cardiovascular risk factors (e.g., hypertension, type 2 diabetes, dyslipidemia)?	March 1, 2005 – February 1, 2013
KQ4c What is the impact of weight loss itself (independent of method) on degenerative joint disease?	March 1, 2005 – February 1, 2013
KQ4d What is the impact of weight loss itself (independent of method) on obstructive sleep apnea?	March 1, 2005 – February 1, 2013
KQ4e What is the impact of weight loss itself (independent of method) on overall health, function, and quality of life?	March 1, 2005 – February 1, 2013
KQ4f What is the impact of weight loss itself (independent of method) on non-alcoholic fatty liver disease?	March 1, 2005 – February 1, 2013
KQ5 What approaches are most effective for maintenance of weight loss (i.e., 6 months and beyond) post intervention, including post-surgery? a. Drugs b. Lifestyle (i.e., diet and exercise) c. Behavioral	September 9, 2010 – February 1, 2013

Table A-3: Key Question Formulation

15 Questions		21 Questions		13 Questions	6 Questions		5 Key Questions
Do any weight loss interventions decrease major adverse cardiovascular events (MACE) and overall mortality?	→	In adults with extreme obesity or BMI≥ 35 kg/m^2 with an obesity-associated condition, what is the long-term (i.e., 3 years, >3 years, 5 years, >5 years) effectiveness of gastric bypass compared to nonintervention with respect to the following cardiovascular outcomes and mortality? • Myocardial infarction • Cerebrovascular event • Peripheral artery disease	→	Eliminated significant overlap In adults with extreme obesity or BMI≥ 35 kg/m^2 with an obesity-associated condition, what is the short and long-term (i.e., 3 years, >3 years, 5 years, >5 years) comparative effectiveness of surgical interventions and associated harms with respect to the following outcomes? • Stroke • Cardiovascular mortality • Overall mortality • Weight loss • Weight maintenance	Shifted focus from surgical interventions to behavioral interventions What is the impact of treatment intensity of clinician-delivered obesity interventions on weight loss outcomes—high intensity vs. low or minimal intensity?	→	Expanded question to include varying levels of intervention. What is the impact of the quality (e.g., type) and quantity (e.g., intensity) of behavioral treatments (i.e., interventions that enhance adherence to diet or exercise) on weight loss outcomes?
	→	In adults with extreme obesity or BMI≥ 35 kg/m^2 with an obesity-associated condition, what is the long-term (i.e., 3 years, >3 years, 5 years, >5 years) effectiveness of gastric bypass compared to nonintervention with respect to the following cardiovascular outcomes and mortality? • Myocardial infarction • Cerebrovascular event • Peripheral artery disease					
	→	In adults with extreme obesity or BMI≥ 35 kg/m^2 with an obesity-associated condition, what is the comparative effectiveness of gastric banding vs. gastric bypass with respect to the following cardiovascular outcomes and mortality? • Myocardial infarction • Cerebrovascular event • Peripheral artery disease					

15 Questions		21 Questions		13 Questions	6 Questions		5 Key Questions
An update on drug therapy is warranted. A secondary question would be if any of short-term drug therapies can lead to sustained weight loss when given as a "jump-start."	→	In adults who are obese or overweight with an obesity-associated condition, what is the comparative effectiveness of pharmacotherapy (i.e., orlistat, lorcaserin, phentermine/topiramate combo) to placebo with respect to the following cardiovascular risk factors: • Hypertension • Type 2 diabetes mellitus • Dyslipidemia • Metabolic syndrome	→	In adults who are obese or overweight with an obesity-associated condition, what is the short and long-term (i.e., 3 years, >3 years, 5 years, >5 years) comparative effectiveness of pharmacotherapy with respect to the following cardiovascular risk factors? • Hypertension • Type 2 diabetes • Dyslipidemia • Metabolic syndrome • Osteoarthritis • Obstructive sleep apnea	What is the comparative effectiveness of medications for weight loss among obese individuals?	→	What is the relative comparative effectiveness of medications approved by the FDA for weight loss among overweight and obese individuals?

15 Questions		21 Questions		13 Questions	6 Questions		5 Key Questions
A review of diet, physical activity, behavioral therapy and drugs should be undertaken to update their effects on cardiovascular risk factors.	→	In adults who are obese or overweight with an obesity-associated condition, what is the comparative effectiveness of diet therapy to placebo with respect to the following cardiovascular risk factors? • Hypertension • Type 2 diabetes mellitus • Dyslipidemia • Metabolic syndrome	→	Excluded by Champions	Which populations would benefit most from obesity treatment? Surgery? a. Obese vs. overweight b. Younger vs. older c. Returning from combat With psychiatric disorders as co-morbid conditions	→	Which populations would benefit or benefit most from non-lifestyle interventions, particularly drug therapy and surgery? a. Obese vs. overweight b. Younger vs. older c. Returning from combat With psychiatric co-morbidity
	→	In adults who are obese or overweight with an obesity-associated condition, what is the comparative effectiveness of physical activity to placebo with respect to the following cardiovascular risk factors? • Hypertension • Type 2 diabetes mellitus • Dyslipidemia • Metabolic syndrome	→	Excluded by Champions			

15 Questions		21 Questions		13 Questions	6 Questions		5 Key Questions
	→	In adults who are obese or overweight with an obesity-associated condition, what is the comparative effectiveness of physical activity to placebo with respect to the following cardiovascular risk factors? • Hypertension • Type 2 diabetes mellitus • Dyslipidemia • Metabolic syndrome	→	Excluded by Champions			
	→	In adults who are obese or overweight with an obesity-associated condition, what is the comparative effectiveness of behavioral therapy to placebo with respect to the following cardiovascular risk factors? • Hypertension • Type 2 diabetes mellitus • Dyslipidemia • Metabolic syndrome	→	In adults who are obese or overweight with an obesity-associated condition, what is the short and long-term (i.e., 3 years, >3 years, 5 years, >5 years) comparative effectiveness of specific behavioral therapy methods with respect to the following cardiovascular risk factors? • Hypertension • Type 2 diabetes • Dyslipidemia • Metabolic syndrome • Osteoarthritis • Obstructive sleep apnea			

15 Questions		21 Questions		13 Questions	6 Questions		5 Key Questions
How much weight loss and from what baseline BMI is treatment effective in ameliorating the pathophysiology or effects of degenerative joint disease and obstructive sleep apnea?	→	In adults who are obese or overweight with an obesity-associated condition, what is the comparative effectiveness of diet therapy to placebo with respect to the following non-cardiovascular risk factors? • Obstructive sleep apnea • Osteoarthritis	→	Excluded by Champions	What is the comparative effectiveness of different diets for weight loss?	→	Excluded by Champions
	→	In adults who are obese or overweight with an obesity-associated condition, what is the comparative effectiveness of physical activity to placebo with respect to the following non-cardiovascular risk factors? • Obstructive sleep apnea • Osteoarthritis	→	Excluded by Champions			
	→	In adults who are obese or overweight with an obesity-associated condition, what is the comparative effectiveness of behavioral therapy to placebo with respect to the following non-cardiovascular risk factors? • Obstructive sleep apnea • Osteoarthritis	→	Excluded by Champions			
	→	In adults who are obese or overweight with an obesity-associated condition, what is the comparative effectiveness of pharmacotherapy to placebo with respect to the following non-cardiovascular risk factors? • Obstructive sleep apnea • Osteoarthritis	→	Excluded by Champions			

15 Questions		21 Questions		13 Questions	6 Questions		5 Key Questions
Are there any diets clearly superior for weight loss and/or modification of obesity-associated conditions?	→	In adults who are obese or overweight with an obesity-associated condition, what is the comparative effectiveness of various diet therapies with respect to the following obesity-associated conditions? • Hypertension • Type 2 diabetes mellitus • Dyslipidemia • Metabolic syndrome • Obstructive sleep apnea • Osteoarthritis	→	Excluded by Champions	What is the impact of weight loss itself on outcomes Morbidity and mortality including a) MACE b) Cardiovascular risk factors (with or without impact on MACE, etc.) c) Degenerative joint disease d) Obstructive sleep apnea	→	What is the impact of weight loss itself (irrespective of etiology of weight loss) on the following outcomes: a) Major adverse cardiovascular events (MACE) (e.g., acute myocardial infarction, ischemic stroke, and death) b) Cardiovascular disease (CVD) risk factors (e.g., hypertension, type 2 diabetes, dyslipidemia) c) Degenerative joint disease/ osteoarthritis d) Obstructive sleep apnea e) Overall health, function, and quality of life f) Non-alcoholic fatty liver disease
Can this guideline evaluate the effectiveness of school-based interventions?	→	In adults what is the comparative effectiveness of school-based interventions to non-school based interventions or nonintervention with respect to preventing obesity or weight gain?	→	In adults what is the comparative effectiveness of school-based interventions to non-school based interventions or nonintervention with respect to preventing obesity or weight gain?	What approaches are most effective for maintenance of weight loss? a) Drugs b) Lifestyle	→	What approaches are most effective for maintenance of weight loss (i.e., 6 months and beyond) post intervention, including post-surgery? a) Drugs b) Lifestyle c) Behavioral

15 Questions		21 Questions		13 Questions	6 Questions		5 Key Questions
In overweight and obese individuals, what is the relationship between treatment intensity (e.g., number of sessions, duration of intervention) of behavioral weight management and weight loss outcomes?	→	In overweight and obese individuals, is intensive behavioral weight management (i.e., 12-26 sessions) associated with improved outcomes, when compared to less intensive approaches?	→	In overweight and obese individuals, is intensive behavioral weight management (i.e., 12-26 sessions) associated with improvement in outcomes, when compared to less intensive approaches?			
In overweight and obese individuals, what is the effect of brief clinician advice and clinician-delivered motivational interventions on patient participation and retention in behavioral weight management interventions?	→	In overweight and obese individuals, what is the comparative effectiveness of brief clinician advice and clinician-delivered motivational interventions vs. nonintervention on patient participation and retention in behavioral weight management interventions?	→	In overweight and obese individuals, what is the comparative effectiveness of brief clinician advice and clinician-delivered motivational interventions vs. nonintervention on patient participation and retention in behavioral weight management interventions?			
In overweight and obese individuals who have experienced clinically significant weight loss from behavioral weight management, what intervention elements are associated with improved weight loss maintenance?							

15 Questions		21 Questions		13 Questions	6 Questions		5 Key Questions
In overweight and obese individuals who have experienced clinically significant weight loss from pharmacological interventions, what are the benefits versus risks for continuing medication use beyond 2 years?	→	In overweight and obese individuals who have experienced clinically significant weight loss from pharmacological interventions, what are the benefits vs. harms for continuing medication use beyond 2 years compared to discontinuation?	→	In overweight and obese individuals who have experienced clinically significant weight loss from pharmacological interventions, what are the benefits vs. harms for continuing medication use beyond 2 years compared to discontinuation?			
For Veterans aged 70 and over, do weight management interventions reduce the future risk of obesity-related conditions, and complications of these conditions?	→	For Veterans > 70 and over who are overweight with an obesity-associated condition or obese, do weight management interventions reduce future risk of obesity-related conditions, and complications of these conditions, when compared with nonintervention?	→	For Veterans > 70 and over who are overweight with an obesity-associated condition or obese, do weight management interventions reduce future risk of the following obesity-related conditions, and complications of these conditions, when compared with nonintervention? • Hypertension • Type 2 diabetes • Dyslipidemia • Metabolic syndrome • Osteoarthritis • Obstructive sleep apnea			

15 Questions		21 Questions		13 Questions	6 Questions		5 Key Questions
For Veterans, does bariatric surgery reduce the future risk of obesity-related conditions, and complications of these conditions, when compared with behavioral interventions and pharmacotherapy?	→	For Veterans with extreme obesity, does bariatric surgery reduce the future risk of obesity-related conditions, and complications of these conditions, when compared with behavioral interventions and pharmacotherapy?	→	For Veterans with extreme obesity, does bariatric surgery reduce the future risk of the following obesity-related conditions and complications of these conditions, when compared with nonsurgical interventions (i.e., behavioral, pharmacotherapy)? • Hypertension • Type 2 diabetes • Dyslipidemia • Metabolic syndrome • Osteoarthritis • Obstructive sleep apnea			
For Veterans and Service members who are overweight but not obese (i.e., BMI 25 - < 30 kg/m^2) do weight management interventions reduce the future risk of obesity-related conditions, and complications of these conditions?	→	For Veterans and Service members who are overweight but not obese (i.e., BMI 25- <30 kg/m^2), do weight management interventions reduce the future risk of obesity-related conditions, and complications of these conditions, when compared with nonintervention?	→	For Veterans and Service members who are overweight but not obese (i.e., BMI 25- <30 kg/m^2), do weight management interventions reduce the future risk of the following obesity-related conditions, and complications of these conditions, when compared with nonintervention? Hypertension • Type 2 diabetes • Dyslipidemia • Metabolic syndrome • Osteoarthritis • Obstructive sleep apnea			

15 Questions		21 Questions		13 Questions	6 Questions		5 Key Questions
For Veterans and Service members returning from recent conflicts, do weight management interventions influence weight loss outcomes?	→	For Veterans and Service members with obesity or BMI≥ 27 kg/m^2 with obesity-related condition who are returning from recent conflicts, do weight management interventions influence weight loss outcomes, when compared with nonintervention?	→	In adults with obesity or BMI≥ 27 kg/m^2 with an obesity-associated condition who are returning from recent conflicts, what is the short and long-term (i.e., 3 years, >3 years, 5 years, >5 years) comparative effectiveness of weight management interventions with respect to weight loss outcomes?			
For Veterans and Service members with co-morbid psychiatric disorders, do weight management interventions influence weight loss outcomes?	→	For Veterans and Service members with obesity or BMI≥ 27 kg/m^2 with obesity related condition and co-morbid psychiatric disorders (i.e., PTSD (post-traumatic stress disorder, TBI-related, depression, anxiety), do weight management interventions influence weight loss outcomes, when compared with no intervention?	→	For Veterans and Service members with obesity or BMI≥ 27 kg/m^2 with obesity related condition and co-morbid psychiatric disorders (i.e., PTSD, TDI-related, depression, anxiety), do weight management interventions influence weight loss outcomes, when compared with no intervention?			

15 Questions		21 Questions		13 Questions	6 Questions		5 Key Questions
			New question suggested by Champions	In adults who are obese or overweight with an obesity-associated condition, what is the short and long-term (i.e., 3 years, >3 years, 5 years, >5 years) comparative effectiveness of surgical interventions with respect to the following cardiovascular risk factors? • Hypertension • Type 2 diabetes • Dyslipidemia • Metabolic syndrome • Osteoarthritis Obstructive sleep apnea			

Conducting the Systematic Review

A number of the key questions were also addressed by the AHRQ systematic evidence review entitled, *Screening for and Management of Obesity and Overweight in Adults* which reviewed literature published through September 9, 2010. [31] For key questions that overlapped with the AHRQ review, the evidence review team focused on new relevant literature published after this date. For those that were not addressed by the AHRQ report, the literature was reviewed dating back to March 2005, prior to which evidence was reviewed by the 2006 CPG Work Group. The date parameters used for each key question are shown in **Table A-2**, above.

Additional inclusion and exclusion criteria were imposed on this systematic review and are described in **Table A-4**, below.

Detailed search strategies were developed for each key question and used to conduct searches in multiple biomedical bibliographic and other databases, including PubMed/Medline, EMBASE, PsycINFO, Database of Abstracts of Reviews of Effectiveness (DARE), Cochrane Central Register of Controlled Trials (CCTR), and the Cochrane Database of Systematic Reviews (COCH). Our search strategy was based on a combination of Medical Subject Headings (MeSH) terminology and text key words, and can be found in **Table A-5**.

The literature search identified over 4,800 titles and abstracts, which were screened and assessed by members of the evidence review team for relevance to the key questions. Over 4,400 abstracts were excluded during this first step, and the remaining 441 full text articles were reviewed. Of these, 369 studies were excluded for one of five reasons **(Box A-1)** and a final set of 72 studies were included in this systematic review. Additionally, since the completion of the evidence synthesis, the Champions reviewed several papers published in peer-reviewed journals. This included reviews, CPGs, editorials, and primary research articles. These were intended to be additive to the information already reviewed and were used to augment rather than create recommendations.

Box A-1: Reasons for Exclusion

- Study is not relevant
- Search date parameters do not apply
- Study is not a controlled trial, a systematic review, or a meta-analysis
- Intervention(s) studies are not of interest
- Study length is six months or less (if applicable)

The evidence review team assessed the quality of the individual studies for each key question, using the United States Preventive Services Task Force (USPSTF) methodology for grading the evidence. [157] The USPSTF has developed a rigorous standard for assessing the quality of the evidence, which is utilized by other guideline development groups, such as AHRQ. Lewin adhered to this methodology in order to help determine the validity, reliability, and generalizability of the evidence. These elements were factored into the development of clinical recommendations for this CPG.

It is important to note that the USPSTF updated its definition of grade C recommendations, effective July 2012. As such, the evidence grades presented in the 2006 evidence review may be different from the evidence grades presented in the 2013 review, based on the revised definitions. The CPG Work Group

for the 2014 CPG critically assessed and graded each recommendation using the updated, 2013 USPSTF approach.

Additionally, the Lewin evidence review team modified the USPSTF grading framework so as to provide for a grade of EO for "Expert Opinion." This change is a direct reflection of the need to develop a CPG that can be used in real practice for Veterans and Service members where evidence for or against a particular intervention is lacking. The analogous USPSTF grade of an I for "Insufficient evidence" may not provide enough guidance for supporting clinical decisions in real-world practice settings, especially for clinical questions that arise frequently in practice.

Convening the Face-to-Face Meeting

In consultation with the Contracting Officer Representative, the Champions, and the Work Group, the Lewin Team convened a two and a half day face-to-face meeting of the CPG Champions and Work Group members on April 15-17, 2013. These experts were gathered to develop and draft the clinical recommendations for an update to the 2006 CPG. Lewin presented findings from the evidence review of the key questions in order to facilitate and inform the process.

Under the direction of the Champions, the Work Group members were charged with interpreting the results of the evidence review, and asked to retain, revise, or reject each recommendation from the 2006 CPG. The members also developed new clinical practice recommendations, not presented in the 2006 CPG, based on the 2013 evidence review. The subject matter experts were divided into four smaller subgroups at this meeting.

Following the drafting of clinical practice recommendations, the Work Group assigned a grade for each recommendation based on a modified USPSTF methodology. Each recommendation was graded by assessing the quality of the overall evidence, or the certainty of the evidence to support the recommendation, and the magnitude of the net benefit of the intervention(s). Each recommendation received a grade of A (offer the service), B (offer the service), C (consider this service for some patients), D (discourage this service), I (if offered, understand that there is a level of uncertainty of evidence) or EO (consider offering this service based purely on expert opinion). The methodology used for grading the recommendations is further described in Appendix B.

Drafting and Submitting the Final CPG

Following the face-to-face meeting, the Champions and Work Group members were given writing assignments for the update of specific sections of the 2006 CPG that would form the narrative text for the 2014 CPG. During this time, the Champions also revised the 2006 algorithms and identified the content for the guideline summary and pocket card, as part of the provider toolkits that will be developed by the Evidence-Based Practice Working Group (EBPWG) following the publication of the 2014 CPG. The algorithms will be included as part of this CPG so as to provide a clear description of the flow of patient care. A final two-and-a-half day face-to-face meeting of the editorial team was held from November 20-22, 2013. The final 2014 CPG was submitted to the EBPWG on March 31, 2014.

Table A-4: Evidence Review Inclusion/Exclusion Criteria

	MAIN FOCUS	CRITERIA
KQ1. What is the impact of the quality (e.g., type) and quantity (e.g., intensity) of behavioral treatments (i.e., anything that enhances adherence to diet or exercise) on weight loss outcomes?		
	▪ Focus is on behavioral interventions that facilitate the adoption and maintenance of weight control behaviors such as altered dietary intake, eating behaviors, and exercise, NOT on the diet and exercise interventions themselves, which we are calling lifestyle interventions. ▪ Includes interventions delivered in primary care settings, the community, or that can be carried out by patients who are seen in primary care practices.	▪ Report weight loss outcomes. ▪ Behavioral intervention that helps patients adhere to a lifestyle intervention (which we define as diet or exercise). ▪ Different types of behavioral treatments – examples of types on page 89 of old guideline (e.g., behavioral counseling sessions, educational sessions, commercial programs such as Weight Watchers). ▪ Intensity – Could refer to who is administering (e.g., self-administered versus clinician-administered), frequency of intervention (e.g., one time versus several sessions), duration (e.g., brief intervention versus longer intervention), larger scale duration (e.g., one month vs several months).
KQ2. What is the relative effectiveness of medications approved by the FDA for weight loss among overweight and obese individuals?		

	▪ Focus is on effectiveness and safety of medications, so there should be comparisons of effectiveness and safety results made between medications.	▪ Report weight loss outcomes.
		▪ Must focus on one or more FDA-approved drugs specifically for obesity compared to each other or to another comparator:
		  ▪ Orlistat (Alli, Xenical)
		  ▪ Lorcaserin (Belviq)
		  ▪ phentermine and topiramate (Qysmia)
		▪ Other comparators can include:
		  ▪ Any FDA-approved drug(s) (e.g., metformin)
		  ▪ Placebo
		  ▪ Other types of intervention(s) (e.g., behavioral, lifestyle, surgery)

MAIN FOCUS		CRITERIA
KQ3. Which populations would benefit most from non-lifestyle interventions, i.e., drug therapy and surgery?		
a.	**Overweight vs. Obese**	

	▪ Focus is on comparison of benefits (and/or harms) from NON-lifestyle interventions for overweight versus obese study populations.
	▪ The most relevant studies will report results separately for the groups being compared (i.e., overweight vs. obese). HOWEVER, also want to include studies that focus the benefits (and/or harms) for only one group (e.g., only overweight), to allow for comparisons across these studies of interventions that are similar.
		▪ NON-lifestyle interventions – Interventions should be drug or surgery NOT diet or exercise.
		▪ For surgical interventions - At a minimum, must report baseline BMI or body weight or waist circumference.
		▪ If only BMI info is available, see if the study meets the BMIs for overweight and obesity
		  ▪ Overweight: BMI ≥ 25 and < 30
		  ▪ Obese: BMI ≥30

b.	**Younger vs. Older**	

	▪ Focus is on comparison of benefits (and/or harms) from NON-lifestyle interventions for younger versus older overweight or obese study populations.
	▪ The most relevant studies will report results separately for the groups being compared (i.e., younger vs. older). HOWEVER, also want to include studies that focus the benefits (and/or harms) for only one group (e.g., only older), to allow for comparisons across these studies of interventions that are similar.
		▪ NON-lifestyle interventions – Interventions should be drug or surgery NOT diet or exercise
		▪ For surgical interventions - At a minimum, must report baseline BMI or body weight or waist circumference.
		▪ If only BMI info is available, see if the study meets the BMIs for overweight and obesity
		  ▪ Overweight: BMI ≥ 25 and < 30
		  ▪ Obese: BMI ≥30

c.	**Returning from combat**	

	▪ Focus is on military returning from combat who are overweight or obese – May be difficult to from abstract if it is focused on this specific population, so be more inclusive for this question.
	▪ For KQ3c, be more inclusive. It may be difficult to tell if they have been to combat even at the full text level.
		▪ NON-lifestyle interventions – Interventions should be drug or surgery NOT diet or exercise
		▪ For surgical interventions - At a minimum, must report baseline BMI or body weight or waist circumference.
		▪ If only BMI info is available, see if the study meets the BMIs for overweight and obesity
		  ▪ Overweight: BMI ≥ 25 and < 30
		  ▪ Obese: BMI ≥30

	MAIN FOCUS	CRITERIA
d	**With psychiatric co-morbidity**	

	▪ Focus is on comparison of benefits (and/or harms) from NON-lifestyle interventions for overweight or obese study populations with a psychiatric/psychological co-morbidity (e.g., PTSD, bipolar disease, anxiety disorders).	▪ NON-lifestyle interventions – Interventions should be drug or surgery NOT diet or exercise
		▪ For surgical interventions - At a minimum, must report baseline BMI or body weight or waist circumference.
		▪ If only BMI info is available, see if the study meets the BMIs for overweight and obesity
		  ▪ Overweight: BMI ≥ 25 and < 30
		  ▪ Obese: BMI ≥30

KQ4. What is the impact of weight loss itself on the following outcomes:		
a.	**Major adverse cardiovascular events (MACE), e.g., acute myocardial infarction, ischemic stroke, and death**	
	▪ Focus is on impact of weight loss on these other outcomes irrespective of intervention used to lose weight.	▪ Includes measures of weight loss. Example **KQ4e**-relevant outcomes: Acute MI, ischemic stroke, death.
b.	**Cardiovascular risk factors (e.g., hypertension, type 2 diabetes, dyslipidemia)**	

	▪ Focus is on impact of weight loss on these other outcomes irrespective of intervention used to lose weight.	▪ Includes measures of weight loss.
		▪ Example **KQ4b** measures:
		  ▪ **Hypertension –** e.g., systolic blood pressure, diastolic blood pressure
		  ▪ **Type 2 diabetes –** e.g., fasting glucose, fasting insulin, fasting glucose to insulin ratio, fasting plasma glucose level/blood glucose level, oral glucose tolerance test, homeostatic model assessment (HOMA),quantitative insulin sensitivity check index, Hemoglobin A1c level (HbA1c).
		  ▪ **Dyslipidemia –** e.g., Total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), non-high density lipoprotein cholesterol (non-HDL-C), apolipoprotein A-1 (Apo A-1), apolipoprotein B (Apo B), apolipoprotein B/apolipoprotein A-1 (Apo B/Apo A-1).

c.	**Degenerative joint disease (DJD)**	
	▪ Focus is on impact of weight loss on these other outcomes irrespective of intervention used to lose weight.	▪ Includes measures of weight loss. ▪ Often also referred to as osteoarthritis (OA). ▪ Will most likely see studies involving hips and knees. ▪ Example **KQ4c** measures: Pain, function, self-reported disability, and patient global evaluation.
d.	**Obstructive sleep apnea (OSA)**	
	▪ Focus is on impact of weight loss on these other outcomes irrespective of intervention used to lose weight.	▪ Includes measures of weight loss. Example **KQ4d** measures: Polysomnograph,, apnea hypopnea index.

	MAIN FOCUS	CRITERIA
e.	**Overall health, function, and quality of life**	
	▪ Focus is on impact of weight loss on these other outcomes irrespective of intervention used to lose weight. ▪ Include studies of symptoms/conditions that are a result of overweight or obesity. ▪ Include studies using validated measures for quality of life, health status, health function.	▪ Includes measures of weight loss. Example **KQ4e**-relevant symptoms/conditions, and measures: ▪ **Symptoms/conditions:** GERD, urinary incontinence, joint pain, respiratory problems, DJD/OA. ▪ **Other measures:** SF-36, quality-adjusted life years (QALYs), health-related quality of life (HRQoL), quality of life (QoL), activities of daily living (ADLs), impact of weight on quality of life-Lite (INQoL-Lite).
f.	**Non-alcoholic fatty liver disease (NAFLD)**	
	▪ Focus is on impact of weight loss on these other outcomes irrespective of intervention used to lose weight. ▪ More serious form of nonalcoholic fatty liver disease is sometimes called nonalcoholic steatohepatitis (NASH).	▪ Includes measures of weight loss. Example **KQ4f**-relevant measures: Hepatic-related mortality or morbidity, histological response (e.g., improvement in degree of fatty liver infiltration, inflammation, and fibrosis), biochemical response.
KQ5. What approaches are most effective for maintenance of weight loss (i.e., 6 months and beyond) post intervention, including post-surgery?		
a.	**Drugs**	
	▪ Focuses on approaches for maintenance of weight loss following any intervention.	▪ Acute phase of intervention is ≤ 6 months; maintenance phase >6 months ▪ Approach must focus on one or more FDA-approved drugs specifically for obesity ▪ Orlistat (Alli, Xenical) ▪ Lorcaserin (Belviq) ▪ phentermine and topiramate (Qysmia)
b.	**Lifestyle Approach**	
	▪ Focuses on approaches for maintenance of weight loss following any intervention.	▪ Acute phase of intervention is ≤ 6 months; maintenance phase >6 months. ▪ Approach must focus on diet and/or exercise.
c.	**Behavioral Approach**	
	▪ Focuses on approaches for maintenance of weight loss following any intervention.	▪ Acute phase of intervention is ≤ 6 months; maintenance phase >6 months. ▪ Approach must have behavioral focus (see KQ1 criteria for examples).

Table A-5: Evidence Review Search Strategy

	PubMed/MEDLINE
Key Question 1: What is the impact of the quality (e.g., type) and quantity (e.g., intensity) of behavioral treatments (i.e., anything that enhances adherence to diet or exercise) on weight loss outcomes?	**<u>Search strategies for non-indexed studies</u>** **#1 Obesity terms:** obesity[tiab] OR obese[tiab] OR overweight[tiab] **#2 Intervention terms:** (physician*[tiab] OR clinician*[tiab] OR collaborative[tiab] OR intens*[tiab] OR brief[tiab]) AND (intervention*[tiab] OR treatment*[tiab] OR therapy[tiab] OR counseling[tiab]) **#3 SR and MA terms:** meta-analysis[tiab] OR systematic review[tiab] OR (review[tiab] AND (comprehensive*[tiab] OR methods*[tiab] OR methodology[tiab])) OR (review[tiab] AND veterans[tiab]) **#4 RCTs:** randomized controlled trial*[tiab] OR randomized control trial*[tiab] OR (clinical trial[tiab] AND (random allocation[tiab] OR random*[tiab] OR double-blind*[tiab] OR single-blind*[tiab])) **#5 Non-indexed items:** ((publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR in process[sb] OR pubmednotmedline[sb] OR oldmedline[sb] OR ((pubstatusnihms OR pubstatuspmcsd) AND publisher[sb])) **<u>Combined search strategy for non-indexed SR/MAs</u>** #1 AND #2 AND #3 AND #5 **<u>Combined search string for non-indexed RCTs</u>** #1 AND #2 AND #4 AND #5

	PubMed/MEDLINE
Key Question 2: What is the relative comparative effectiveness of medications approved by the FDA for weight loss among overweight and obese individuals?	**<u>Search strategies for indexed studies</u>** **#1 Obesity terms:** (Overweight[Majr] OR Obesity[Majr]) **#2 Intervention terms:** Anti-obesity agents[MeSH] OR Obesity/drug therapy[MeSH] OR Overweight/drug therapy[MeSH] OR pharmaceutical*[tiab] OR pharmacological*[tiab] OR medication*[tiab] OR drug[tiab] OR drugs[tiab] OR drug therap*[tiab] OR drug treatment*[tiab] OR orlistat[tiab] OR lorcaserin[tiab] OR phentermine[tiab] OR topiramate[tiab] OR Xenical[tiab] Alli[tiab] OR Belviq[tiab] OR Qsymia[tiab] OR sibutramine[tiab] OR metformin[tiab] OR mazindol[tiab] OR diethylpropion[tiab] OR fluoxetine[tiab] OR exenatide[tiab] OR liraglutide[tiab] OR pramlintide[tiab] OR bupropion OR naltrexone[tiab] OR Contrave[tiab] OR zonisamide[tiab] **#2A: Safety terms:** Drug Toxicity[MeSH] OR adverse effects[Subheading] OR safety[tiab] OR adverse[tiab] OR toxicity[tiab] **#3 SR and MA terms:** Meta-Analysis[PT] OR Systematic[sb] OR (Review[PT] AND (systematic*[tiab] OR comprehensive*[tiab] OR methods*[tiab] OR methodology[tiab])) OR (Review[PT] AND Veterans[MeSH]) OR meta-analysis[tiab] OR systematic review[tiab] OR (review[tiab] AND veterans[tiab]) **#4 RCTs:** Randomized Controlled Trial[PT] OR Randomized Controlled Trials[MeSH] OR randomized controlled trial*[tiab] OR randomized control trial*[tiab] OR (Clinical Trial[PT] AND (Random Allocation[MeSH] OR random*[tiab] OR Double-blind Method[MeSH] OR double blind*[tiab])) NOT (Editorial[PT] OR Letter[PT] OR Comment[PT] OR Case Reports[PT] OR Review[PT]) **#5 Search parameters:** (("2005/03/01"[PDAT] : "2013/01/30"[PDAT]) AND English[lang]) NOT ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms]) **<u>Combined search strategy:</u>** **Indexed SRs and MAs:** #1 AND #2 AND #3 AND #5 **Indexed RCTs:** #1 AND #2 AND #4 AND #5 **Indexed SRs and MAs – Safety Subset:** #1 AND #2 AND #2A AND #3 AND #5 **Indexed RCTs – Safety Subset:** #1 AND #2 AND #2A AND #4 AND #5

	PubMed/MEDLINE
	Search strategies for non-indexed studies **#1 Obesity terms:** obesity[tiab] OR overweight[tiab] **#2 Intervention terms:** Anti-obesity agent*[tiab] OR pharmaceutical*[tiab] OR pharmacological*[tiab] OR medication*[tiab] OR drug[tiab] OR drugs[tiab] OR drug therap*[tiab] OR drug treatment*[tiab] OR lorcaserin[tiab] OR phentermine[tiab] OR topiramate [tiab] OR Xenical[tiab] Alli[tiab] OR Belviq[tiab] OR Qsymia[tiab] OR sibutramine[tiab] OR metformin[tiab] OR mazindol[tiab] OR diethylpropion[tiab] OR fluoxetine[tiab] OR exenatide[tiab] OR liraglutide[tiab] OR pramlintide[tiab] OR bupropion OR naltrexone[tiab] OR Contrave[tiab] OR zonisamide[tiab] **#2A: Safety terms:** safety[tiab] OR adverse[tiab] OR toxicity[tiab] **#3 SR and MA terms:** meta-analysis[tiab] OR systematic review[tiab] OR (review[tiab] AND (comprehensive*[tiab] OR methods*[tiab] OR methodology[tiab])) OR (review[tiab] AND veterans[tiab]) **#4 RCTs:** randomized controlled trial*[tiab] OR randomized control trial*[tiab] OR (clinical trial[tiab] AND (random allocation[tiab] OR random*[tiab] OR double-blind*[tiab] OR single-blind*[tiab])) **#5 Non-indexed items:** ((publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR in process[sb] OR pubmednotmedline[sb] OR oldmedline[sb] OR ((pubstatusnihms OR pubstatuspmcsd) AND publisher[sb])) **Combined search strategy:** **Non-indexed MAs and SRs** #1 AND #2 AND #3 AND #5 **Non-indexed RCTs** #1 AND #2 AND #4 AND #5 **Non-indexed MAs and SRs – Safety subset** #1 AND #2 AND #2A AND #3 AND #5 **Non-indexed RCTs – Safety subset** #1 AND #2 AND #2A AND #4 AND #5

	PubMed/MEDLINE
Key Question 3: Which populations would benefit most from non-lifestyle interventions, i.e., drug therapy and surgery? a. Obese vs. overweight b. Younger vs. older c. Returning from combat d. With psychiatric co-morbidity	**<u>Search strategy for indexed studies</u>** **#1 Intervention terms:** (Anti-obesity agents[MeSH] OR Obesity/drug therapy[MeSH] OR Overweight/drug therapy[MeSH] OR pharmaceutical*[tiab] OR pharmacological*[tiab] OR medication*[tiab] OR drug[tiab] OR drugs[tiab] OR drug therap*[tiab] OR drug treatment*[tiab] OR orlistat[tiab] OR lorcaserin[tiab] OR phentermine[tiab] OR topiramate [tiab] OR Xenical[tiab] Alli[tiab] OR Belviq[tiab] OR Qsymia[tiab] OR sibutramine[tiab] OR metformin[tiab] OR mazindol[tiab] OR diethylpropion[tiab] OR fluoxetine[tiab]) OR (Bariatric Surgery[MeSH] OR Obesity/surgery[Mesh] OR Overweight/surgery[MeSH] OR gastric banding[tiab] OR sleeve gastrectomy[tiab]) **a. Obese vs. Overweight** **#2** (Overweight[MeSH:NoExp] AND Obesity[MeSH]) **b. Younger vs. older** **#3** ((Overweight[Majr] OR Obesity[Majr]) AND (Age Factors[MeSH] OR age group*[tiab])) **c. Returning from combat** **#4** ((Overweight[Majr] OR Obesity[Majr]) AND (Military Personnel[MeSH] OR Veterans[MeSH OR seamen[tiab] OR airmen[tiab] OR active duty[tiab] OR service members[tiab] OR reservist*[tiab])) **d. Psychiatric comorbidity** **#5** ((Overweight[Majr] OR Obesity[Majr]) AND Mental Disorders[MeSH]) **#6 SR and MA terms:** Meta-Analysis[PT] OR Systematic[sb] OR (Review[PT] AND (systematic*[tiab] OR comprehensive*[tiab] OR methods*[tiab] OR methodology[tiab])) OR (Review[PT] AND Veterans[MeSH]) OR meta-analysis[tiab] OR systematic review[tiab] OR (review[tiab] AND veterans[tiab]) **#7 RCTs:** Randomized Controlled Trial[PT] OR Randomized Controlled Trials[MeSH] OR randomized controlled trial*[tiab] OR randomized control trial*[tiab] OR (Clinical Trial[PT] AND (Random Allocation[MeSH] OR random*[tiab] OR Double-blind Method[MeSH] OR double blind*[tiab])) NOT (Editorial[PT] OR Letter[PT] OR Comment[PT] OR Case Reports[PT] OR Review[PT]) **#8 Search parameters:** (("2005/03/01"[PDAT] : "2013/01/30"[PDAT]) AND English[lang]) NOT ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms]) **<u>Combined search strategy</u>** **Indexed SR/MAs:** #1 AND #2 AND #6 AND #8 #1 AND #3 AND #6 AND #8 #1 AND #4 AND #6 AND #8 #1 AND #5 AND #6 AND #8 **Indexed RCTs:** #1 AND #2 AND #7 AND #8 #1 AND #3 AND #7 AND #8 #1 AND #4 AND #7 AND #8 #1 AND #5 AND #7 AND #8

	PubMed/MEDLINE
	<u>Search strategy for non-indexed studies</u> **#1 Intervention terms:** (Anti-obesity agent*[tiab] OR pharmaceutical*[tiab] OR pharmacological*[tiab] OR medication*[tiab] OR drug[tiab] OR drugs[tiab] OR drug therap*[tiab] OR drug treatment*[tiab] OR lorcaserin[tiab] OR phentermine[tiab] OR topiramate [tiab] OR Xenical[tiab] Alli[tiab] OR Belviq[tiab] OR Qsymia[tiab] OR sibutramine[tiab] OR metformin[tiab] OR mazindol[tiab] OR diethylpropion[tiab] OR fluoxetine[tiab]) OR (bariatric surg*[tiab] OR ((obesity[tiab] OR overweight[tiab]) AND surgery[tiab]) OR gastric banding[tiab] OR sleeve gastrectomy[tiab]) **a. Obese vs. Overweight** #2 (overweight[tiab] AND (obesity[tiab] OR obese[tiab])) **b. Younger vs. older** #3 ((overweight[tiab] OR obesity[tiab] OR obese[tiab]) AND age group*[tiab] OR age factor*[tiab] OR (younger[tiab] AND older[tiab])) **c. Returning from combat** #4 ((overweight[tiab] OR obesity[tiab] OR obese[tiab]) AND (military[tiab] OR army[tiab] OR armed forces[tiab] OR navy[tiab] OR sailor*[tiab] OR seamen[tiab] OR air force[tiab] OR airmen[tiab] OR marine*[tiab] OR coast guard[tiab] OR soldier*[tiab] OR active duty[tiab] OR service members[tiab] OR reservist*[tiab] OR veteran*[tiab])) **d. Psychiatric comorbidity** #5 (overweight[tiab] OR obesity[tiab] OR obese[tiab]) AND (mental disorder*[tiab] OR psych*[tiab]) **#6 SR and MA terms:** meta-analysis[tiab] OR systematic review[tiab] OR (review[tiab] AND (comprehensive*[tiab] OR methods*[tiab] OR methodology[tiab])) OR (review[tiab] AND veterans[tiab]) **#7 RCTs:** randomized controlled trial*[tiab] OR randomized control trial*[tiab] OR (clinical trial[tiab] AND (random allocation[tiab] OR random*[tiab] OR double-blind*[tiab] OR single-blind*[tiab])) **#8 Non-indexed items:** ((publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR in process[sb] OR pubmednotmedline[sb] OR oldmedline[sb] OR ((pubstatusnihms OR pubstatuspmcsd) AND publisher[sb])) **<u>Combined search strategy</u>** **Non-Indexed SR/MAs:** #1 AND #2 AND #6 AND #8 #1 AND #3 AND #6 AND #8 #1 AND #4 AND #6 AND #8 #1 AND #5 AND #6 AND #8 **Non-indexed RCTs:** #1 AND #2 AND #7 AND #8 #1 AND #3 AND #7 AND #8 #1 AND #4 AND #7 AND #8 #1 AND #5 AND #7 AND #8

	PubMed/MEDLINE
Key Question 4: What is the impact of weight loss itself on the following outcomes? a. Major adverse cardiovascular events (MACE), e.g., acute myocardial infarction, ischemic stroke, and death b. Cardiovascular risk factors (e.g., hypertension, type 2 diabetes, dyslipidemia) c. Degenerative joint disease d. Obstructive sleep apnea e. Overall health, function, and quality of life (QoL) f. Non-alcoholic fatty liver disease	**<u>Search strategy for indexed studies</u>** **#1 Obesity terms:** (Overweight[Majr] OR Obesity[Majr]) AND Weight Loss[MeSH] **#2 Intervention terms:** **(**(Cardiovascular Diseases[MeSH] OR Myocardial Infarction[MeSH] OR Stroke[MeSH] OR Hypertension[MeSH] OR Diabetes Mellitus, Type 2[MeSH] OR Dyslipidemias[MeSH] OR Hypercholesterolemia[MeSH] OR (cardiovascular*[tiab] AND (Risk Factors[MeSH] OR Risk Assessment[MeSH] OR risk*[tiab] OR adverse event*[tiab])) **OR** (Osteoarthritis[MeSH] OR degenerative joint disease[tiab]) OR (Sleep Apnea, Obstructive[MeSH] OR sleep apnea[tiab]) **OR** (Activities of Daily Living[MeSH] OR Quality of Life[MeSH] OR Quality-Adjusted Life Years[MeSH] OR Health[MeSH] OR Health Status[MeSH] OR Treatment Outcome[MeSH] OR QoL[tiab] OR health related quality of life[tiab] OR health-related quality of life[tiab] OR HRQL[tiab] OR SF-36[tiab]) **OR** ((Fatty Liver[MeSH] AND non-alcoholic[tiab]) OR Non-alcoholic Fatty Liver Disease[Supplementary Concept] OR non-alcoholic fatty liver[tiab] OR nonalcoholic fatty liver[tiab] OR NAFLD[tiab] OR non-alcoholic steatohepatitis[tiab] OR nonalcoholic steatohepatitis[tiab])**)** **#3 SRs and MAs:** Meta-Analysis[PT] OR Systematic[sb] OR (Review[PT] AND (systematic*[tiab] OR comprehensive*[tiab] OR methods*[tiab] OR methodology[tiab])) OR (Review[PT] AND Veterans[MeSH]) OR meta-analysis[tiab] OR systematic review[tiab] OR (review[tiab] AND veterans[tiab]) **#4 RCTs:** Randomized Controlled Trial[PT] OR Randomized Controlled Trials[MeSH] OR randomized controlled trial*[tiab] OR randomized control trial*[tiab] OR (Clinical Trial[PT] AND (Random Allocation[MeSH] OR random*[tiab] OR Double-blind Method[MeSH] OR double blind*[tiab])) NOT (Editorial[PT] OR Letter[PT] OR Comment[PT] OR Case Reports[PT] OR Review[PT]) **#5 Search parameters:** (("2005/03/01"[PDAT] : "2013/01/30"[PDAT]) AND English[lang]) NOT ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms]) **<u>Combined search strategy:</u>** **Indexed SR/MAs** #1 AND #2 AND #3 AND #5 **Indexed RCTs** #1 AND #2 AND #4 AND #5

	PubMed/MEDLINE
	<u>Search strategy for non-indexed studies</u> **#1 Obesity terms:** (obesity[tiab] OR overweight[tiab]) **AND** Weight loss[tiab] OR weight reduction[tiab] **#2 Intervention terms:** **(**(cardiovascular disease*[tiab] OR myocardial infarction*[tiab] OR heart attack*[tiab] OR stroke[tiab] OR hypertension[tiab] OR high blood pressure[tiab] OR diabetes[tiab] OR dyslipidemia*[tiab] OR hypercholesterolemia[tiab] OR cardiovascular risk*[tiab] OR risk factor*[tiab] OR (cardiovascular[tiab] AND (death[tiab] OR mortality[tiab])) OR (cardiovascular*[tiab] AND adverse event*[tiab])) **OR** (osteoarthritis[tiab] OR degenerative joint disease[tiab]) **OR** (sleep apnea[tiab]) **OR** (activities of daily living[tiab] OR quality of life[tiab] OR QoL[tiab] OR HRQL[tiab] OR Health[tiab] OR SF-36[tiab]) **OR** (non-alcoholic fatty liver[tiab] OR nonalcoholic fatty liver[tiab] OR NAFLD[tiab] OR non-alcoholic steatohepatitis[tiab] OR nonalcoholic steatohepatitis[tiab])**)** **#3 SRs and MAs;** meta-analysis[tiab] OR systematic review[tiab] OR (review[tiab] AND (comprehensive*[tiab] OR methods*[tiab] OR methodology[tiab])) OR (review[tiab] AND veterans[tiab]) **#4 RCTs:** randomized controlled trial*[tiab] OR randomized control trial*[tiab] OR (clinical trial[tiab] AND (random allocation[tiab] OR random*[tiab] OR double-blind*[tiab] OR single-blind*[tiab])) **#5 Search parameters:** ((publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR in process[sb] OR pubmednotmedline[sb] OR oldmedline[sb] OR ((pubstatusnihms OR pubstatuspmcsd) AND publisher[sb])) **<u>Combined search strategy</u>** **Non-indexed SR/MAs** #1 AND #2 AND #3 AND #5 **Non-indexed RCTs** #1 AND #2 AND #4 AND #5

	PubMed/MEDLINE
Key Question #5: What approaches are most effective for maintenance of weight loss (i.e., 6 months and beyond) post intervention, including post-surgery? a. Drugs b. Lifestyle ***c.*** Behavioral	**<u>Search strategies for indexed studies</u>** **#1 Obesity terms:** (Overweight[Majr] OR Obesity[Majr]) AND Weight Loss[MeSH] **#2 Maintenance terms:** maintenance[tiab] OR maintain*[tiab] OR management[tiab] OR effectiveness[tiab] OR sustained[tiab] OR duration[tiab] OR long-term[tiab] OR follow-up[tiab] **#3 SRs and MAs:** Meta-Analysis[PT] OR Systematic[sb] OR (Review[PT] AND (systematic*[tiab] OR comprehensive*[tiab] OR methods*[tiab] OR methodology[tiab])) OR (Review[PT] AND Veterans[MeSH]) OR meta-analysis[tiab] OR systematic review[tiab] OR (review[tiab] AND veterans[tiab]) **#4 RCTs:** Randomized Controlled Trial[PT] OR Randomized Controlled Trials[MeSH] OR randomized controlled trial*[tiab] OR randomized control trial*[tiab] OR (Clinical Trial[PT] AND (Random Allocation[MeSH] OR random*[tiab] OR Double-blind Method[MeSH] OR double blind*[tiab])) NOT (Editorial[PT] OR Letter[PT] OR Comment[PT] OR Case Reports[PT] OR Review[PT]) **#5 Search parameters:** (("2005/03/01"[PDAT] : "2013/01/30"[PDAT]) AND English[lang]) NOT ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms]) **<u>Combined search strategy</u>** **Indexed SR/MAs:** #1 AND #2 AND #3 AND #5 **Indexed RCTs:** #1 AND #2 AND #4 AND #5

	PubMed/MEDLINE
	Search strategies for indexed studies **#1 Obesity terms:** (obesity[tiab] OR overweight[tiab]) AND (weight loss[tiab] OR weight reduction[tiab]) **#2 Maintenance terms:** maintenance[tiab] OR maintain*[tiab] OR management[tiab] OR effectiveness[tiab] OR sustained[tiab] OR duration[tiab] OR long-term[tiab] OR follow-up[tiab] **#3 SRs and MAs:** meta-analysis[tiab] OR systematic review[tiab] OR (review[tiab] AND (comprehensive*[tiab] OR methods*[tiab] OR methodology[tiab])) OR (review[tiab] AND veterans[tiab]) **#4 RCTs:** randomized controlled trial*[tiab] OR randomized control trial*[tiab] OR (clinical trial[tiab] AND (random allocation[tiab] OR random*[tiab] OR double-blind*[tiab] OR single-blind*[tiab])) **#5 Search parameters:** ((publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR in process[sb] OR pubmednotmedline[sb] OR oldmedline[sb] OR ((pubstatusnihms OR pubstatuspmcsd) AND publisher[sb])) **Combined search strategy** **Non-indexed SR/MAs:** #1 AND #2 AND #3 AND #5 **Non-indexed RCTs:** #1 AND #2 AND #4 AND #5

	PubMed/MEDLINE		
EMBASE			
Key Question 1: What is the impact of the quality (e.g., type) and quantity (e.g., intensity) of behavioral treatments (i.e., anything that enhances adherence to diet or exercise) on weight loss outcomes?	**Set**	**Items**	**Description**
	S1	90447	S OBESITY/MAJ
	S2	89653	S (PRIMARY()MEDICAL()CARE OR GENERAL()PRACTICE)/DE
	S3	2776454	S OBESITY(L)THERAPY OR THERAPY/MAJ OR (PATIENT()EDUCATION OR HEALTH()EDUCATION OR COUNSELING OR RISK()REDUCTION OR BEHAVIOR()THERAPY OR HEALTH()PROMOTION)/DE
	S4	409	S S1 AND S2 AND S3
	S7	276	S S4/ENG,HUMAN AND PD>20050228
	S8	276	S S7 AND DT=JOURNAL
	S9	246	S S8 NOT DT=(LETTER OR EDITORIAL)
	S10	222	S S9 NOT FS=MEDLINE
	S11	6	S S10 AND (META()ANALYSIS OR SYSTEMATIC()REVIEW)/DE
	S12	36	S S10 AND (RANDOMIZED()CONTROLLED()TRIAL OR CONTROLLED()CLINICAL()TRIAL)/DE
Key Question 2: What is the comparative effectiveness of medications approved by the FDA for weight loss among overweight and obese individuals?	**RCTs**		
	Set	**Items**	**Description**
	S1	10250	S OBESITY(L)DRUG()THERAPY/DE
	S2	6611	S S1/MAJ
	S3	75968	S (ORLISTAT OR LORCASERINE OR PHENTERMINE OR TOPIRAMATE OR XENECAL OR ALLI OR BELVIQ OR QSYMIA OR SIBUTRAMINE OR METFORMIN OR MAZINDOL OR DIETHYLPROPION OR FLUOXETINE)/TI,AB,DE
	S11	909025	S (RANDOMIZED()CONTROLLED()TRIAL OR CONTROLLED()CLINICAL()TRIAL OR COHORT ANALYSIS OR COMPARATIVE STUDY)/DE OR CASE()CONTROL?()STUD?/TI,AB
	S15	2994	S S2 AND S3

	PubMed/MEDLINE		
	S16	544	S S15 AND S11
	S17	325	S S16 AND PD>20050228
	S18	303	S S17/ENG,HUMAN
	S19	266	S S18 NOT FS=MEDLINE
	S20	234	S S19 NOT (INFANT OR CHILD OR ADOLESCENT)/DE
	SR/MAs		
	Set	**Items**	**Description**
	S1	10250	S OBESITY(L)DRUG()THERAPY/DE
	S2	6611	S S1/MAJ
	S4	350	S S2 AND (META()ANALYS? OR METAANALYS? OR SYSTEMATIC()REVIEW? OR REVIEW?(3N)(RESEARCH OR LITERATURE))/TI,AB,DE
	S5	250	S S4 AND (OUTCOME? OR EFFECTIVE? OR WEIGHT()LOSS)/TI,AB,DE
	S6	171	S S5 AND PD>20050228
	S7	165	S S6/ENG,HUMAN
	S8	152	S S7 NOT FS=MEDLINE

	PubMed/MEDLINE		
Key Question 3: Which populations would benefit most from non-lifestyle interventions, i.e., drug therapy and surgery? a. Obese vs. overweight b. Younger vs. older c. Returning from combat d. With psychiatric co-morbidity	**3a**		
	Set	**Items**	**Description**
	S1	24527	S (OBESITY(L)DT OR OBESITY(L)SURGERY OR ANTIOBESITY()AGENTS OR BARIATRIC()SURGERY)/DE
	S2	3706	S OBESITY/DE AND (LORCASERINE OR PHENTERMINE OR TOPIRAMATE OR XENECAL OR ALLI OR BELVIQ OR QSYMIA OR SIBUTRAMINE OR METFORMIN OR MAZINDOL OR DIETHYLPROPION oR FLUOXETINE OR ORLISTAT)/TI,AB
	S3	26406	S S1 OR S2
	S4	17644	S S3/ENG AND PD>20050228 AND DT=JOURNAL
	S5	16269	S S4 NOT DT=(LETTER OR EDITORIAL)
	S6	14722	S S5 NOT FS=MEDLINE
	S7	1153	S S6 AND OBESITY/DE AND OVERWEIGHT/TI,AB
	S8	106201	S (META()ANALYSIS OR SYSTEMATIC()REVIEW)/DE
	S9	351289	S (CONTROLLED()CLINICAL()TRIAL OR RANDOMIZED()CONTROLLED()TRIAL)/DE
	S10	64	S S7 AND S8
	S11	261	S S7 AND S9
	S12	239	S S11 NOT S10
	S13	179	S S12 AND OBESITY/MAJ
	3b		

	PubMed/MEDLINE		
	Set	**Items**	**Description**
	S1	24527	S (OBESITY(L)DT OR OBESITY(L)SURGERY OR ANTIOBESITY()AGENTS OR BARIATRIC()SURGERY)/DE
	S2	3706	S OBESITY/DE AND (LORCASERINE OR PHENTERMINE OR TOPIRAMATE OR XENECAL OR ALLI OR BELVIQ OR QSYMIA OR SIBUTRAMINE OR METFORMIN OR MAZINDOL OR IETHYLPROPION OR FLUOXETINE OR ORLISTAT)/TI,AB
	S3	26406	S S1 OR S2
	S4	17644	S S3/ENG AND PD>20050228 AND DT=JOURNAL
	S5	16269	S S4 NOT DT=(LETTER OR EDITORIAL)
	S6	14722	S S5 NOT FS=MEDLINE
	S14	243	S S6 AND (AGE(3N)(GROUP? OR FACTOR?))/TI,AB
	S15	6	S S14 AND S8
	S16	**27**	S S14 AND S9
	S17	**27**	S S16 NOT S15
	3c		
	Set	**Items**	**Description**
	S1	24527	S (OBESITY(L)DT OR OBESITY(L)SURGERY OR ANTIOBESITY()AGENTS OR BARIATRIC()SURGERY)/DE
	S2	3706	S OBESITY/DE AND (LORCASERINE OR PHENTERMINE OR TOPIRAMATE OR XENECAL OR ALLI OR BELVIQ OR QSYMIA OR SIBUTRAMINE OR METFORMIN OR MAZINDOL OR DIETHYLPROPION OR FLUOXETINE OR ORLISTAT)/TI,AB

	PubMed/MEDLINE		
	S3	26406	S S1 OR S2
	S4	17644	S S3/ENG AND PD>20050228 AND DT=JOURNAL
	S5	16269	S S4 NOT DT=(LETTER OR EDITORIAL)
	S6	14722	S S5 NOT FS=MEDLINE
	S8	106201	S (META()ANALYSIS OR SYSTEMATIC()REVIEW)/DE
	S9	351289	S (CONTROLLED()CLINICAL()TRIAL OR RANDOMIZED()CONTROLLED()TRIAL)/DE
	S18	1	S S6 AND (MILITARY()PERSONNEL OR VETERANS)/DE
	S19	**0**	S S17 AND S8
	S20	**0**	S S18 AND S9
	3d		
	Set	**Items**	Description
	S1	24527	S (OBESITY(L)DT OR OBESITY(L)SURGERY OR ANTIOBESITY()AGENTS OR BARIATRIC()SURGERY)/DE
	S2	3706	S OBESITY/DE AND (LORCASERINE OR PHENTERMINE OR TOPIRAMATE OR XENECAL OR ALLI OR BELVIQ OR QSYMIA OR SIBUTRAMINE OR METFORMIN OR MAZINDOL OR DIETHYLPROPION OR FLUOXETINE OR ORLISTAT)/TI,AB
	S3	26406	S S1 OR S2
	S4	17644	S S3/ENG AND PD>20050228 AND DT=JOURNAL

	PubMed/MEDLINE		
	S5	16269	S S4 NOT DT=(LETTER OR EDITORIAL)
	S6	14722	S S5 NOT FS=MEDLINE
	S8	106201	S (META()ANALYSIS OR SYSTEMATIC()REVIEW)/DE
	S9	351289	S (CONTROLLED()CLINICAL()TRIAL OR RANDOMIZED()CONTROLLED()TRIAL)/DE
	S21	445	S S6 AND (MENTAL()DISEASE)/DE
	S22	32	S S21 AND S8
	S23	46	S S21 AND S9
	S24	39	S S23 NOT S22

	PubMed/MEDLINE		
	Set	**Items**	**Description**
Key Question 4: What is the impact of weight loss itself on the following outcomes? a. Major adverse cardiovascular events (MACE), e.g., acute myocardial infarction, ischemic stroke, and death b. Cardiovascular risk factors (e.g., hypertension, type 2 diabetes, dyslipidemia) c. Degenerative joint disease d. Obstructive sleep apnea e. Overall health, function, and quality of life (QoL) f. Non-alcoholic fatty liver disease	**S1**	16738	S OBESITY/MAJ AND WEIGHT()REDUCTION/DE
	S2	10854	S S1/ENG AND PD>20050228 AND DT=JOURNAL
	S3	10169	S S2 NOT DT=(LETTER OR EDITORIAL)
	S4	8847	S S3 NOT FS=MEDLINE
	S5	32256	S (CARDIOVASCULAR()DISEASE AND RISK()FACTOR)/DE
	S6	514494	S (HYPERTENSION OR NON()INSULIN()DEPENDENT()DIABETES()MELLITUS OR DYSLIPIDEMIA OR HYPERCHOLESTEROLEMIA OR OSTEOARTHRITIS)/DE
	S7	526096	S (ACUTE()HEART()INFARCTION OR CEREBROVASCULAR()ACCIDENT OR MORTALITY)/DE
	S8	685846	S (HEALTH()STATUS OR QUALITY()OF()LIFE OR DAILY()LIFE()ACTIVITY OR TREATMENT()OUTCOME)/DE
	S9	37917	S (NONALCOHOLIC()FATTY()LIVER OR SLEEP()APNEA()SYNDROME)/DE
	S10	3361	S S4 AND (S5 OR S6 OR S7 OR S8 OR S9)
	S11	106201	S (META()ANALYSIS OR SYSTEMATIC()REVIEW)/DE
	S12	351289	S (CONTROLLED()CLINICAL()TRIAL OR RANDOMIZED()CONTROLLED()TRIAL)/DE
	S13	169	S S10 AND S11
	S14	423	S S10 AND S12
	S15	30	S S13 AND WEIGHT()REDUCTION/MAJ

	PubMed/MEDLINE		
	S16	108	S S14 AND WEIGHT()REDUCTION/MAJ
	S17	97	S S16 NOT S15
Key Question 5: What approaches are most effective for maintenance of weight loss (i.e., 6 months and beyond) post intervention, including post-surgery? a) Drugs b) Lifestyle c) Behavioral	**Set**	**Items**	**Description**
	S1	16738	S OBESITY/MAJ AND WEIGHT()REDUCTION/DE
	S2	10854	S S1/ENG AND PD>20050228 AND DT=JOURNAL
	S3	10169	S S2 NOT DT=(LETTER OR EDITORIAL)
	S4	8847	S S3 NOT FS=MEDLINE
	S5	106201	S (META()ANALYSIS OR SYSTEMATIC()REVIEW)/DE
	S6	351289	S (CONTROLLED()CLINICAL()TRIAL OR RANDOMIZED()CONTROLLED()TRIAL)/DE
	S7	1760	S S4 AND (MAINTENANCE OR MAINTAIN? OR MANAGEMENT OR EFFECTIVENESS OR SUSTAINED OR DURATION OR LONG-TERM OR FOLLOW()UP)(5N)(WEIGHT)/TI,AB
	S8	91	S S7 AND S5
	S9	283	S S7 AND S6
	S10	1080	S S4 AND (MAINTENANCE OR MAINTAIN? OR SUSTAINED OR DURATION OR LONG-TERM OR FOLLOW()UP)(3N)(WEIGHT)/TI,AB
	S11	47	S S10 AND S5
	S12	168	S S10 AND S6
	S13	157	S S12 NOT S11

	PubMed/MEDLINE		
PsycINFO			
	Set	**Items**	**Description**
	S1	13560	S OBESITY/DE (1973) FROM 11
	S2	1040999	S (HEALTH()CARE OR THERAPY OR THERAPIES OR INTERVENTION? OR EDUCATION OR TREATMENT? OR COUNSELING OR HEALTH()PROMOTION OR PATIENT()CARE)/TI,AB,DE
	S3	166386	S (PHYSICIAN? OR CLINICIAN? OR DOCTOR? OR PRACTITIONER?)/TI,AB,DE
	S4	83619	S S2(S)S3
Key Question 1: What is the impact of the quality (e.g., type) and quantity (e.g., intensity) of behavioral treatments (i.e., anything that enhances adherence to diet or exercise) on weight loss outcomes?	S5	537	S S4 AND S1
	S6	2377910	S PT=PEER REVIEWED JOURNAL
	S7	404	S S5 AND S6
	S8	325720	S (META ANALYS? OR METAANALYS? OR REVIEW OR REVIEWS)/TI,AB,DE
	S9	89	S S7 AND S8
	S10	71129	S (PROSPECTIVE()STUD? OR CLINICAL()TRIAL? OR EMPIRICAL()STUD? OR CONTROLLED()TRIAL? OR RETROSPECTIVE()STUD? OR COMPARATIVE()STUD?)/TI,AB,DE
	S11	33	S S7 AND S10
	S12	27	S S11 NOT S9
	S13	22	S S12 AND PD>20050228 Set for study types
	S14	71	S S9 AND PD>20050228 Set for reviews/meta analysis)

	PubMed/MEDLINE		
Key Question 2: What is the comparative effectiveness of medications approved by the FDA for weight loss among overweight and obese individuals?	**RCTs**		
	Set	**Items**	**Description**
	S1	14235	S (OBESITY OR OVERWEIGHT)/DE
	S2	12245	S S1/MAJ
	S3	7519	S S2 AND PD>20050228
	S4	7344	S S3/ENG
	S5	298633	S (DRUG()THERAPY OR MEDICATION? OR PHARMACEUTICAL? OR DRUG OR DRUGS OR ANTI()OBESITY()AGENT?)/TI,AB,DE,ID
	S6	6759	S (LORCASERINE OR PHENTERMINE OR TOPIRAMATE OR XENECAL OR ALLI OR BELVIQ OR QSYMIA OR SIBUTRAMINE OR METFORMIN OR MAZINDOL OR DIETHYLPROPION OR FLUOXETINE OR ORLISTAT)/TI,AB
	S7	553	S S4 AND (S5 OR S6)
	S8	103333	S (META()ANALYS? OR METAANALYS? OR SYSTEMATIC()REVIEW? OR REVIEW?(3N)(RESEARCH OR LITERATURE))/TI,AB,DE
	S9	23	S S8 AND S7
	S10	48981	S (CLINICAL()TRIAL? OR CONTROLLED()TRIAL? OR COMPARATIVE()STUD? OR OBSERVATIONAL()STUD?)/TI,AB,DE
	S11	65	S S10 AND S7
	S12	21	S S9 AND PT=PEER REVIEWED JOURNAL [Set for reviews]
	S13	62	S S11 AND PT=PEER REVIEWED JOURNAL
	S14	54	S S13 NOT S12

	PubMed/MEDLINE		
Key Question 3: Which populations would benefit most from non-lifestyle interventions, i.e., drug therapy and surgery? a) Obese vs. overweight b) Younger vs. older c) Returning from combat d) With psychiatric co-morbidity	**3a**		
	Set	**Items**	**Description**
	S1	14254	S (OBESITY OR OVERWEIGHT)/DE
	S2	7683	S S1 AND PD>20050228 AND PT= PEER REVIEWED JOURNAL
	S3	7484	S S2/ENG
	S4	459	S S3 AND (DRUG()THERAPY OR SURGERY)/DE
	S5	130	S S3 AND (LORCASERINE OR PHENTERMINE OR TOPIRAMATE OR XENECAL OR ALLI OR BELVIQ OR QSYMIA OR SIBUTRAMINE OR METFORMIN OR MAZINDOL OR DIETHYLPROPION OR FLUOXETINE OR ORLISTAT OR GASTRIC()BANDING OR SLEEVE()GASTRECTOMY)/TI,AB
	S6	504	S S4 OR S5
	S7	96	S S6 AND OBESITY/DE AND OVERWEIGHT/TI,AB,DE
	S8	103470	S (META()ANALYS? OR METAANALYS? OR SYSTEMATIC()REVIEW? OR REVIEW?(3N)(RESEARCH OR LITERATURE))/TI,AB,DE
	S9	49061	S (CLINICAL()TRIAL? OR CONTROLLED()TRIAL? OR COMPARATIVE()STUD? OR OBSERVATIONAL()STUD?)/TI,AB,DE
	S10	3	S S7 AND S8
	S11	20	S S7 AND S9
	S12	18	S S11 NOT S10
	3b		
	Set	**Items**	**Description**
	S1	14254	S (OBESITY OR OVERWEIGHT)/DE
	S2	7683	S S1 AND PD>20050228 AND PT= PEER REVIEWED JOURNAL
	S3	7484	S S2/ENG

	PubMed/MEDLINE		
	S4	459	S S3 AND (DRUG()THERAPY OR SURGERY)/DE
	S5	130	S S3 AND (LORCASERINE OR PHENTERMINE OR TOPIRAMATE OR XENECAL OR ALLI OR BELVIQ OR QSYMIA OR SIBUTRAMINE OR METFORMIN OR MAZINDOL OR DIETHYLPROPION OR FLUOXETINE OR ORLISTAT OR GASTRIC()BANDING OR SLEEVE()GASTRECTOMY)/TI,AB
	S6	504	S S4 OR S5
	S8	103470	S (META()ANALYS? OR METAANALYS? OR SYSTEMATIC()REVIEW? OR REVIEW?(3N)(RESEARCH OR LITERATURE))/TI,AB,DE
	S9	49061	S (CLINICAL()TRIAL? OR CONTROLLED()TRIAL? OR COMPARATIVE()STUD? OR OBSERVATIONAL()STUD?)/TI,AB,DE
	S13	**5**	S S6 AND (AGE(3N)(GROUP? OR FACTOR?))/TI,AB,DE
	S14	**0**	S S13 AND S8
	S15	**1**	S S13 AND S9
	3c		
	Set	**Items**	**Description**
	S1	14254	S (OBESITY OR OVERWEIGHT)/DE
	S2	7683	S S1 AND PD>20050228 AND PT= PEER REVIEWED JOURNAL
	S3	7484	S S2/ENG
	S4	459	S S3 AND (DRUG()THERAPY OR SURGERY)/DE
	S5	130	S S3 AND (LORCASERINE OR PHENTERMINE OR TOPIRAMATE OR XENECAL OR ALLI OR BELVIQ OR QSYMIA OR SIBUTRAMINE OR METFORMIN OR MAZINDOL OR DIETHYLPROPION OR FLUOXETINE OR ORLISTAT OR GASTRIC()BANDING OR SLEEVE()GASTRECTOMY)/TI,AB
	S6	504	S S4 OR S5
	S8	103470	S (META()ANALYS? OR METAANALYS? OR SYSTEMATIC()REVIEW? OR REVIEW?(3N)(RESEARCH OR LITERATURE))/TI,AB,DE
	S9	49061	S (CLINICAL()TRIAL? OR CONTROLLED()TRIAL? OR COMPARATIVE()STUD? OR OBSERVATIONAL()STUD?)/TI,AB,DE
	S13	5	S S6 AND (AGE(3N)(GROUP? OR FACTOR?))/TI,AB,DE
	S14	0	S S13 AND S8
	S15	1	S S13 AND S9
	S16	0	S S6 AND (MILITARY()PERSONNEL OR VETERANS)/DE

	PubMed/MEDLINE		
	3d		
	Set	**Items**	**Description**
	S1	14254	S (OBESITY OR OVERWEIGHT)/DE
	S2	7683	S S1 AND PD>20050228 AND PT= PEER REVIEWED JOURNAL
	S3	7484	S S2/ENG
	S4	459	S S3 AND (DRUG()THERAPY OR SURGERY)/DE
	S5	130	S S3 AND (LORCASERINE OR PHENTERMINE OR TOPIRAMATE OR XENECAL OR ALLI OR BELVIQ OR QSYMIA OR SIBUTRAMINE OR METFORMIN OR MAZINDOL OR DIETHYLPROPION OR FLUOXETINE OR ORLISTAT OR GASTRIC()BANDING OR SLEEVE()GASTRECTOMY)/TI,AB
	S6	504	S S4 OR S5
	S8	103470	S (META()ANALYS? OR METAANALYS? OR SYSTEMATIC()REVIEW? OR REVIEW?(3N)(RESEARCH OR LITERATURE))/TI,AB,DE
	S9	49061	S (CLINICAL()TRIAL? OR CONTROLLED()TRIAL? OR COMPARATIVE()STUD? OR OBSERVATIONAL()STUD?)/TI,AB,DE
	S17	18	S S6 AND (PSYCHIATRIC()DISORDERS OR MENTAL()ILLNESS OR MENTAL()DISORDERS)/DE
	S18	0	S S17 AND S8
	S19	0	S S17 AND S9

	PubMed/MEDLINE		
Key Question 4: What is the impact of weight loss itself on the following outcomes? a) Major adverse cardiovascular events (MACE), e.g., acute myocardial infarction, ischemic stroke, and death b) Cardiovascular risk factors (e.g., hypertension, type 2 diabetes, dyslipidemia) c) Degenerative joint disease d) Obstructive sleep apnea e) Overall health, function, and quality of life (QoL) f) Non-alcoholic fatty liver disease	**Set**	**Items**	**Description**
	S1	14254	S (OBESITY OR OVERWEIGHT)/DE
	S2	3017	S S1 AND WEIGHT(3N)(LOSS OR REDUC?)/TI,AB
	S3	1383	S S2 AND PT=PEER REVIEWED JOURNAL AND PD>20050228
	S4	1343	S S3/ENG
	S5	31	S S4 AND (MYOCARDIAL INFARCTIONS OR STROKE OR HYPERTENSION OR DIABETES MELLITUS OR HYPERCHOLESTEROLEMIA)/DE
	S6	13	S S4 AND (CARDIOVASCULAR DISORDERS AND (RISK()FACTORS OR MORTALITY))/DE
	S7	122	S S4 AND (QUALITY OF LIFE OR SLEEP APNEA OR LIVER DISORDERS OR HEALTH STATUS OR TREATMENT OUTCOMES)/DE
	S8	159	S S5 OR S6 OR S7
	S9	11	S S8 AND (META()ANALYS? OR METAANALYS? OR SYSTEMATIC()REVIEW? OR REVIEW?(3N)(RESEARCH OR LITERATURE))/TI,AB,DE
	S10	32	S S8 AND (CLINICAL()TRIAL? OR CONTROLLED()TRIAL? OR COMPARATIVE()STUD? OR OBSERVATIONAL()STUD?)/TI,AB,DE
	S11	0	S S10 NOT S8

	PubMed/MEDLINE		
Key Question 5: What approaches are most effective for maintenance of weight loss (i.e., 6 months and beyond) post intervention, including post-surgery? a) Drugs b) Lifestyle c) Behavioral	**Set**	**Items**	**Description**
	S1	14254	S (OBESITY OR OVERWEIGHT)/DE
	S2	3017	S S1 AND WEIGHT(3N)(LOSS OR REDUC?)/TI,AB
	S3	1383	S S2 AND PT=PEER REVIEWED JOURNAL AND PD>20050228
	S4	1343	S S3/ENG
	S12	758	S S4 AND (MAINTENANCE OR MAINTAIN? OR MANAGEMENT OR EFFECTIVE? OR SUSTAIN? OR DURATION OR LONG()TERM OR FOLLOW()UP)/TI,AB
	S13	41	S S12 AND (META()ANALYS? OR METAANALYS? OR SYSTEMATIC()REVIEW? OR REVIEW?(3N)(RESEARCH OR LITERATURE))/TI,AB,DE
	S14	150	S S12 AND (CLINICAL()TRIAL? OR CONTROLLED()TRIAL? OR COMPARATIVE()STUD? OR OBSERVATIONAL()STUD?)/TI,AB,DE
	S15	107	S S14 AND OBESITY/MAJ
	S16	97	S S15 AND (CLINICAL()TRIAL? OR CONTROLLED()TRIAL?)/TI,AB
	S17	85	S S16 NOT S13

Appendix B: Grading the Recommendations

The graded recommendations in this Clinical Practice Guideline (CPG) are based on two main dimensions: 1) **net benefit** of an intervention and 2) **certainty** of evidence associated with that net benefit.

Net benefit (or impact) refers to benefit minus harm of an intervention. As shown in **Table B-1**, the four categories of net benefit are: substantial, moderate, small, and zero/negative. For example, a substantial benefit could result from high benefit and minimal harm. These categories only reflect the order of magnitude of net benefit, they do *not* reflect *how certain* we are of that magnitude of net benefit.

Table B-1: U.S. Preventive Services Task Force (USPSTF) Recommendations – Net Benefit [157]

Level of Net Benefit	Description
Substantial	More than a small relative impact on a frequent condition with a substantial burden of suffering; *or* A large impact on an infrequent condition with a significant impact on the individual patient level.
Moderate	A small relative impact on a frequent condition with a substantial burden of suffering; *or* A moderate impact on an infrequent condition with a significant impact on the individual patient level.
Small	A negligible relative impact on a frequent condition with a substantial burden of suffering; *or* A small impact on an infrequent condition with a significant impact on the individual patient level.
Zero or Negative	Negative impact on patients; *or* No relative impact on either a frequent condition with a substantial burden of suffering, or an infrequent condition with a significant impact on the individual patient level.

Certainty refers to the level of certainty that is associated with a net benefit. The level of certainty is greater with stronger evidence (i.e., from well-designed and well-conducted studies). As shown in **Table B-2**, the three levels of certainty are high, medium, and low. Higher certainty suggests that the observed net benefit (regardless of its magnitude as described in Fig. 2) is correct. For any given magnitude of net benefit (whether it is substantial or zero), the certainty can range from high to low.

When considering what grade should accompany a recommendation, it may help to consider these two dimensions separately before arriving at a grade. That is, based on the health outcomes in the available

evidence, “How big is the net benefit here?” Then, based on the strength of that available evidence, “How certain are we that this net benefit (no matter its size) is real?”

Table B-2: USPSTF Recommendations – Certainty [157]

Level of Certainty*	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: The number, size, or quality of individual studies. • Inconsistency of findings across individual studies. • Limited generalizability of findings to routine primary care practice. • Lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: • The limited number or size of studies. • Important flaws in study design or methods. • Inconsistency of findings across individual studies. • Gaps in the chain of evidence. • Findings not generalizable to routine primary care practice. • Lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.

**The USPSTF defines certainty as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general, primary care population. The USPSTF assigns a certainty level based on the nature of the overall evidence available to assess the net benefit of a preventive service.*

The **Grade of the recommendation** is based on a framework that combines the two dimensions, as shown in **Table B-3**. As described above, the grade depends on both net benefit and certainty. For example, in the USPSTF grading scheme, a grade of A is assigned to a recommendation that is based on a high certainty of a substantial net benefit. Three combinations of certainty and net benefit can yield a grade of B. Note that, in the USPSTF framework, any recommendation associated with low certainty of net benefit results in a recommendation of I, regardless of the magnitude of net benefit.

Certainty of Net Benefit	Magnitude of Net Benefit			
	Substantial	Moderate	Small	Zero/Negative
High	A	B	C	D
Moderate	B	B	C	D
Low	Insufficient			

Table B-3: USPSTF Recommendations – Grade [157]
Given: 1) the level of certainty that a net benefit exists and 2) the magnitude of that net benefit, what grade of recommendation do we assign?

Grade A indicates that the certainty of evidence is high that the magnitude of net benefits is substantial.

Grade B indicates that the certainty of evidence is moderate that the magnitude of net benefits is either moderate or substantial, or that the certainty of evidence is high that the magnitude of net benefits is moderate.

Grade C indicates that the certainty of the evidence is either high or moderate that the magnitude of net benefits is small.

Grade D indicates that the certainty of the evidence is high or moderate that the magnitude of net benefits is either zero or negative.

Grade I indicates that the evidence is insufficient to determine the relationship between benefits and harms (i.e., net benefit).

Table B-4 defines each grade of recommendation, along with an associated suggestion for practice. For example, a grade of A (which is based on a high certainty of substantial net benefit, as noted above) means that an intervention is recommended and that the suggestion for practice is to offer/provide this intervention. A grade of C means a recommendation to selectively offer/provide the intervention to individual patients based on professional judgment and patient preference and that the suggestion for practice is to provide the intervention to patients depending on individual circumstances.

Table B-4: USPSTF Recommendations

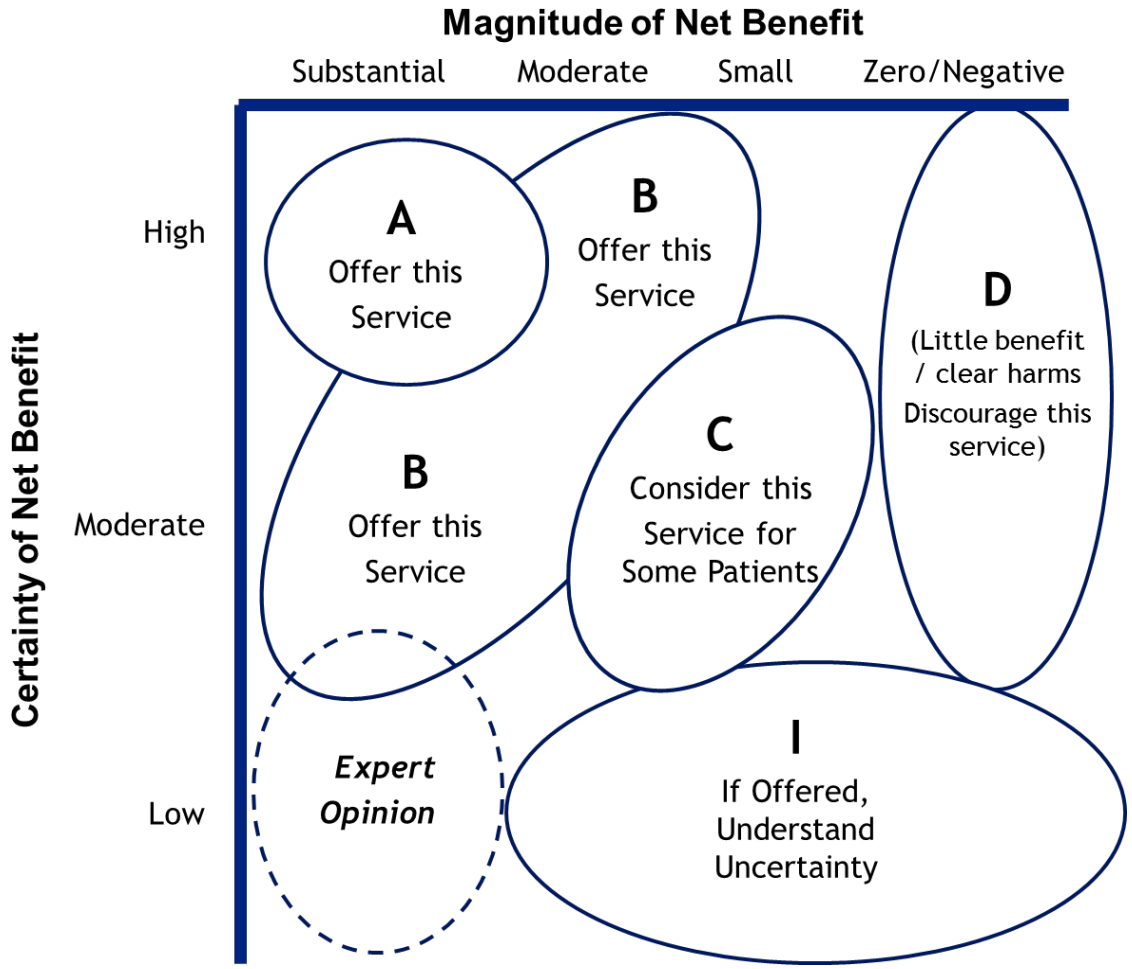
Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.

Grade	Definition	Suggestions for Practice
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Grade of EO for Expert Opinion: During the face-to-face meeting, the Champions and Work Group members used a variation of the USPSTF grading framework to provide for a grade of EO for "Expert Opinion." Given that evidence-based clinical practice guidelines have to be used in real practice for Veterans and Service members, a grade of I for insufficient evidence may not provide enough guidance for supporting clinical decisions in practice. In particular, we considered certain instances in which evidence suggests a substantial or moderate net benefit, but the certainty/strength of that evidence is low. In those instances, rather than concluding that the evidence is insufficient to support a clinical decision, we may rely on considered EO to set forth a recommendation. A grade EO does *not* imply that the evidence is strong (it is still low). It does suggest that the magnitude of net benefit (substantial or moderate) is of sufficient clinical importance to make a recommendation, even if it is based on low certainty (weak evidence).

Figure B-1 is a framework that incorporates Expert Opinion. The dimensions of Net Benefit of an intervention and Certainty of evidence still correspond to the USPSTF framework, and grades of recommendation (A, B, C, D, I) are the same, except for the use of EO in place of I in one sector of the framework. We made slight modifications in this framework to make the cross-walk from USPSTF more clear and better reflect the sense of our Work Group discussions.

Figure B-1: Framework with Expert Opinion



Appendix C: Evidence Table

	2006	2014			
Recommendation	**GRADE**	**Evidence**	**Certainty of Evidence**	**Magnitude of Net Benefit**	**Grade**
Screening and Assessment					
1. Screen adult patients to establish a diagnosis of overweight or obesity by calculating body mass index (BMI), and document the presence of overweight or obesity in the medical record.	N/A →	[26] [31] [71]	Moderate	Moderate	B
2. Screen for overweight and obesity at least annually.					EO
3. Assess for the presence of obesity-associated conditions among overweight patients or patients with increased waist circumference.	N/A	[26] [32] [31] [71] [158] [159] [160]	Moderate	Moderate	B
4. Perform a targeted assessment on overweight and obese patients. In addition to the basic medical history and physical examination, assess for factors contributing to obesity.	EO →	**Additional supporting literature:** [9] [74] [98]			EO
Normal Weight Patients					
5. Consider providing normal weight patients with information and behavioral counseling regarding healthy diet and physical activity behaviors, in order to maintain a healthy weight.	EO	[26] [34]	Moderate	Small	C

	2006	2014			
Recommendation	**GRADE**	**Evidence**	**Certainty of Evidence**	**Magnitude of Net Benefit**	**Grade**
Overweight Patients Without Obesity-Associated Condition(s)					
6. Consider providing overweight patients without obesity-associated conditions with information and behavioral counseling regarding healthy diet and physical activity behaviors, in order to pursue a healthy weight.	I	[26] [34]	Moderate	Small	C
Overweight Patients With Obesity-Associated Condition(s)					
7. Offer comprehensive lifestyle intervention to achieve weight loss and to improve blood pressure and/or glucose control in overweight patients.	A →	**Additional supporting literature:** [26] [38] [43] [46] [31] [71] [73]		→	A
8. Offer comprehensive lifestyle intervention to overweight patients with dyslipidemia for weight loss and to improve lipid levels.	B →	**Additional supporting literature:** [38] [46] [31] [71]	High	Small →	B
9. Current evidence is insufficient to recommend for or against offering comprehensive lifestyle intervention for weight loss to overweight patients with degenerative joint disease, non-alcoholic fatty liver disease and/or obstructive sleep apnea to reduce harms of these conditions.	C	[51] [52] [53] [54] [161] [162]	Low	N/A	I

	2006	2014			
Recommendation	**GRADE**	**Evidence**	**Certainty of Evidence**	**Magnitude of Net Benefit**	**Grade**
Obese Patients					
10. Offer obese patients comprehensive lifestyle intervention for weight loss to improve lipid levels, blood pressure, and/or glucose control.	A →	**Additional supporting literature:** [39] [41] [43] [46] [31] [71]		→	A
11. Offer obese patients comprehensive lifestyle intervention for weight loss, to reduce harms of obstructive sleep apnea.	B →	**Additional supporting literature:** [38] [53]		→	B
12. Consider offering obese patients comprehensive lifestyle intervention for weight loss, to reduce harms of degenerative joint disease.	C →	**Additional supporting literature:** [54] [161]		→	C
13. Current evidence is insufficient to support weight loss through comprehensive lifestyle intervention for reducing harms of non-alcoholic fatty liver disease.	N/A	[143] [162]	Low	N/A	I
Shared Decision-Making					
14. Reach a shared understanding with overweight and obese patients about the risks of overweight and obesity, and the benefits of weight management.	EO →	[55] [56]		→	EO

	2006	2014			
Recommendation	**GRADE**	**Evidence**	**Certainty of Evidence**	**Magnitude of Net Benefit**	**Grade**
General Treatment Principles of Weight Loss					
15. Perform an in-depth clinical assessment in order to assess the risks and benefits of different weight management treatments and to develop a weight management plan.	EO →	**Additional supporting literature:** [9] [74] [98]		→	EO
16. Use motivational interviewing techniques to evoke patient motivation to accept and participate in weight loss treatments.	EO →	[68] [69]		→	EO
17. Convey the importance of weight loss and maintenance as a lifelong commitment rather than a brief episode of treatment.	N/A	[81] [82]			EO
18. Offer patients at least 12 contacts within 12 months of a comprehensive lifestyle intervention that combines dietary, physical activity and behavioral strategies.	N/A	[26] [31] [71] [73]	Moderate	Moderate	B
19. Plan a net deficit of 500 to 1,000 kcal/day addressing both diet and physical activity to achieve a weight loss of 0.5 to 2 pounds per week, resulting in a 5-10% reduction in body weight over 6 months.	B	[39] [46] [110] [109] [107] [105]	High	Substantial	A
20. Assess adherence to the weight loss program one-to-two times per month by measuring the patient's weight and providing feedback and ongoing support.	N/A	[26] [31] [71]			EO
21. Re-evaluate the treatment plan for patients who have lost an average of less than 0.5 pound per week.	N/A	[39] [46]			EO

	2006	2014			
Recommendation	**GRADE**	**Evidence**	**Certainty of Evidence**	**Magnitude of Net Benefit**	**Grade**
22. Offer patients who have met their weight loss goals a comprehensive maintenance program consisting of behavioral components and ongoing support.	B →	**Additional supporting literature:** [31] [71] [73] [81] [82] [83] [84]		→	B
Behavioral Approaches					
23. Offer comprehensive lifestyle interventions for weight loss, in either individual or group setting.	N/A	[26] [31] [71] [73]			B
24. Offer telephone-based comprehensive lifestyle intervention for weight loss, either as an alternative or an adjunct to face-to-face intervention.	B →	**Additional supporting literature:** [73] [88]		→	B
25. There is insufficient evidence for or against offering internet-based comprehensive lifestyle intervention for weight loss, as an alternate or adjunct to face-to-face intervention.	B	[71] [90] [91]	Low	N/A	I

	2006	2014			
Recommendation	**GRADE**	**Evidence**	**Certainty of Evidence**	**Magnitude of Net Benefit**	**Grade**
Dietary Approaches					
26. Offer any of several diets that produce a caloric deficit and have evidence for weight loss efficacy and safety (e.g., low-carbohydrate, Dietary Approaches to Stop Hypertension (DASH), low-fat).	B	[73] [93] [94] [95] [96] [97] [98]	High	Substantial	A
27. Offer very-low-calorie diets for weight loss, but only for short durations (12-16 weeks) and under close medical supervision.	B →			→	B
28. Offer meal replacements to achieve low-calorie or very low-calorie diets.	A →			→	A
Physical Activity Approaches					
29. Offer physical activity elements (e.g., home fitness, lifestyle, or structured/supervised physical activities), that can be combined to produce a caloric deficit leading to weight loss.	A →			→	A
30. Offer physical activity options that include short intermittent bursts (at least 10 minutes) as well as longer continuous exercise.	A →			→	A
31. Offer, as part of a comprehensive lifestyle intervention, moderate-intensity physical activity performed for at least 150 minutes/week to result in weight loss.	N/A	[39] [46]	High	Substantial	A
32. Offer, as part of comprehensive lifestyle intervention, moderate-intensity physical activity performed for 200-300 minutes per week to prevent weight regain after initial weight loss.		[99] [73] [74]	N/A	N/A	EO

Recommendation	2006 GRADE	2014 Evidence	2014 Certainty of Evidence	2014 Magnitude of Net Benefit	2014 Grade
Pharmacotherapy					
33. Offer pharmacotherapy with the combination phentermine/topiramate extended-release to patients with a body mass index (BMI) ≥30 kg/m^2 and to those with a BMI ≥27 kg/m^2 who also have obesity-associated conditions, as an adjunct to comprehensive lifestyle intervention, when lifestyle interventions alone do not produce the desired weight loss.	N/A	[128] [129] [130]	High	Substantial	A
34. Offer pharmacotherapy with orlistat or lorcaserin to patients with a body mass index (BMI) ≥30 kg/m^2 and to those with a BMI ≥27 kg/m^2 who also have obesity-associated conditions, as an adjunct to comprehensive lifestyle intervention, when lifestyle interventions alone do not produce the desired weight loss.	N/A	[121] [122] [123] [124] [125] [126] [127] [130] [131]	High	Moderate	B
35. Offer pharmacotherapy (i.e., orlistat, lorcaserin, combination phentermine/topiramate extended-release), as an adjunct to comprehensive lifestyle intervention, to patients with obesity-associated conditions, for its beneficial effects on type 2 diabetes, hypertension, and/or dyslipidemia.	N/A	[121] [124] [125] [126] [127] [128] [131] [132] [163] [164]	High	Moderate	B

	2006	2014			
Recommendation	**GRADE**	**Evidence**	**Certainty of Evidence**	**Magnitude of Net Benefit**	**Grade**
36. Offer patients who achieve their weight loss goal, a program that includes continued medication use for weight maintenance.	N/A	[124] [125] [130] [131] [163]	Moderate	Moderate	B
Bariatric Surgery					
37. Offer bariatric surgery, as an adjunct to comprehensive lifestyle intervention, for weight loss in adult patients with a body mass index (BMI) >40 kg/m^2 or those with BMI 35.0-39.9 kg/m^2 with one or more obesity-associated conditions.	B →	**Additional supporting evidence:** [132]		→	B
38. Offer bariatric surgery, as an adjunct to comprehensive lifestyle intervention, to improve some obesity-associated conditions in adult patients with a body mass index (BMI) ≥35.0 kg/m^2.	B	[50] [132] [133] [135] [136] [137] [138] [139] [140] [29]	High	Substantial	A
39. Current evidence is insufficient to assess the balance of benefits and harms of offering bariatric surgery as an adjunct to comprehensive lifestyle intervention for weight loss or to improve some obesity-associated conditions, to patients over age 65, or with a body mass index (BMI) <35 kg/m^2.	I →	**Additional supporting evidence:** [132]		→	I

	2006	2014			
Recommendation	**GRADE**	**Evidence**	**Certainty of Evidence**	**Magnitude of Net Benefit**	**Grade**
40. Engage all patients who are candidates for bariatric surgery in a general discussion of the benefits and potential risks. If more detailed information is requested by the patient to assist in the decision-making process, a consultation with a bariatric surgical team should occur.	N/A	[74] [98] [154]			EO
41. Provide lifelong follow-up after bariatric surgery to monitor adverse effects and complications, dietary restrictions, adherence to weight management behaviors and psychological health.	N/A	[74] [98] [154]			EO

Appendix D: Body Mass Index (BMI) Calculation Chart

Upper Limit Border Points For Category Of Overweight/Obesity By Height (inches)					
BMI (kg/m^2)	**25**	**30**	**35**	**40**	**45**
Height			**Stage 1**	**Stage 2**	**Stage 3**
(inches)	**Normal**	**Overweight**	**Obese**		
58	119	143	167	191	215
59	124	148	173	198	222
60	128	153	179	204	230
61	132	158	185	211	238
62	136	164	191	218	246
63	141	169	197	225	254
64	145	174	204	232	262
65	150	180	210	240	270
66	155	186	216	247	278
67	159	191	223	255	287
68	164	197	230	262	295
69	169	203	236	270	304
70	174	209	243	278	313
71	179	215	250	286	322
72	184	221	258	294	331
73	189	227	265	302	340
74	194	233	272	311	350
75	200	240	279	319	359
76	205	246	287	328	369
Adapted from NHLBI, 2000 [9]					

Appendix E: Obesity-Associated Conditions

There are many conditions that can be considered to be exacerbated by overweight or obesity. This Appendix addresses the effects of weight loss on some of the more common obesity-associated conditions listed in the **Box E-1**.

Box E-1: Common Obesity-Associated Conditions*

- Hypertension**
- Type 2 diabetes and pre-diabetes**
- Dyslipidemia**
- Metabolic syndrome
- Obstructive sleep apnea
- Degenerative joint disease
- Non-alcoholic fatty liver disease

*Increased waist circumference is considered an obesity comorbidity equivalent

** At least moderate evidence exists for modifying these conditions with weight loss

Hypertension

Both the Diabetes Prevention Program (DPP) and Look AHEAD trials were designed to evaluate the effectiveness of intensive behavioral lifestyle interventions on cardiovascular risk factors. The DPP [46] was a three year study that randomized 3,234 patients (mean age 51 years) with impaired glucose tolerance to intensive lifestyle intervention, metformin (850 mg twice daily), or placebo. The goals of the intensive lifestyle modification were a weight reduction of at least 7% of initial body weight through consumption of a healthy low-calorie, low-fat diet and to engage in physical activity of moderate intensity for at least 150 min/week. A 16-lesson curriculum was taught by case managers on an individual basis during the first six months followed by subsequent individual (usually monthly) and group sessions with case managers designed to reinforce behavioral change. By the end of the 24-week curriculum, 50% of the intervention group had achieved the weight loss goal and after an average of 2.8 years, the mean weight loss was 0.1, 2.1, and 5.6 kg in the placebo, metformin, and lifestyle intervention groups, respectively ($P<0.001$). Seventy-four percent met the goal of at least 150 minutes of physical activity per week. Daily caloric intake decreased by 249, 296, and 450 kcal in the placebo, metformin, and lifestyle-intervention group, respectively. The impact of the intensive behavioral lifestyle intervention on the development of type 2 diabetes will be discussed in the section on diabetes below.

The Look AHEAD trial was a four year study that randomized 5,145 type 2 diabetic patients aged 45-76 years who were overweight or obese to intensive lifestyle intervention or a control group of standard diabetes support and education. [39] The goal of the intensive lifestyle group was designed to induce at least a 7% weight loss at year one and to maintain this weight loss in subsequent years. They received a reduced caloric intake (1200–1800 kcal per day based on initial weight) using a portion-controlled diet with liquid meal replacements and recommendations to use other portion-controlled items. Additionally, they were instructed to have at least 175 minutes of physical activity per week. The intensive lifestyle intervention consisted of weekly group and individual counseling in the first six months, three sessions per month for the next six months, and two sessions per month for the remainder of the study. After four years, the intervention group lost 6.15% vs. 0.88% in the control group.

In the DPP, the prevalence of hypertension at three years was attenuated in the lifestyle group but increased in the metformin and placebo groups. Furthermore, the lifestyle group had a 27% less use of drug therapy to treat hypertension compared to metformin or placebo. [40] In the Look AHEAD trial, those in the lifestyle group after four years had significantly improved systolic blood pressure (SBP) (-5.33 vs. -2.97 mm Hg; P < .001) and diastolic blood pressure (DBP) (-2.92 vs. -2.48 mm Hg; P = .01) compared to controls. [39]

A systematic review that evaluated the long-term effects of weight loss on hypertension outcome measures in adults, included randomized controlled studies (RCT) performed on participants with a body mass index (BMI) ≥28 kg/m^2 with a follow-up of >2 years. [41] Previous reviews on shorter term studies indicate a drop in blood pressure of 1 mmHg for every 1 kg of weight loss. [42] The findings of the review suggested that for 10 kg of weight loss, decreases of 4.6 mmHg in DBP and 6 mmHg in SBP may be expected. The model excluded studies with surgical interventions that exhibited huge weight losses with dramatic blood pressure changes.

A review by Witham et al. reported that in the Trial of Nonpharmacologic Intervention in the Elderly, the interventional group had a significant reduction in SBP, compared to baseline and control at three months (4.0 vs. 0.8 mmHg, P < 0.001). Similarly, a meta-analysis by Horvath et al. reported a significant difference in the reduction of SBP in favor of dietary interventions with a weighted mean different (WMD) of −6.26 mm Hg (95% CI, −9.82 to −2.70 mm Hg. For DBP, studies showed a significant difference in the reduction of DBP in favor of dietary interventions with a WMD of −3.41 mm Hg (95% CI, −5.55 to −1.27 mm Hg). [43]

The recent Look AHEAD trial showed that after 10 years of follow-up, SBP (not DBP) was significantly reduced in the interventional group vs. control group. [38]

Weight loss induced by orlistat is somewhat effective in treating hypertension in overweight and obese patients. A meta-analysis of five RCTs revealed that after one year of treatment, average SBP and DBP reductions were significantly greater with orlistat than placebo (–9.4 versus –4.6 mmHg systolic and –7.7 versus –5.6 mmHg diastolic). [165]

A more recent Cochrane Collaborative Review showed that orlistat resulted in placebo-subtracted SBP reductions of 1.5 mm Hg (95% CI 0.9 to 2.2 mm Hg; 13 studies) and DBP reductions of 1.4 mm Hg (95% CI 0.7 to 2.0 mm Hg; 12 studies). [122]

Bariatric surgery in obese patients has the most dramatic effect on blood pressure reduction after weight loss. The Swedish Obesity Study (SOS) is a prospective controlled study of 2010 subjects received bariatric surgery for obesity. The procedure received in this cohort was vertical banded gastroplasty in 68.1%, adjustable or nonadjustable gastric banding in 18.7% and gastric bypass in 13.2%. Patients experienced a 4 to 5 mmHg reduction in blood pressure at two years post-surgery. At 10 years, the impact of bariatric surgery on blood pressure differed according to the type of procedure performed; gastric bypass patients had the largest reductions in blood pressure of 5 to 10 mmHg, while gastric banding patients experienced a 2 mmHg increase in SBP and only a 1 mmHg reduction in DBP. [135] The prospective controlled Utah-based study showed that at six years, 42% of patients receiving gastric

bypass surgery had complete remission of hypertension. [136] In a meta-analysis of mostly non-RCTs or uncontrolled case series, hypertension resolved in 61.7% and resolved or improved in 78.5% of the study subjects. [137] A 2012 systematic review of 58 controlled trials showed that hypertension improved or resolved in 62.5% of patients. [138] A meta-analysis of 16 studies by Li et al. reported that laparoscopic Roux-en-y gastric bypass had a similar effect in resolving hypertension (pooled mean difference of 8.27, 95% CI: 6.89-9.66, p<0.00001) compared with laparoscopic sleeve gastrectomy. [139]

Type 2 Diabetes

Weight loss through behavioral lifestyle changes has had a favorable effect on preventing type 2 diabetes. During the Finnish Diabetes Prevention Study (FDPS), the risk of diabetes was reduced by 58% (P<0.001) in subjects of the intervention group who received individualized counseling aimed at reducing weight through modifications in diet and physical activity. The reduction in the incidence of diabetes was directly associated with changes in lifestyle. The cumulative incidence of diabetes after four years was 11% (95% CI: 6-15%) in the intervention group and 23% (95% CI: 17-29%) in the control group. [45]

In the DPP (see hypertension above) trial, the associated reduction in incidence of type 2 diabetes was 58% in the lifestyle group and 31% in the metformin group compared to placebo. [46] A 10-year follow-up study offered lifestyle intervention to all groups. Diabetes incidence was reduced by 34% in the lifestyle group and 18% in the metformin group compared to placebo. [47]

A meta-analysis of the FDPS and three additional diabetes prevention studies showed the relative risk of type 2 diabetes was reduced by about 50% in the lifestyle group compared to the control group. [48]

A 2011 Agency for Healthcare Research and Quality (AHRQ) meta-analysis of five weight loss trials in diabetics or pre-diabetics showed a statistically significant reduction in fasting blood glucose (WMD, -5.3 mg/dl). [31]

For those with existing type 2 diabetes, lifestyle interventions have shown a favorable effect. In the Look AHEAD trial (see hypertension above), after a four year follow-up period, the lifestyle group had a 11.5% and 7.3% partial or complete remission rates of diabetes at one and four years, respectively. [39]

The use of drug therapy for weight loss and type 2 diabetes has been evaluated by numerous trials. [166-169] In the largest and longest duration orlistat study to date, 3,305 non-diabetic obese adults with normal or impaired glucose tolerance received orlistat 120 mg three times a day plus lifestyle changes or lifestyle changes alone for four years. [124] At the end of the study, the cumulative incidence of diabetes was 9% with lifestyle changes alone and 6.2% with orlistat plus lifestyle changes, corresponding to a 37.3% relative risk reduction and a number needed to treat of 35 (P = 0.003). Differences in diabetes incidence were detectable in the impaired glucose tolerance subgroup. The mean weight loss after four years was significantly greater with orlistat (5.8 vs. 3.0 kg with placebo; P < 0.001). [124] Furthermore, weight loss with orlistat improved fasting glucose and A1C in adults with type 2 diabetes and other components of the metabolic syndrome. [166-169]

A 2011 meta-analysis of nine RCTs with orlistat showed that subjects with type 2 diabetes or pre-diabetes experienced a statistically significant 5.7 mg/dl greater decline in fasting glucose at 12 to 18 months compared to placebo. When only subjects with type 2 diabetes were included (four trials), fasting glucose decreased 12 mg/dl (WMD 12.1 mg/dl, 95% CI, -21.9 to -2.4). [31]

The greatest impact on diabetes is seen following bariatric surgery. The largest prospective study evaluating the long-term impact of bariatric surgery on type 2 diabetes is the SOS. [135] In this prospective controlled trial, obese subjects who underwent gastric surgery for weight loss were matched with conventionally treated obese control subjects; 4,047 subjects were followed for at least two years and 1,703 subjects were followed for 10 years. The subjects in the surgical intervention group had a BMI of 34 or more (men) or 38 or more (women) and were between ages 37 to 60 years. At both the two and 10-year follow-up, the surgical intervention group had a significantly greater weight loss. In addition, the incidence rate of diabetes was markedly lower in the surgically treated group compared to the control group after two and 10 years. [135]

Kashyap randomized 60 subjects with a mean A1C of 9.7% and a BMI of 36 to intensive medical therapy (IMT), IMT plus Roux-en-Y gastric bypass, or IMT plus sleeve gastrectomy. The weight loss (kg) and A1C at 24 months in the three groups was -0.5, -25.4, -22.5 and 8.4, 6.7, 7.1, respectively. [140]

In a systematic review by Vest et al., 73% of participants showed statistically significant postoperative resolution or improvement in their baseline diabetes at follow-up. [138] There was a reduction in 10-year coronary heart disease Framingham Risk Score from 5.9% to 3.3%. A Cochrane review found that weight loss associated with surgery was significantly better at reducing diabetes co-morbidity than non-surgical interventions. [132]

Another systematic review and meta-analysis was performed on bariatric surgery and its impact on health outcomes. [137] From the 708 studies included for evaluation, the mean age was 38.97 years (16.20 – 63.60) with a mean BMI of 46.85 kg/m^2 (range 32.30 – 68.80 kg/m^2). In this meta-analysis, bariatric surgery resulted in the ability to discontinue all diabetes related medications and maintenance of normal blood glucose levels in 76.8% of all patients. Additionally, 86% of patients were found to have resolution or improvement of their diabetes.

Li et al. performed a meta-analysis of 16 studies comparing laparoscopic Roux-en-Y gastric bypass vs. sleeve gastrectomy for morbid obesity and diabetes. [139] They found that Roux-en-Y gastric bypass had a better effect at resolving diabetes as 12 months compared to sleeve gastrectomy (OR 2.46, 95% CI 1.48-4.09, p <0.00001).

While the positive effects of bariatric surgery are known for those with BMI > 35, less is known for lesser degrees of obesity. An AHRQ comparative effectiveness review evaluated this question and found that weight loss at one and two years was 15-20 kg and 11-23 kg, respectively and A1C decreased 2.6-3.7 and 1.8-3.1 percentage points at one and two years, respectively. [141] The strength of evidence was moderate for Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding, and sleeve gastrectomy in treating obese patients with a BMI between 30-35 kg/m^2 in the short-term. Of note there was low strength of evidence for short-term harms and no long-term data was available.

In summary, bariatric surgery is effective for improvements in type 2 diabetes in patients with a BMI > 35 kg/m^2. It is also effective short-term for those with a BMI 30-35 kg/m^2.

Dyslipidemia

A systematic review of the long-term lipid outcomes of weight loss in studies published between 1966 and 2001 was conducted by Poobalan and colleagues (2004). Thirteen long-term studies on participants with a BMI of greater than or equal to 28 kg/m^2 with a follow-up of more than two years were included. Cholesterol had a significant positive linear relationship with weight change (r = 0.89) where change in weight explained about 80% of the cholesterol difference variation. For every 10 kg weight loss, a drop of 0.23 mmol/L (8.9 mg/dl) in cholesterol may be expected for a person who is overweight or obese. [49]

A 2011 meta-analysis of 16 trials showed that the weight loss intervention group had a statistically greater decline compared to the control group at 12 to 18 months of 5.8 mg/dl for total cholesterol, 4.9 mg/dl for low-density lipoprotein (LDL) cholesterol, and 11.1 mg/dl for triglycerides; there was no difference for high-density lipoprotein (HDL) cholesterol. [31]

In the DPP (see hypertension above), triglyceride levels fell significantly more in the intensive lifestyle group (-25.4 mg/dl) than in the placebo (-11.9 mg/dl) or metformin (-7.4 mg/dl) groups. HDL cholesterol level significantly increased in the lifestyle group (+1.0 mg/dl) compared with the metformin (+0.3 mg/dl) and placebo groups (-0.1 mg/dl). Lifestyle also positively altered the LDL phenotype compared to metformin or placebo ($p < 0.001$). Drug therapy for hyperlipidemia was 25% less for the lifestyle group compared to the metformin and placebo groups. Total cholesterol and LDL cholesterol levels did not change. [46]

In Look AHEAD (see hypertension), statistically significant changes occurred in the lifestyle vs. control groups for HDL cholesterol (+3.67 vs. +1.97 mg/dl) and triglycerides (-25.26 vs. -19.75 mg/dl). The benefits remained at 4 years only for HDL cholesterol. Reductions in LDL cholesterol were greater with the control group but did not differ after adjustment for medication use. [39]

In overweight and obese patients, orlistat has been shown to have a positive effect on dyslipidemia. A 2011 AHRQ meta-analysis of 12 RCTs showed that at 12 to 18 months, overweight and obese subjects on orlistat had a statistically greater decline over placebo of 12.6 mg/dL in total cholesterol and 11.4 mg/dl in LDL cholesterol. HDL cholesterol also declined (0.9 mg/dl, 95% CI, -1.7 to -0.1); triglycerides did not change (WMD, -4.8, 95% CI, -10.4 to 0.7). [31]

Hutton performed a systematic review of 17 studies involving 10,041 subjects comparing orlistat 120 mg three times per day with placebo or an inactive control along with a hypocaloric diet over a one year period. Relative risks for weight losses of 5% and 10% were 1.74 (95% CI: 1.57, 1.91) and 1.96 (1.74, 2.21), favoring the orlistat groups. There was a consensus opinion among these studies that orlistat is effective for improving both weight loss and serum lipid profiles in obese patients at low and high cardiovascular risk and in obese patients with type 2 diabetes. [170]

Orlistat has a beneficial effect on serum cholesterol concentration that is independent of weight loss alone. The decrease in serum LDL cholesterol concentrations after weight loss with orlistat therapy is greater than after placebo therapy, even after adjusting for percentage of weight loss. The mechanism responsible for this additional lipid lowering effect may be related to orlistat's effect in blocking both dietary cholesterol and triglyceride absorption. [171-173]

Hypertriglyceridemia is improved with bariatric surgery. [135,137] In the SOS study the incidence of hypercholesterolemia did not differ between the control and surgery groups, but the incidence of hypertriglyceridemia was significantly decreased at two and 10 years in the surgery group. [135]

A systematic review by Vest et al. showed that after a mean follow-up of 57.8 months and an average excess weight loss of 54%, 65% of subjects undergoing bariatric surgery had significant postoperative resolution or improvement of their hyperlipidemia at follow-up. The total of at least 5000 patients was included with the exception of LDL cholesterol measurement, which was conducted in 2101 patients. The mean age was 41.7 years and the mean was BMI 47.1. Total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides changes from baseline to follow-up were – 29.1 mg/dl, - 25.0 mg/dl, +8.6 mg/dl and -61.2 mg/dl, respectively; all changes were significant compared to baseline states. [138] Colquitt et al. reported on a large cohort study included in their systematic review and found that after 10 years, a greater proportion of people who had received weight loss surgery recovered from hypertriglyceridemia and low HDL cholesterol; there was no change in total cholesterol and LDL cholesterol was not reported. [132]

In summary, the results of the available evidence suggest that lifestyle interventions to promote weight loss in obese subjects consistently result in short-term (less than two years) improvement in triglycerides, total cholesterol and LDL cholesterol but not HDL cholesterol. Long-term reductions (greater than two years) occur consistently in triglycerides. These improvements have not been shown to affect MACE. Drug therapy with orlistat and bariatric surgery, which both produce greater weight loss than lifestyle interventions, has been shown to improve total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides. Bariatric surgery has been shown long-term (10 years) to improve triglycerides and HDL cholesterol.

Metabolic Syndrome

Metabolic syndrome is characterized by the presence of multiple interrelated risk factors for cardiovascular disease. Most patients with metabolic syndrome are overweight or obese. The metabolic syndrome is identified by the presence of three or more of the components listed in **Table E-1**.

Table E-1: Diagnosis of Metabolic Syndrome [174]

Three or more of the following risk factors indicate metabolic syndrome:	Defining Level
Abdominal Obesity: Men† Women	Waist Circumference (WC): Greater than 102 cm (>40 in) Greater than 88 cm (>35 in)
Triglycerides	Greater than or equal to 150 mg/dl
HDL cholesterol:	

Three or more of the following risk factors indicate metabolic syndrome:	Defining Level
Men Women	Less than 40 mg/dl Less than 50 mg/dl
Blood pressure	Greater than or equal to 130/85 mmHg
Fasting glucose	Greater than or equal to 100 mg/dl

† Some men can develop multiple metabolic risk factors when the WC is only marginally increased, e.g., 37–39 inches (94–102 cm). Such persons may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in WC.

Clinical trials show that modifying three major components of the metabolic syndrome—atherogenic dyslipidemia, hypertension, and the prothrombotic state — will reduce the risk for cardiovascular disease. [175]

To achieve maximal benefit from the modification of multiple metabolic risk factors, the underlying insulin resistant state must become a target of therapy. The safest, most effective, and preferred means to reduce insulin resistance is weight reduction in overweight and obese persons and increased physical activity.

One RCT evaluated the effect of orlistat on the metabolic syndrome in overweight and obese patients. In this study, orlistat plus a hypocaloric diet was more effective than a hypocaloric diet alone in reducing body weight, waist circumference, fasting glucose, A1c, and blood pressure. [166]

Two RCTs were identified that specifically examined the impact of bariatric surgery on the metabolic syndrome. O'Brien et al. found metabolic syndrome in 37.5% at baseline vs. 2.7% at two years after laparoscopic adjustable gastric banding (LAGB) ($P < 0.001$) vs. the control group of 37.5% and 24%. The between group difference at two years was significant ($P = 0.006$). [133] Dixon et al. found metabolic syndrome in 29 of 30 patients at baseline and nine of 30 patients two years after LAGB ($P < 0.001$), the control did not have any change. The between group difference was significant ($P < 0.001$). [50] Additionally, though specific components of the metabolic syndrome have been evaluated in only these studies, three major components of the metabolic syndrome, hypertension, diabetes and dyslipidemia are typically positively affected by bariatric surgery (see above).

In summary, one RCT involving orlistat and two RCTs involving bariatric surgery showed favorable improvement in metabolic syndrome.

Sleep Apnea

Obstructive sleep apnea (OSA) is generally divided into mild, moderate and severe based on an apnea-hyponea index (AHI) of 5-15, 15-30, and >30, respectively. Severe OSA is associated with increased overall mortality [176] and heart failure. [177] In all of the studies reviewed, qualify of life or overall satisfaction was not assessed. Furthermore, long-term studies are not available to report effects of treatment on mortality or consequent morbidity e.g., pulmonary hypertension, arrhythmias, or heart failure. The primary outcome measure is usually the apnea-hypopnea index.

An RCT conducted by Dixon et al. randomized patients to a conventional weight loss program that included regular consultations with a dietitian and physician and the use of very low-calorie diets as necessary, or to bariatric surgery (laparoscopic adjustable gastric banding). The mean age in the surgery group was 47.4 years and the mean BMI was 46.3 kg/m^2. At two years, patients in the bariatric surgery group lost a mean of 27.8 kg compared with a loss of 5.1 kg among the conventional group ($p < 0.001$). Both groups experienced a statistically significant decrease in total AHI from baseline to two years, with a decrease from 65.0 events/hour to 39.5 events/hour in the surgical group and 57.2 events/hour to 43.2 events/hour in the conventional group. The between group differences were not significant despite substantially greater weight loss with surgical therapy. Additionally, the surgery group had greater improvement in scores in health-related quality of life on the Short Form-36 (SF-36) components of physical role, general health, vitality and the physical component summary. Both groups improved on daytime sleepiness as measured by the Epworth Sleepiness Scale (ESS) and the six minute walk test but there were no significant between-group differences. [50]

A meta-analysis by Anandam et al. reported the effects of dietary weight loss in treating OSA among obese patients with severe apnea. The mean age was 53.1 years and the mean pre and post-dietary intervention BMI was 39.6 and 33.8 kg/m^2. The random-effects pooled results of AHIat pre and post-dietary interventions were 52.5 and 28.3 events per hour, respectively (p <0.001). The combined reduction in AHI was 44%. Additionally, two studies evaluated daytime sleepiness and/or quality of life (QoL). ESS was improved in one study that lacked a control arm, in the other study, there was no change in ESS or QoL as measured by the SF-36 questionnaire between intervention and control groups at 24 months. [51]

Thomasouli et al. conducted a meta-analysis on two groups of patients. In the first analysis, three studies compared the effect of continuous positive airway pressure (CPAP) and diet vs. diet alone on 278 participants. The age range was 49 to 54 years and the BMI range was 29 to 43.8 kg/m^2. The CPAP group had improvement in daytime sleepiness as measured by the ESS but no significant change in weight loss or QoL as measured by the Nottingham Health Profile. [52]

In the second meta-analysis, six studies compared intensive lifestyle intervention with usual care in a total of 483 participants with an age range of 46.9 to 61 years and a BMI range of 28.3 to 36.7 kg/m^2. The intervention group, with an overall weight loss of 5.65 kg, had a significant reduction in AHI of -4.55 events/hour compared to control but no difference in the ESS; QoL was not measured. In this meta-analysis, most of the participants came from one study, the Sleep AHEAD Study. Sleep AHEAD was a subset of the Look AHEAD trial that randomized 264 patients with type 2 diabetes and OSA to intensive lifestyle intervention (ILI) or diabetes support and education (DSE). The mean age was 61.2 years, BMI 36.7 kg/m^2, and AHI 23.2. The weight loss was 10.6 kg vs. 0.6 kg in the ILI and DSE groups, respectively. At one year follow-up, the ILI group had a decrease in AHI of 5.4 while the DSE group increased AHI by 4.2 ($P < 0.001$) for an adjusted mean decrease in AHI of 9.7 relative to the DSE group. Remission of OSA, which was defined by AHI < 5 events/hour, occurred in 13.6% of ILI participants and 3.5% of DSE participants. Additionally, the percent of patients who had severe OSA at one year was twice as great in the DSE vs. ILI groups. The greatest benefit was seen in men, in those who lost the most weight, and in those with more severe apnea at baseline. [53]

Thomasouli et al. also included a systematic review that found no significant changes with breathing and aerobic exercise or dietary advice and hypotherapy. One RCT of very low energy vs. usual diet did find an improvement in AHI (values not reported). [52]

In summary, these studies show that there is significant improvement in AHI following weight loss in obese patients. There is no evidence for a consistent positive effect on daytime sleepiness or QoL. Furthermore, there is no evidence that bariatric surgery gives better outcomes for OSA than lifestyle interventions. Thus there is a small relative impact of weight loss on OSA.

Osteoarthritis

The American College of Rheumatology recommends weight loss for osteoarthritis of the knee in overweight or obese patients. [178] Very strong epidemiological associations are found between excess weight and the presence of lower body osteoarthritis. In the Framingham observational study, patients who lost weight had better osteoarthritis outcomes than those who did not. [179] In the Ulm Osteoarthritis Study, overweight (OR 5.9, 95% CI 2.0-18) and obesity (odds ratio [OR] 8.1; 95% CI 2.2-28) were strongly associated with bilateral knee osteoarthritis but not bilateral hip osteoarthritis. [180] Hence, the most modifiable risk factor for osteoarthritis is body weight.

However, few RCTs have addressed the effect of weight loss on osteoarthritis and of these, only one involved overweight patients. ADAPT was a single blind randomized controlled trial of overweight and obese sedentary adults with osteoarthritis. Of the 316 subjects (mean age of 69 years and BMI of 34 kg/m^2) randomized to 18 months of exercise, diet, exercise plus diet, and control, 252 completed the study. The diet (-4.9%) and exercise plus diet (-5.7%) groups lost significantly more weight than the control group. Relative to the control group, significant improvements occurred with the diet and exercise group in self-reported physical function, six minute walk distance, stair-climb time, and knee pain. The exercise group had improvement in six minute walk distance while the diet only group did not have any improvement. [180]

A subset of ADAPT was randomized to receive biomechanical testing of which 76 completed the entire data collection. Patients were divided into a high (-10.2%), low (-2.7%) and no (+1.5%) weight loss groups. A biomechanical model was used to calculate knee joint forces from data collected during gait analysis. Maximum knee compressive forces were lower with greater weight loss ($P = 0.05$), primarily due to lower hamstring forces ($p = 0.04$). Walking velocity and radiographic progression were not significantly changed by the weight loss groups. [161] This suggests that long-term high weight loss may result in biomechanical improvement in obese patients with osteoarthritis.

Christensen et al. provided a systematic review and meta-analysis of the four RCTs involving weight loss intervention in patients with osteoarthritis. [54] Mean age was 67.2 years and mean baseline BMI was 34.0 kg/m^2. The intervention group lost 6.1 kg more than the control group. The weighted pooled effect size was 0.2 ($P = 0.05$) for pain and 0.23 ($P=0.02$) for self-reported disability. Data from 117 randomized patients evaluating the Lequesne index of pain, maximum distance walked, and activities of daily showed a non-significant weight pooled effect size of 0.58 ($P=0.25$). Of the four studies analyzed, three were by the same author.

In summary, obese patients suffering from osteoarthritis of the knees may benefit from weight loss primarily by improving self-reported disability.

Non-Alcoholic Fatty Liver Disease

Overweight and obesity are thought to play a role in the development of non-alcoholic fatty liver disease (NAFLD) whose histology resembles alcohol-induced liver injury. It encompasses a broad range of conditions from simple fatty liver to advanced cirrhosis. The inflammatory state of non-alcoholic fatty liver disease is known as non-alcoholic steatohepatitis (NASH). It would be reasonable to hypothesize that weight loss, either through diet and exercise, the use of weight loss medications, and/or bariatric surgery would decrease the progression of NAFLD and improve NASH.

A Cochrane Collaboration Review by Peng and Wang found seven randomized trials focusing on the effect of weight loss on NAFLD. Five used lifestyle modifications and two used orlistat. The review concluded though there seemed to be some benefit of diet and exercise modification for NAFLD patients with regards to steatosis, there was no difference in the development of fibrosis. None of the studies included QoL as a measure. [162] The data was not sufficient to determine the true effect of weight loss on NAFLD because of small sample size and high risk of bias.

Bariatric surgery may have a better effect on improving NAFLD. Mathurin et al. conducted a single center non-randomized, non-controlled prospective study of bariatric surgery in 381 severely obese patients. They looked at clinical, biologic and histologic data at one and five years post bariatric surgery. At 5 years, almost all patients had low levels of NAFLD, but fibrosis had increased. [181]

A systematic review and meta-analysis done by Mummadi et al. looked at 15 studies on bariatric surgery and liver histology. They concluded that steatosis, steatohepatitis and fibrosis appear to improve in most patients who lose weight after bariatric surgery. However, this meta-analysis was based on small observational, non-randomized studies with significant heterogeneity among the studies. [142]

A Cochrane Collaboration Review by Chavez-Tapia et al. focused specifically on NASH in obese patients. No randomized trials were found but 21 prospective or retrospective cohort studies were evaluated. Eleven studies reported improvement of liver function tests, eleven studies reported improvement in histological markers of inflammation, and eighteen studies reported a significant improvement in the degree of steatosis. However, only six studies showed improvement in fibrosis and four studies described worsening fibrosis. The studies included in this review did not directly report adverse events rates after bariatric surgery. [143]

In summary, though lifestyle and drug therapy with orlistat appear to be promising for NAFLD and NASH, lack of sufficient data and high risk for bias preclude any firm recommendations. Similarly, bariatric surgery appears to be promising as most studies show improvement in histologic scores such as steatosis. However, one of the most important histologic markers, fibrosis, has been shown to worsen, particularly in the larger studies that followed patients for longer periods of time. As worsening fibrosis is a strong predictor of advanced NAFLD, no definitive recommendation can be made for or against surgery.

Overall Health, Function and Quality of Life

QoL is significantly reduced by obesity and regardless of co-existing disease; obesity independently reduces QoL in proportion to a patient's weight. [182] Therefore, weight loss would be expected to produce change in QoL. As with most obesity-associated conditions, the magnitude of weight loss may be the primary determinant in outcome.

The literature search found two systematic reviews and three RCTs; all were rated as good quality. The systematic review by Verhaeghe et al. evaluated the effectiveness of lifestyle interventions in 14 RCT involving those with severe mental disorders. Five of these studies evaluated QoL. Of these only one of the studies reported a statistically significant weight loss in the intervention group; one showed non-significant weight loss and the other three studies did not report significance. Of these five studies, three used one of the variations of the Clinical Global Impressions (CGI) scale and only one found a significant difference between the interventional and control groups. The only study to report significant weight loss did not have any changes in CGI. A fourth study showed only improvement in subjective ratings of general health and empowerment but none in health and well-being based on the health-related QoL as measured by the Short Form 36 (SF-36) and Lehman Quality of Life Questionnaire. The final RCT showed no difference in psychological well-being or social relationship. [183]

Christensen performed a meta-analysis of four RCTs of weight loss in patients with degenerative joint disease. Pain responses were analyzed from combined data of 417 randomized patients with a mean age of 63-69 years and BMI of 29-36. A significant difference in weight loss of 6.1 kg (95% CI 4.7 to 7.6 kg; p,0.001) occurred in the intervention group compared to the control group. There was a non-significant weighted pooled effect size for pain of 0.2 (95% CI 0 to 0.39; p=0.05). Self-reported disability produced a weighted pooled ES of 0.23 (95% CI 0.04 to 0.42; p=0.02). [54]

Witham's systematic review found two studies, one which was included in Christensen's review of weight loss in patients with osteoarthritis. The additional study showed significant improvement in QoI in post-menopausal women as measured by the SF-36. [43]

Imayama et al. conducted a randomized trial of 439 overweight or obese post-menopausal women with a mean age of 58 years. After 12 months of diet, exercise, diet and exercise and control, the weight loss was 7.2, 2.0, and 8.9 kg, respectively compared to controls. Compared to controls, health-related QoL (HRQoL) assessed by the SF-36 improved in four of eight domains in the diet and exercise group and one domain (vitality) in the diet group; the exercise group showed no differences. [184]

Hope et al. analyzed HRQoL data from their previously conducted RCT of African-Americans aged 25-70 years with a BMI between 30 and 50 kg/m^2. Initially, 237 were enrolled in phase one that was 10 weeks of weight control counseling classes. One-hundred thirty-four (57%) completed this phase and 128 agreed to be randomized to phase two of which 87 completed one of three weight maintenance arms for an additional 8-18 months: continued group counseling classes, a self-help program facilitated by an outreach worker, or usual care. Of the eight domains accessed by the SF-36 HRQoL, only vitality and general health were improved with weight loss in phase one; in phase two, no domains were associated with weight change. Of note, in phase one, the median weight change was -1.27 kg and 13% of

participants lost at least 5% of their baseline body weight; in phase two, the median weight change was +0.36 kg and 11.5% lost at least 5% of their baseline body weight. [185]

Several studies have evaluated QoL outcomes in obese patients with sleep apnea who underwent weight loss interventions. Dixon et al. found at two years the surgery group, which lost a mean of 27.8 kg compared to the control group that lost a mean of 5.1 kg, had greater improvement in scores on the HRQoLSF-36 components of physical role, general health, vitality and the physical component summary. [50] Anandam's systematic review found one RCT that showed no change in QoL as measured by the SF-36 questionnaire at 24 months. [51] Thomasouli's meta-analysis on three studies showed no difference between intervention and control groups on weight changes or QoL. [52]

Bariatric surgery provided more consistent results in QoL. The recently published prospective controlled Utah study evaluated health outcomes to include QoL. [136] At six years, those receiving surgery with a mean weight loss of 27.7% of initial body weight had improvements in SF-36 physical component score and total QoL compared to the control group which did not have weight loss; SF-36 mental health component was not significantly different. O'Brien et al. conducted a RCT of 60 patients and the surgical group (laparoscopic adjustable gastric banding) compared to the control non-surgical group had improvements at two years on five of the eight domains of the SF 36. [133] Livingston et al. reported on the 11 studies evaluating the effect of bariatric surgery on QoL. [144] Improvements in QoL were consistent and were significant enough to outweigh surgical complications. Gastric bypass appears to give the greatest benefit though laparoscopic vs. open procedures did not differ significantly. A more recent Cochrane review reported that the Swedish Obesity Study had significant improvements compared to baseline and control at two years in all measures of QoL. However at 10 years, current health perception, social interaction, obesity-related problems, overall mood and depression no longer were significantly different compared to the control non-surgical group and the surgery group experienced significantly more anxiety. [132]

Wing et al. evaluated the effects of weight loss on urinary incontinence in overweight or obese women who suffered from 10 or more urinary incontinence episodes per week. Three-hundred thirty-eight women who received an intensive six month lifestyle program were randomized 2:1 to a 12 month weight maintenance interventional group or a structured education control group. Compared to those who gained weight, those who lost at least 5% of their body weight were more likely to achieve at least a 70% reduction in urinary incontinent episodes at 6, 12, and 18 months. [186]

In summary, QoL improvements are consistently reported following bariatric surgery, which routinely produces weight loss of >20% of baseline weight. However, long-term this benefit appears to diminish. Non-surgical interventions produce lesser degrees of weight loss and have variable results on various measures of QoL. Overall, there appears to be no significant improvement in QoL. However subgroups, particularly those with osteoarthritis, urinary incontinence or post-menopausal state may have some modest benefit.

Appendix F: Motivational Interviewing

If an assessment of the patient's motivation indicates that the patient is not ready to commit to recommended weight loss treatment, an intervention based on motivational interviewing may be considered. William Miller and Stephen Rollnick, the developers of motivational interviewing, describe motivational interviewing as "a collaborative conversational style for strengthening a person's own motivation and commitment for change." [59] See **Box F-1** for a list of the principles and core strategies of motivational interviewing.

Evidence for Effectiveness of Motivational Interviewing

There is now considerable evidence that using motivational interviewing increases the likelihood that a patient will follow through with treatment recommendations across a wide range of health behaviors. [59,61-65,68]

Box F-1: Principles and Core Strategies of Motivational Interviewing

1. Resist directing
2. Understand the patient's motivation
3. Listen with empathy
4. Empower the patient by building confidence
5. Ask open-ended questions to promote understanding and evoke change talk
6. Provide affirmations, reflections, and summaries to deepen understanding, build a therapeutic relationship and support motivation for change

A 2011 meta-analysis of 12 trials assessed the benefit of motivational interviewing as a component of weight loss interventions. In studies reporting body weight as an outcome, use of motivational interviewing was shown to significantly enhance weight loss, though the effect was small (1.47 kg greater than control treatments). In studies reporting change in body mass index (BMI), motivational interviewing produced greater, but non-significant, reduction in weight of 0.25 kg/m^2 over controls. [68] Among the studies reviewed, those that produced the greatest amount of weight loss employed motivational interviewing as an adjunct to group-based behavioral weight loss programs and in these studies, motivational interviewing appeared to improve adherence to the behavioral weight loss program. [68,187] However, the small number of studies included in this meta-analysis limits the generalizability of these conclusions. Only two studies investigated the impact of a single or a brief motivational interviewing intervention and this Work Group is unaware of any studies that show motivational interviewing leads to increased follow through after referral to a comprehensive lifestyle intervention for weight loss.

In a small observational study among primary care physicians and their obese patients, use of motivational interviewing-consistent behaviors (e.g., expression of empathy, a collaborative style) was associated with both increased confidence in improving nutrition and a greater likelihood of subsequent weight loss. [188,189]

Even when use of motivational interviewing skills does not produce a commitment to engage in treatment, their use may increase patient interest in participating in treatment in the future. For example, exploring the patient's reasons for losing weight may elicit "change talk," a harbinger of future change. [59] Exploration of barriers to change may identify opportunities for problem solving or elicit

interest in learning how to overcome barriers. Affirming the patient's interest in small steps toward change (e.g., learning about healthy eating, increasing physical activity) may lead to small changes that build confidence and motivation. Offering the opportunity to participate in weight loss interventions keeps the door open for future active engagement in treatment.

Motivational Interviewing Approaches and Strategies

Applying motivational interviewing has been described as a four element process: 1) engaging the patient, building a relationship and exploring the patient's motivation through open-ended questions (see below); 2) focusing on a specific area of concern (e.g., weight, physical inactivity) and sharing information about risk and benefits of change; 3) evoking "change talk" and "commitment language" to build motivation and guide the patient toward action; and 4) planning next steps. [59] Each process is associated with specific communication strategies and skills. For example, the key components of patient engagement include: open-ended questions about motivation; reflections; affirmations; and summaries. The four processes of motivational interviewing need not be sequential; rather, the clinician moves among the four processes based on the patient responses and flow.

When engaging, motivation may be explored through open-ended questions about a patient's current efforts to manage their weight, recent attempts to lose weight, the importance the patient places on weight loss, the reasons they might consider actively participating in weight management, and their level of confidence in undertaking weight loss. Examples of questions are shown below. Any one of these questions fosters engagement and understanding of the patient's motivation. These same questions may also be used for evoking change talk and commitment language.

- "What are you currently doing to manage your weight?"
- "On a scale from 0-10, with 10 being the extremely important and zero being not at all important, how important is weight loss to you?"
    - "What makes you say 'X' (patient's rating) and not a 'Y' (lower number)?"
    - "What would have to happen for you to rate importance as a 'Z' (higher number)?"
- "What are, or have been, your reasons for participating in a weight loss program?"
- "What helped you to be successful, or not, with weight loss in the past?"
- "What do you know about the benefits of weight loss as it relates to your condition(s)/symptom(s)?"
- "On a scale from 0-10, with 10 being the extremely confident, how confident are you that you can lose weight and keep it off?"
    - "What makes you say 'X' (patient's rating) and not a 'Y' (lower number)?"
    - "What would have to happen for you to rate confidence as a 'Z' (higher number)?"

Another core strategy of motivational interviewing is recognizing, reflecting and affirming any "change talk" or "commitment language" that is expressed by the patient, either in response to questions, or spontaneously. So, if the patient says, "It's very important for me to lose weight because I don't want to get diabetes like my mother. I need to be there for my kids," the clinician might respond, "So losing weight is pretty important to you. You want to avoid getting diabetes and be available to your family."

These types of reflections may stimulate even more change talk as well as commitment to change. If this happens, the clinician can offer an affirmation. "You have a good understanding of the risks of excess weight and sound committed to working on managing your weight."

As discussed in the Shared Decision-Making section of this guideline, it may be helpful to share information about the risks of overweight and obesity as well as the benefits of weight loss. Proponents of motivational interviewing suggest asking permission before sharing (e.g., "Would it be ok if I shared some information about how excess weight may be contributing to your high blood pressure?"). Asking permission to share information supports patient autonomy and promotes patient engagement. Patients rarely say no, and when they say yes, they may be more receptive to the information that is provided. When sharing information, consider addressing the "5 Rs," which are adapted from the US Public Health Service Treating Tobacco Use and Dependence guideline. [190]

The Five Rs are:

- Relevance: connection between overweight and current symptoms, disease, and medical history
- Risks: risks of continued overweight status, tailored to individual risk of developing obesity-associated conditions, or complications if obesity-associated conditions are present
- Rewards: potential benefits for losing excess weight to the patient's medical, functional and psychosocial well-being
- Roadblocks: share potential options, strategies and resources to address barriers to weight loss
- Repetition: repeat use of motivational interviewing at subsequent visits if motivation remains

Learning Motivational Interviewing

Learning motivational interviewing requires specific experiential skill-based training as well as post-training follow-up activities that provide opportunities to practice and apply skills. [191] Clinicians interested in learning more about motivational interviewing or enhancing their proficiency in the use of these skills may take advantage of training programs, resources and tools that are available in the Veterans Health Administration (VHA) and Department of Defense (DoD) . In the VHA, motivational interviewing training resources are available through the Employee Education System (EES). Clinicians may access EES-supported motivational interviewing training that has been tailored for primary care clinicians by contacting facility-based Health Behavior Coordinators. An online version of motivational interviewing training, "Brief Motivational Interviewing for Veterans" (TMS Course #VA 9123), is available at Veterans Affairs Learning University at: https://www.tms.va.gov/learning/user/login.jsp. This training features a video vignette demonstrating clinician use of effective motivational interviewing skills with an obese Veteran with diabetes. The following texts are also valuable resources:

- Miller, W. R., & Rollnick, S. (2013). *Motivational Interviewing: Helping People Change (Third Edition.* New York: The Guilford Press.
- Rollnick, S., Miller, W. R., & Butler, C. C. (2008). *Motivational Interviewing in Health Care: Helping Patients Change Behavior*. New York: The Guilford Press.
- Rosengren, D. B. (2009). *Building Motivational Interviewing Skills: A Practitioner Workbook*. New York: The Guilford Press.

Appendix G: Comprehensive Lifestyle Intervention and Behavioral Approaches

In this guideline, we define "comprehensive lifestyle interventions" for weight loss as interventions that combine three critical "lifestyle" components (i.e. dietary, physical activity and behavioral components) and provide at least 12 intervention sessions over a 12 month period. This definition is based on the 2011 Agency for Healthcare Research and Quality (AHRQ) evidence synthesis that found that "intensive" (i.e., 12 or more session in 12 months) "multicomponent behavioral interventions" were associated with significantly greater weight loss than less intensive interventions. [31,71] High intensity interventions (12 or more sessions) achieved a total weight loss of 4 to 7 kg in intervention groups compared to 1.5 to 4 kg of weight loss in less intensive interventions. [31,71] As noted in the discussion section of this guideline, the AHRQ evidence synthesis findings led to the 2012 U.S. Preventive Services Task Force (USPSTF) recommendation that patients with a body mass index (BMI) of 30 kg/m^2 or higher should be offered or referred to "intensive, multicomponent behavioral interventions." This recommendation received a B Grade, indicating that the USPSTF found there is high certainty that the net benefit is moderate. [26]

We have chosen to use the term "comprehensive lifestyle intervention" in our recommendations, rather than "intensive multicomponent behavioral intervention" (the term used by USPSTF), because the word "lifestyle" is more descriptive and suggests a central focus on dietary and physical activity behaviors. The term lifestyle was used to describe the Diabetes Prevention Program (DPP) weight loss intervention that has become a model for weight loss intervention program [46] and lifestyle is also used in other recent reviews of effective weight management interventions [73] as well as the American Heart Association/American College of Cardiology/The Obesity Society Guideline for the Management of Overweight and Obesity in Adults. [74]

The USPSTF recommendation specifies that "multicomponent behavioral interventions" (or comprehensive lifestyle intervention) include the following behavioral approaches: setting weight loss, diet and physical activity goals; addressing barriers to change; self-monitoring; and strategizing how to maintain lifestyle changes. [26] These interventions usually also feature other specific behavioral strategies that are derived from theory-driven behavior change research. These include stimulus control, problem solving, cognitive restructuring, behavioral approaches to slow down eating, and relapse prevention training. [72,73] For more details, see published treatment manuals, [192] the published description of the Diabetes Prevention Program, [46] or see the descriptions of specific behavioral strategies below. [192] Evidence also suggests that no single type of behavioral strategy is superior to the others and that use of multiple strategies is much more effective than one strategy alone. [9,31,73]

Studies published after the AHRQ systematic review provides additional evidence that comprehensive lifestyle interventions result in significant weight loss. A systematic review of 16 primary care based studies published between January 1999 and December 2011 found that high-intensity weight loss counseling (more than one session per month) delivered by primary-care physicians resulted in moderate, though not clinically significant, weight loss. [78] Studies that relied on physicians alone to

deliver the lifestyle intervention produced inconsistent results. Physician-delivered interventions that resulted in statistically significant weight loss included the use of a structured and tailored protocol to assist physicians with delivery of weight loss counseling and regular contact between patients and physicians. However, high-intensity weight loss counseling delivered by non-physicians, meal replacements delivered in conjunction with dietitian counseling, and referral to commercial weight loss center programs accompanied by regular monitoring by a primary-care physician were effective in producing clinically significant weight loss. [78] These results confirm the importance of intensity of the comprehensive lifestyle intervention as a determinant of weight loss outcomes in primary care settings and suggest that interventions that are delivered by non-physician interventionists (with primary care clinician follow-up and support) are more likely to lead to clinically significant weight loss than interventions delivered by physicians alone. [78] These findings, as well as findings from other reviews, also suggest that referral to evidence-based commercial programs can be used as a component of a primary-care supported comprehensive lifestyle intervention. [73]

Three recently completed high quality trials tested comprehensive lifestyle interventions delivered in primary care settings. [75-77] These trials were all funded by the National Heart, Lung, and Blood Institute as components of the Practice-based Opportunities for Weight Reduction (POWER) consortium. All of the active intervention arms across the three studies provided two years of intensive intervention (i.e., more than 12 intervention contacts during the first year) delivered by trained counselors/coaches either in-person in the primary care setting, via telephone, or via a web-based interface. All three studies reported that the intensive intervention arms (which included dietary, physical activity, behavioral and supportive components) produced significantly greater weight loss than usual care conditions. Two of the studies [76,77] also reported that intervention arms produced a significantly higher percentage of patients achieving greater than a 5% reduction in body weight after two years than control conditions (38% and 41% versus 19% [control] in the Appel trial; 35% versus 22% [control] in the Wadden trial). In the Wadden study, [77] one of the two active conditions also included a “tool-kit” that offered meal replacements, orlistat or sibutramine chosen by participants in consultation with their providers. This enhanced condition outperformed the counseling alone condition. In the Appel trial, [76] there was no significant difference in weight loss outcomes between the two intervention conditions, one of which provided in-person weight loss support; the other provided patients with weight loss support remotely, via telephone, website and e-mail. Two of the trials also demonstrated significant improvements in cardiovascular risk factors in intervention groups compared to controls. [75,77] Taken together, these three POWER trials demonstrate the effectiveness and impact of delivering intensive, though pragmatic, comprehensive lifestyle interventions in real-world primary care settings.

Specific Behavioral Strategies Featured in Comprehensive Lifestyle Interventions

Goal Setting involves setting realistic specific goals for behavior change. The goal includes the specific action to be taken and when, where, how, how long, and how often the individual will engage in that behavior. Writing down the goal and keeping a record of progress with self-monitoring helps the individual monitor progress toward goals that might be modified as goals are attained. Attaining goals motivates continued adherence to changing behaviors. An example of a behavioral goal for increased physical activity: “I will walk around the block for 20 minutes at a brisk pace every day at 11:30 A.M. If it

rains, I will do 20 minutes of low-impact aerobics in the living room." A goal for making healthier food choices: "I will eat at least three servings of fruit per day."

Self-monitoring is perhaps the most often employed and the most important, behavioral strategy. This involves recording all instances of the behaviors in question. For weight management purposes, individuals record all details of food intake, physical activity, and body weight on a daily basis. Record-keeping often includes information about times of day and associated thoughts, feelings, places and events that might affect food intake and physical activity. This record-keeping allows individuals to identify eating and physical activity patterns, cues, and measurement of actual food intake and physical activity. Awareness of these factors promotes the development of specific actions to address unhealthy behaviors.

Stimulus control *or* ***cue reduction*** strategies refer to efforts to change the environmental signals or cues for any specific behavior, in this case, eating and/or sedentary behaviors. Examples include removing unhealthy food from sight, eating only at the table rather than in the living room, not watching TV when eating, avoiding fast food restaurants, having healthy snacks immediately available, having walking shoes placed in a convenient spot where they will be noticed, and so on. The overall idea is to eliminate signals for inappropriate eating and substitute cues for helpful weight control behaviors in their place.

Positive reinforcement refers to the provision of rewards for desirable behavior.

Contingency management is establishing a defined schedule for the delivery of either rewards or punishments. Accordingly, a reward is delivered "contingent upon" completion of a specified behavior or performance of a desired behavior (e.g., staying within a certain caloric intake for a day or performing 30 minutes of exercise). Positive reinforcement is generally preferred over punishment to alter weight control behaviors, because people develop a positive association between desirable behaviors and receipt of reward. In this fashion, the desirable behavior eventually becomes self-rewarding.

Stress management is utilized in treatment of numerous conditions to reduce felt stress, because excess stress often stimulates inappropriate or self-defeating behavior. In weight control, excessive stress frequently leads to over-eating and/or failure to exercise. Stress management includes a wide variety of techniques such as relaxation training, biofeedback training, stimulus control, cognitive restructuring, social support, assertiveness training, problem solving, and skill training. Taken together, the patient becomes more resistant to becoming overly stressed and more capable of coping with and reducing felt stress when it is noticed.

Problem solving involves training the patient to more effectively analyze problems which might otherwise lead to inappropriate or self-defeating behavior such as over-eating. Once contributing factors are accurately analyzed, possible solutions are considered and evaluated for the pros, cons, and probable outcome of each solution and a workable solution is agreed upon.

Skill training refers to training a patient in those skills that are likely to enhance success. For example, weight control patients are taught skills in evaluating the caloric content of various foods and in planning ahead to avoid overly tempting eating situations. Patients might also be taught skills in eating

more slowly, cooking more healthfully, or refusing offers for second helpings or dessert from relatives or friends who might be pressuring them to overindulge.

Social support is widely acknowledged to facilitate almost every difficult behavior and to improve coping in troublesome situations. People receive encouragement, positive reinforcement, emotional empathy and support, and guidance from others. A comforting (and stress reducing) feeling of "not being alone" comes from being in the presence of others who are in the same difficult situation, as occurs in weight control groups, Alcoholics Anonymous, cancer support groups, and many others.

Cognitive therapy or "cognitive restructuring" is a process whereby individuals are taught to become fully aware of negative or self-defeating thoughts, to counteract those thoughts, and to then replace them with more realistic, adaptive, and positive thoughts. Those thoughts then stimulate more desirable behaviors. Negatively oriented, discouraging, self-defeating, over-reactive, and unrealistic thoughts mediate inappropriate and/or maladaptive behavior. People are frequently not fully aware of thoughts such as "I MUST clean my plate!", "I'll just DIE if I can't have that piece of cake!" or "Taking a walk is really going to HURT!" These thoughts often lead to engaging in undesirable behavior. Cognitive therapy can be used to identify and modify dysfunctional thoughts and attitudes about weight regulation.

Relapse-prevention training helps people respond productively to lapses in their efforts to adopt new behaviors or reduce and avoid maladaptive behaviors. Lapses are inevitable during efforts to change any health behavior. However, many people respond quite negatively to lapses and experience feelings of guilt or shame, as well as negative, self-defeating thoughts (such as "I am a failure!" or "I'll never be successful at managing my weight."). Relapse prevention approaches help people to reframe lapses as learning opportunities rather that failures and helps them to use cognitive restructuring to address negative thinking and problem solving strategies to both proactively and reactively plan ways of managing situations that lead to lapses. Role-playing and even "planned lapses" are used to help people practice adaptive responses to lapses.

Appendix H: Dietary Elements

For all the diets listed below, formal consultation with a registered dietitian is advised.

Low-Calorie Diets

The Academy of Nutrition and Dietetics (A.N.D) Evidence Analysis Library Adult Weight Management Guideline and the 2009 A.N.D Position Paper on Weight Management found strong evidence to support the statement, "An individualized reduced calorie diet is the basis of the dietary component of a comprehensive weight management program. Reducing dietary fat and/or carbohydrates is a practical way to create a caloric deficit of 500 to 1,000 kcal below estimated energy needs and should result in a weight loss of one to two pounds per week." [98]

Low-calorie diets (LCDs) recommend a minimum calorie intake (1,000-1,200 kcal per day for women; 1,200 to 1,600 kcal per day for men) combined with physical activity to produce a negative energy balance, typically an energy deficit of 500 - 1,000 kcal/day. This type of program offers a range of food choices which may improve compliance and enhance nutritional balance. [101,102]

Thirty-four randomized controlled trials (RCTs) reviewed by the National Heart, Lung, and Blood Institute (NHLBI) cited a mean weight loss of 8% over 3 to 12 months. [9] All of the studies showed LCDs can achieve weight loss.

Five studies published between 1988 and 1990 involving moderate caloric restriction over a period of 21 weeks were reviewed by Wadden et al. (1993) and found to have a weight loss of 8.5 kg. Follow-up at 53 weeks showed a mean weight loss of 5.6 kg. [193]

Leslie et al. (2002) compared an energy deficit diet of 800-1,800 kcal/day with a generalized low-calorie (GLC) diet of 1,500 kcal/day. The study included a 12 week weight loss period and a 12 week maintenance period. For participants who completed the 12 week period, the energy deficit group lost 4.3 kg and the GLC group lost 5 kg. Between 12 and 24 weeks, the overall weight gain was 0.9 kg for the energy deficit group and 1.4 kg for the GLC group. Following the maintenance phase, triglyceride levels remained significantly reduced and HDL levels were increased. [194]

McManus et al. (2001) compared a moderate-fat diet (35% of total calories) to a low-fat diet (20% of total calories), where dietary energy intake was limited to 1,200 kcal/day for women and 1,500 kcal/day for men, combined with behavioral modification and physical activity. At 18 months, the moderate-fat diet group had a weight loss of 4.1 kg (and 3.5 kg at 30 months) and the low-fat diet group had a weight gain of 2.9 kg. When only those adhering to the program were included in the analyses, the moderate-fat group had lost 4.8 kg at 12 and 18 months; the low-fat group had lost 5 kg at 12 months and 2.9 kg at 18 months. [195]

Four RCTs have also shown that the use of LCDs alone can lead to significant reductions in abdominal fat, as measured by waist circumference (WC). In reducing WC, LCDs may therefore lead to reductions in risk/severity of weight-related morbidity. [9]

Very-Low-Calorie Diets

The 2009 Academy of Nutrition and Dietetics (A.N.D.) Position Paper on Weight Management found Level I evidence to support the statements, “Adherence to a very-low-calorie diet (VLCD), defined as 800 kcal or 6 to 10 kcal/kg or less, results in significant weight loss…Adherence to a very-low-calorie diet results in lower calorie intake and therefore significantly greater initial weight loss than reduced-calorie diets." The A.N.D found significant weight loss during the initial period following a VLCD, but weight regain varies “based on differences in weight maintenance strategies.” [100]

VLCDs became popular in the 1970s and include, but are not limited to, the use of liquid formulas or Protein-Sparing Modified Fasts (PSMF) and may limit dietary intake to as little as 400-500 kcal/day. Programs in the 1970s, often labeled “liquid protein diets,” contained inadequate sources of protein, vitamins, minerals, and electrolytes and were reported to be linked to fatal dysrhythmias. Newer products are nutritionally complete and typically offer daily caloric intake levels of between 400 and 800 kcal/day.

A VLCD will result in substantial weight loss within 12-16 weeks. When put on such extreme restrictions of diet and combined with physical activities, the energy deficit is increased significantly and weight loss will occur. The PSMF is a specific form of a VLCD and is an aggressive means of losing weight. It includes no carbohydrates and has a daily protein allowance of high biologic value of 1.5 g/kg of ideal body weight. [196] In a non-randomized study of 150 patients, Hamdy showed that a short-term PSMF lasting eight weeks produced statistically significant improvements in glucose control and blood pressure. [197] However, any form of VLCD diet requires close follow-up and should only be used when high levels of monitoring by trained medical personnel are available. [74]

A meta-analysis of six randomized trials of VLCDs vs. LCDs found a weight loss at six months of 16.1 kg vs. 9.7 kg, respectively. [198] However, there was no statistically significant difference at one year following maximal weight loss. Similarly, Foster and colleagues and Rossner et al. showed that VLCDs between 400-600 kcal/day were no more effective than those allowing 800-1,000 kcal/day. [199,200]

It is a common belief that weight loss achieved at a slow rate is better preserved than if the weight is lost more rapidly. However, Astrup et al. suggest that initial weight loss is positively, not negatively, related to long-term weight maintenance. Analyzing 19 controlled trials of low-fat diets vs. moderate-fat diets lasting two to 12 months, they found evidence to support that a greater initial weight loss induced without changes in lifestyle (e.g., liquid formula diets or anorectic drugs) improves long-term weight maintenance when it is followed by a one to two year integrated weight maintenance program consisting of lifestyle interventions involving dietary change, behavioral therapy, and increased physical activity. According to this study, there is evidence to suggest that a greater initial weight loss as the first step of a weight management program may result in improved sustained weight maintenance. [201]

Most research maintains that participants of a structured weight loss program regain all of their weight loss within five years after the initial weight loss. A meta-analysis by Anderson et al. examined the long-term weight loss maintenance of individuals completing a structured weight loss program. Twenty nine

studies, all conducted in the US, included participants in a structured weight loss program and provided follow-up data for two years or more following the program. The data show that successful VLCDs were associated with significantly greater weight loss maintenance than were successful LCDs at all years of follow-up. The percentage of individuals at four or five years of follow-up for VLCDs and LCDs were 55.4% and 79.7%, respectively. Weight loss maintained at 4.5 years of follow-up was 7.1 kg (95% CI, 6.1, 8.1 kg) for the VLCD group and only 2.0 kg (95% CI, 1.5, 2.5 kg) for the LCD group; weight loss maintenance did not differ significantly between women and men. Six studies reported that groups who exercised more had significantly greater weight loss maintenance than did those who exercised less. The authors concluded that five years after completing a structured weight loss program, the average individual maintained a weight loss of >3 kg and a reduced weight of >3% of initial body weight. After VLCDs or weight loss of 20 kg or more, individuals maintained significantly more weight loss than after LCDs or weight losses of <10 kg. [202]

In conclusion, VLCDs may be useful to induce rapid weight loss and motivate obese patients in the early stages of a weight loss program. They should, however, be followed up with a maintenance program if the weight loss is to be sustained.

Low-Fat Diets

During the 1980s and 90s, low-fat diets were promoted by some as the key to weight loss producing a plethora of low-fat foods on the market. Many of these low-fat foods replaced the fat with carbohydrates. The focus of these diets is on the type of calories consumed. Individuals are encouraged to eat complex carbohydrate and high fiber foods (low-calorie density). [102] The Look AHEAD and Diabetes Prevention Program (DPP) trials both used low-fat diets as the cornerstone of their dietary therapy. [38,46] The Centers for Disease Control and Prevention (CDC) has launched the National Diabetes Prevention Program based on the Diabetes Prevention Program (http://www.cdc.gov/diabetes/prevention/index.htm).

A Cochrane review examined 12 RCTs, which varied in length from 6 to 18 months, and found fat restricted diets (providing up to 30% of total calories from fat) to be no better than calorie restricted diets in achieving long-term weight loss in people who are overweight or obese. There was also no significant difference in body mass index (BMI), percent body fat, or waist-to-hip ratio between the groups at 6, 12 and 18 months of follow-up. This review indicated that participants lost more weight on the control diets, but this difference was not statistically significant. [203]

In comparison, the NHLBI report (based on nine studies) states that restricting fat alone (20-30% of total calories from fat) helps promote weight loss by producing a reduced-calorie intake. Furthermore, restricting fat and overall calories together produces a greater weight loss. The authors concluded that there is little evidence that low-fat diets (per se) cause weight loss independent of other dietary energy reduction. [9] Therefore, reducing dietary fat as well as total calories is needed to promote weight loss.

In the meta-analysis by Astrup et al., a reduction in dietary energy from fat was significantly associated with a spontaneous weight loss of 3.2 kg more in the intervention group compared with the control group of overweight participants. Weight loss was dependent on the pretreatment bodyweight – the

heavier the participant, the greater the weight loss. However, no trials involving groups of subjects with a BMI greater than 30 kg/m^2 fulfilled the inclusion criteria, so the authors did not draw any conclusions for obese subjects. [201]

For those who would benefit from low-density lipoprotein (LDL) cholesterol lowering, the 2013 American Heart Association (AHA)/American College of Cardiology/The Obesity Society Guideline on Lifestyle Management to Reduce Cardiovascular Risk [74] recommends a diet consistent with that advocated by the Dietary Approaches to Stop Hypertension (DASH) Eating Plan, [204] the AHA Diet and Lifestyle Recommendations, [205] and the Dietary Guidelines for Americans. [206,207] As an example, the DASH diet for a 2,100 kcal eating plan includes 27% of total calories from fat, 6% from saturated fat, 18% from protein, 55% from carbohydrate, and 150 mg cholesterol per day. The DASH type diet lowered LDL-cholesterol by approximately 11%. [74] The Adult Treatment Panel III [208] and other groups [209,210] recommend the similar Therapeutic Lifestyle Changes (TLC) diet to reduce LDL cholesterol. Short-term controlled feeding studies have shown that the TLC-diet, which consists of less than 20% up to 30% of daily calories from fat, typically decreases total cholesterol and LDL-cholesterol by 7- 9% and 10-20%, respectively. Details of the TLC and DASH diets may be found in **Table H-3** and **Table H-4**.

A recent Cochrane systematic review suggested that it is the modification in dietary fat (i.e., replacement of saturated fat with unsaturated fat) or a reduction in dietary fat with modification of fat content which reduces cardiovascular risk. A reduction in dietary fat alone did not result in this benefit. [211] Direct comparisons between reduced and modified fat diets are lacking as are studies evaluating the types of fat useful to replace saturated fats.

As a low-fat diet is typically higher in carbohydrates, the effect on triglycerides and high-density lipoprotein (HDL) cholesterol is not as favorable. Medical history should be considered when choosing a suitable low-fat diet. See the VA/DoD Dyslipidemia Guideline[3] for a complete review of low-fat diet therapies.

Low-Carbohydrate Diets

Low-carbohydrate diets have become increasingly popular due to their purported rapid initial weight loss. The low-carbohydrate, high-protein diet, promoted extensively by Atkins and others, is one of the most popular weight loss approaches. [102] There is no consensus in the literature as to what level of carbohydrates per day constitutes a low-carbohydrate diet. A review of English language studies of high-protein, low-carbohydrate ketogenic diets published since 1966 showed wide variations in design, carbohydrate content (0-901 grams/day), total caloric content (525-4629 kcal/day), diet duration (4-365 days), and participant characteristics (e.g., baseline weight range, 57-217 kg). Despite this, there is fair evidence to suggest that short-term, low-carbohydrate diets (6 months or less) result in greater weight loss than conventional, reduced-calorie or low-fat diets (see discussion below). Low-carbohydrate diets, with carbohydrate intake between 20 and 40 grams of carbohydrates/day, will result in weight loss over a three to six month period.

[3] See VA/DoD Clinical Practice Guidelines – Management of Dyslipidemia (LIPIDS) http://www.healthquality.va.gov/lipids/

Low-carbohydrate diets are theoretically designed to promote ketosis, lipid oxidation, satiety, and increased energy expenditure with negative energy balance and weight loss as a result. [102,212-215] Opponents contend that there may be serious medical consequences of a low-carbohydrate diet with greatest risk in patients with cardiovascular disease, type 2 diabetes, dyslipidemia, or hypertension. The accumulation of ketones may affect insulin metabolism and liver and kidney function. Salt and water depletion may cause postural hypotension, fatigue, constipation, and nephrolithiasis. Additionally, too much animal protein and fat may promote hyperlipidemia, and renal function may be impaired. [213,216] It should be noted however, that many of these consequences are theoretical and have yet to be substantiated.

Low-carbohydrate diets compared to low-fat diets have been shown to result in greater weight loss at six months. [73] For example, Yancy et al. reported that a low-carbohydrate ketogenic diet program had better participant retention and greater weight loss compared with a low-fat diet, among 120 subjects that were overweight and hyperlipidemic. At 24 weeks, weight loss was greater in the low-carbohydrate diet group than in the low-fat diet group (mean change -12.9% vs. -6.7%; $P < 0.001$). [217]

Overall, the data for 12 months and longer is less supportive. A meta-analysis was performed on 1415 subjects from 13 studies evaluating very-low-carbohydrate ketogenic diets (VLCKD) with no more than 50 g carbohydrate per day vs. a low-fat diet (< 30% of energy from fat). The VLCKD compared to the low-fat diet had a greater decrease in body weight, albeit small (weighted mean difference of -0.91 kg) at 12 months. The mean weight loss in the VLCKD group was 5.2 kg. [97] Longer duration trials that compared low-carbohydrate diets with low-fat, calorie restricted diets have shown no difference in weight loss outcome after 12 months. [212,218,219] Hu et al. conducted a meta-analysis of 23 trials involving 2,788 participants and found that the change in body weight was not statistically significant after a follow-up of 6-24 months in the low-carb vs. low-fat groups (weight mean change of -6.1 vs. -5.0 kg, respectively). [96] Nordmann's meta-analysis of five trials involving 447 participants similarly showed that though weight loss was greater in the low-carbohydrate vs. low-fat at six months, this was not found after 12 months. [220] Wadden concluded that low-carbohydrate diets produce greater short-term weight loss than low-fat diets but this advantage is typically lost by one year. [73] An evidence analysis by The Academy of Nutrition and Dietetics came to the same conclusion. [216]

All of the above studies concluded that the weight loss observed in those following a low-carbohydrate diet was likely not due to the macronutrient composition of meals, but instead to a reduction in total caloric intake. Bravata further suggests that low-carbohydrate diets are safe, but concluded that no weight loss beyond that which would be expected by the amount of caloric reduction is provided, irrespective of how those calories were delivered. [213]

Brehm et al. attempted to answer some of these hypotheses. The study demonstrated that women consuming a low-carbohydrate diet lose more weight than women consuming a low-fat diet over several months. The more pronounced weight loss in the low-carbohydrate dieters is not explained by increased resting energy expenditure, thermic effect of food, or physical activity and cannot be accounted for by their reported energy intake. The difference between the low-fat and low-carbohydrate diets could not be explained by different energy intake. The authors stated at their conclusion "the major point is that

the principal means of voluntarily shifting energy balance to promote weight loss is restriction of intake and increase in expenditure. At present, the best methods for accomplishing these lifestyle changes for prolonged periods of time remain elusive." [221]

In terms of cardiovascular benefit, several meta-analyses show consistent results. The low-carbohydrate vs. low-fat group had short-term (generally 6-12 months) improvements in HDL-cholesterol and triglycerides and worsening in total cholesterol and LDL-cholesterol. [97,220-222] Diastolic blood pressure in the low-carbohydrate compared to the low-fat group was shown to be improved short-term in one meta-analysis, [97] but not others. [220,222] Systolic blood pressure was not different between the two groups. None of the studies showed improvement in glucose control with one diet compared to the other.

Low-Glycemic Index Diets

The concept of glycemic index was first proposed in 1981 as an assessment of a dietary carbohydrate's post-prandial effect on blood glucose. [223] The glycemic index is defined as the incremental area under the blood glucose response curve after consumption of 50 grams of available carbohydrate from a test food, divided by the area under the curve after consumption of 50 grams of carbohydrates from a reference food. [224] Weight loss associated with the glycemic index has been a studied component of some of the trials. Wadden's review of 3 studies lasting 12 months showed no weight loss benefit. [73]

The Academy of Nutrition and Dietetics (A.N.D) Evidence Analysis Library Adult Weight Management Guideline and the 2009 A.N.D. Position Paper on Weight Management found strong evidence to state, "A low glycemic index diet is not recommended for weight loss or weight maintenance as part of a comprehensive weight management program, since it is has not been shown to be effective in these areas." [98,100]

With regards to cardiovascular co-morbidity, a Cochrane Heart Group review concluded that there is little evidence to recommend a low-glycemic index diet for the purpose of improving cardiovascular risk factors. [225]

Low-Energy Density Diets

Energy density is defined as the amount of energy (calories) in a given weight of food (grams). The aim of this diet is to meet or stay below an energy intake goal per day. Foods that are low in energy density contain fewer calories and allow the participant to consume a greater amount of food (in grams); foods high in energy density contain more calories and require the consumption of less food. [226,227] Carbohydrates and proteins contain 4 kcal/gram; fat contains 9 kcal/gram. Fat content is directly related to energy density; water content is inversely related although neither relationship is perfect in that all foods with the same energy density do not have the same fat and water content. Fiber content is also a factor. [227] Foods that are higher in energy density are also likely to be more palatable. [226] There is limited, short-term, evidence of the effectiveness of low-energy density diets. [227] Low-energy-density

diets can be successfully applied since they help lower calorie intake without reducing food volume and help individuals avoid feeling hungry and deprived.

Mediterranean Diets

Since the release of the 2006 guideline, the Mediterranean diet has emerged as a popular diet. This diet encourages a higher intake of unsaturated fats such as olive oil and increased servings of fruits, vegetables and whole grains. Shai et al. randomized 322 obese participants with a mean age of 52 years and mean BMI of 31 kg/m^2 to low-fat restricted calorie (LF-R), Mediterranean restricted calorie (MED-R) or low-carbohydrate non-restricted calorie (LC-NR) diet for two years. [228] The mean weight loss in the LF-R, MED-R, and LC-NR groups were 3.3 kg, 4.6 kg, and 5.5 kg, respectively. The MED-R and LC-NR lost significantly more weight than the LF-R group. All groups decreased in waist circumference and blood pressure but there were no between group differences. HDL cholesterol, triglycerides, and ratio of total cholesterol to HDL cholesterol improved the most in the LC-NR group. LDL cholesterol did not change significantly within groups. For the 36 participants with diabetes, only those in the MED-R group had a decrease in fasting plasma glucose levels (-32.8 mg/dl) while the other two groups had an increase. However, the A1C decreased more in the LC-NR group (-0.9%) than in the LF-R (0.4%) and MED-R (0.5%) groups. Overall, the Mediterranean diet was better than the low-fat diet but not as good as the low-carbohydrate diet.

Another study evaluated the occurrence of primary cardiovascular outcomes in 7447 participants without but at high risk for cardiovascular disease into one of three diets: Mediterranean diet supplemented with extra-virgin olive oil (MED-O), Mediterranean diet supplemented with mixed nuts (MED-N), and a control group that received advice to reduce dietary fat. [229] The approximate mean age and BMI was 67 years and 30 kg/m^2, respectively. After interim analysis, the trial was stopped after a mean follow-up of 4.8 years. The hazard ratio for myocardial infarction, stroke, or cardiovascular death was 0.70 and 0.72 in the MED-O and MED-N groups, respectively compared to the control group.

Meal Replacement

Commercial meal replacements (MR) have become increasingly popular as a strategy among people trying to lose weight and have emerged as one of the most cost-effective self-help tools for weight loss and maintenance. [230-232] Fifteen percent of women and thirteen percent of men reportedly use MRs as their weight loss strategy, suggesting that they can easily be incorporated into the lifestyle of the participant. [233]

Heymsfield and colleagues conducted the first systematic evaluation of RCTs using MR plans for long-term weight management and found that MRs safely and effectively produce significant sustainable weight loss and improve weight-related risk factors of disease. [234]

Flechtner-Mors et al. showed that structured meal plans, which provide good nutrition and portion control for one or two meals a day, improve risk factors for metabolic syndrome and help patients make

healthy food choices, including increased consumption of fruits and vegetables. [235] MRs are also safe and effective for weight management in patients with type 2 diabetes.

Intake of two meal replacements per day (e.g., pre-packaged energy bars, drinks or shakes) and a sensible third meal (e.g., steamed vegetables, grilled chicken and fresh fruit) produce weight loss; one MR per day, combined with sensible eating, enables weight maintenance. Improved outcomes were seen among those who satisfied between meal hunger with snacks that included fruits, vegetables, or a meal replacement bar. In general, those who added frequent water intake and exercise to their daily regimens had greater short and long-term success. [234]

In one study, two-thirds of 252 patients chose to use MRs at least once daily. [236] After six months, weight loss was 8.62 ± 1.81 kg for women and 7.03 ± 3.72 kg for men. Participants of another study found the MR strategy convenient to use and provided manageable dining out options. [233] Management of and compliance on the diet, therefore, was good, supporting the notion that MRs offer an effective alternate strategy for long-term dieting.

In an RCT by Kreider et al., obese women were randomly assigned to one of two lifestyle approaches. During the initial phase of the trial, women were assigned to either:

- A meal replacement program (MRP) where they participated in the Special K Challenge program, which included advice on how to reduce dietary energy intake and participation in an exercise program; or
- A structured diet and exercise program (SDE) where they participated in the Curves diet program followed by a 9-week diet plan and a supervised Curves exercise program three days/week

During the maintenance phase, participants in the MRP condition continued the Special K Challenge program, met with a registered dietitian every two weeks and were encouraged to increase physical activity. Those in the SDE program continued the Curves diet program and were instructed to follow a 2,100 kcal/day weight maintenance plan. SDE participants also met with a registered dietitian every two weeks to discuss diet compliance and engaged in a supervised Curves exercise program three days/week. [237]

Participants in the SDE group averaged 62 minutes more vigorous physical activity per week than the MRP group ($p = 0.004$). Participants in the SDE group also lost significantly more weight than the MRP group after 10, 14, 22 and 34 weeks of dieting and training ($p = 0.001$). SDE participants also loss significantly more fat mass at all maintenance time points ($p = 0.01$), as well as centimeters from the hips (all $p = 0.001$). BMI also decreased to a greater degree in the SDE group at all maintenance time points (all $p < 0.05$).

The A.N.D Evidence Analysis Library Adult Weight Management Guideline and the 2009 A.N.D. Position Paper on Weight Management found strong evidence to recommend with the following caveats that "people who have difficulty with self-selection and/or portion control, [may consider] meal replacements (e.g. liquid meals, meal bars, or calorie-controlled packaged meals)…as part of the diet

component of a comprehensive weight management program. Substituting one or two daily meals or snacks with meal replacements is a successful weight loss and weight maintenance strategy." [98,100]

Commercial Diet Programs

The imperative for effective weight loss methods has stimulated the promotion of numerous alternative diet plans, most of which are based on some modification of macronutrient content (i.e., low-carbohydrate and high-carbohydrate diets).

Dansinger et al. compared the relative merits of four of the most popular weight loss diets. [238] These included the Atkins (carbohydrate restriction), Ornish (fat restriction), Weight Watchers (calorie and portion size restriction), and Zone (high-glycemic-load carbohydrate restriction and increased protein) diets. In the year-long study, 160 people that were overweight and obese were randomly assigned to one of these four regimens. All participants were generally healthy but had at least one additional major risk factor for heart disease, such as high blood pressure, elevated blood cholesterol, increased blood sugar levels, or diabetes. Findings after one year were that weight loss among participants averaged 4.7 to 7 lbs. On average, participants on the Atkins plan lost 4.6 lbs, participants on the Weight Watchers plan lost 6.6 lbs, participants on the Zone plan lost 7.1 lbs, and participants on the Ornish plan lost 7.3 lbs. One year adherence was 53%, 65%, 65%, and 50% for the Atkins, Weight Watchers, Zone and Ornish plans, respectively. Approximately half of the patients on Atkins and Ornish and 35% of those on Zone and Weight Watchers dropped out before the one year mark. The researchers concluded that the strongest predictor of weight loss was not the type of diet, but compliance with the diet plan that was given to subjects. Dietary adherence, as opposed to diet composition, appears to be the most important factor in short-term weight loss for obese individuals subscribing to a diet program for weight reduction. [238]

Tsai et al. reviewed 1,500 weight loss studies of adults in an effort to describe the components, costs, and efficacy of the major commercial and organized self-help weight loss programs in the United States. [239] Using those studies, plus additional data supplied by the programs themselves, this systematic review examined nine plans: Weight Watchers, Jenny Craig, L.A. Weight Loss and eDiets.com; the self-help groups Take Off Pounds Sensibly (TOPS) and Overeaters Anonymous (OA); and three medically supervised commercial programs, Optifast, Health Management Resources, and Medifast/Take Shape for Life.

With the exception of one trial with Weight Watchers, in which participants lost 5.3% at one year and 3.2% at 2 years compared to the control group which lost 1.5% and 0%, respectively, the evidence to support the use of the major commercial and self-help weight loss programs is modest or nonexistent. Commercial interventions available over the Internet and organized self-help programs produced minimal weight loss. The authors' conclusion was that additional controlled trials are needed to assess the efficacy and cost-effectiveness of these interventions. However, "practitioners can support patients' participation in commercial or organized self-help programs by reviewing changes in weight and health complications at office visits and by monitoring patients' efforts to improve their eating and activity habits." [239]

Wadden et al. reviewed six RCTs that evaluated Jenny Craig, Nutrisystem, and Weight Watchers. [73] Two trials that evaluated Jenny Craig showed a mean weight loss compared to control group at 6 and 12 months of 7.2 kg and 7.3 kg vs. 0.3 kg and 0.7 kg, respectively. One trial evaluated Nutrisystem whereby one group received Nutrisystem plus behavioral treatment for 24 weeks while the second group received diabetes support and education for 12 weeks followed by Nutrisystem plus behavioral treatment for the final 12 weeks. The weight loss for the group receiving Nutrisystem for the entire 24 weeks was -7.1% and -9.7% at 12 and 24 weeks, respectively. Weight loss for the group receiving Nutrisystem only during the final 12 weeks was -0.4% and -5.3% at 12 and 24 weeks, respectively. For Weight Watchers, a more recent trial was evaluated that was not included in Tsai's review. In the largest RCT involving 772 participants, those in the Weight Watchers group vs. usual care lost 4.06 kg vs. 1.77 kg, respectively at 12 months. The conclusion was that commercial weight loss programs may be a viable option for those "who cannot obtain traditional lifestyle modification in community settings or academic medical centers." [73] Access however could be limited by cost.

Supplemental Tables

Table H-1: Popular Diet Programs

Type of diet	Program
High-fat Low-carbohydrate	Atkins Diet ™ South Beach ™ Sugar Busters ® The Carbohydrate Addict's Diet ® Protein Power
High-protein Moderate-carbohydrate	Zone Diet ®
Moderate-fat Balanced nutrient Low-calorie	Jenny Craig Nutri-Systems ® Weight-Watchers ® LA Weight Loss ® Mediterranean Diet
Very low-calorie	Medifast ® Optifast ®
Meal replacements	SlimFast ™
Low-fat Very low-fat	Dean Ornish Program Pritikin Program ™

Table H-2: Low-Calorie Diet – General Guideline [9]

Nutrient	Recommended Intake
Calories	To achieve and maintain desired weight
Total Fat	30% or less of total calories
Saturated Fat	7 – 10% of total calories
Polyunsaturated Fat	Up to 10% of total calories
Monounsaturated Fat	Up to 15% of total calories
Cholesterol	Less than 300 mg/day
Protein	Approximately 15% of total calories
Carbohydrate	55% or more of total calories

Nutrient	Recommended Intake
Sodium Chloride	No more than 100 mmol/day (approximately 2.4 grams of sodium or 6 grams of sodium chloride)
Calcium	1,000 – 1,500 mg/day
Fiber	20 – 30 grams/day

Table H-3: Nutrient Composition of the Therapeutic Lifestyle Changes (TLC) Diet [9]

Nutrient	Recommended Intake
Saturated Fat*	Less than 7% of total calories
Polyunsaturated Fat	Up to 10% of total calories
Monounsaturated Fat	Up to 20% of total calories
Total Fat	25 – 35% of total calories
Carbohydrate**	50 – 60% of total calories
Fiber	20 – 30 grams/day
Protein	Approximately 15% of total calories
Cholesterol	Less than 200 mg/day
Total calories (energy)***	Balance dietary energy intake and expenditure to maintain desirable body weight/prevent weight gain

* Trans fatty acids are another low-density lipoprotein cholesterol-raising fat that should be kept as a low intake.
** Carbohydrate should be derived predominantly from foods rich in complex carbohydrates including grains, especially whole grains, fruits, and vegetables.
*** Daily calorie expenditure should include at least moderate physical activity (contributing approximately 200 kcal per day).

Table H-4: Nutrient Composition of the Dietary Approaches to Stop Hypertension (DASH) Diet [204]

Nutrient	Recommended Intake
Saturated Fat	6% of total calories
Total Fat	27% of total calories
Carbohydrate	55% of total calories
Fiber	30 grams/day
Protein	18% of total calories
Cholesterol	150 mg/day
Total calories (energy)*	Balance dietary energy intake and expenditure to maintain desirable body weight/prevent weight gain.

*Daily calorie expenditure should include at least 30 minutes of moderate physical activity/day. To avoid weight gain, the total should be approximately 60 minutes per day.

Table H-5: Grain Group [240,241]

1 Grain serving = 80 calories, 15 grams carbohydrate, 0-1 grams fat

Nutrient	Recommended Intake
Breads	**Serving Size**
Bread: White, Whole wheat, Pumpernickel, Rye	1
Bread, reduced-calorie	2
White, Whole Wheat Pita, reduced-calorie	½
Tortilla, corn or flour (6 inch across)	1
Bagel, 4 oz	¼
English Muffin	½
Hamburger or hot dog bun	½
Cereals, Grains and Pasta	
Bran cereals (concentrated)	⅓ cup
Bran cereals (flaked)	½ cup
Cereal, unsweetened, ready to eat	¾ cup
Cereal, sugar frosted, ready to eat	½ cup
Cereal (cooked)	½ cup
Rice, white or brown (cooked)	⅓ cup
Grits	½ cup
Pasta, white, whole wheat (cooked)	½ cup
Noodles, egg (cooked)	½ cup
Couscous (cooked)	1/2cup
Crackers and Snacks	
Popcorn (plain)	3 cups
Animal crackers	8
Pretzels, thin	12
Saltines	6
Whole wheat crackers, no fat added	2-5 (¾ oz)
Graham crackers, squares	3

** Choose high fiber starchy foods whenever possible.*

Table H-6: Vegetable Group [240,241]

Non-starchy vegetable list

1 Vegetable serving = 25 calories, 5 grams carbohydrate, 0 grams fat

1/2 cup cooked vegetables or vegetable juice

1 cup raw vegetables

Nutrient	Recommended Intake
Artichoke	Mixed vegetables (without corn, peas, pasta)
Artichoke hearts	Mushrooms
Asparagus	Okra
Beans (green, waxed, Italian)	Onions
Bean sprouts	Pea pods
Beets	Peppers (all types)
Broccoli	Radishes
Brussels Sprouts	Rutabaga
Cabbage	Salad greens
Carrots	Spinach
Cauliflower	Summer squash

Nutrient	Recommended Intake
Celery	Tomato
Cucumber	Tomato or vegetable juice
Eggplant	Turnips
Green onions or scallions	Water chestnuts
Greens (collard, kale, mustard, turnip)	Watercress
Kohlrabi	Zucchini
Leeks	

Starchy vegetable list

1 Vegetable serving = 80 calories, 15 grams carbohydrate, 0-1 gram fat

Nutrient	Recommended Intake
	Serving Size
Corn	½ cup
Corn on cob (6 inch)	½ (3 inch portion)
Dried beans, peas and lentils cooked	½ cup
Miso	3 Tbsp
Mixed vegetables (with corn, peas)	1 cup
Potato, baked, boiled (medium)	½ or ½ cup
Potato, mashed	½ cup
Sweet potato, yam	½ cup
Squash: winter (acorn, butternut)	1 cup

Table H-7: Oil Group [240,241]

1 Oil serving = 45 calories, 5 grams fat

Nutrition	Recommended Intake
***Monounsaturated Fats**	**Serving Size**
Avocado	2 tablespoons (Tbsp)
Oil (canola, olive, peanut)	1 teaspoon (tsp)
Nuts (almonds, cashews)	6 nuts
Nut Butters: almond, cashew, peanut	½ Tbsp
Olives, black	8 large
Polyunsaturated Fats	
Mayonnaise, reduced fat	1 Tbsp
Nuts, walnuts	4 halves
Oil: corn, flaxseed, safflower, soybean, sunflower	1 tsp
Salad dressing, regular	1 Tbsp
Salad dressing, reduced fat	2 Tbsp
****Saturated Fats**	
Butter, stick	1 tsp
Bacon	1 slice
Coconut, shredded	2 Tbsp
Cream cheese, regular	1 Tbsp
Cream cheese, reduced fat	1½ Tbsp
Oil: coconut, palm, palm kernel	1 tsp
Sour cream, regular	2 Tbsp
Sour cream, reduced fat	3 Tbsp

**Beneficial, heart healthy fats, however, use in moderation.*
***Limit as often as possible.*

Table H-8: Fruit Group [240,241]
1 Fruit serving = 60 calories, 15 grams carbohydrate, 0 grams fat

Nutrition	Recommended Intake
Fresh, frozen, no sugar added fruit	**Serving Size**
Apple	1
Applesauce	½ cup
Apricots	4
Banana (9 inch)	½
Blackberries, raw	¾ cup
Blueberries, raw	¾ cup
Cherries, raw	12
Cantaloupe (5 inch diameter)	⅓ melon
Fruit cocktail	½ cup
Grapefruit, medium	½
Grapes	15
Honeydew melon	⅛ melon
Kiwi	1
Mandarin Oranges, canned	¾ cup
Mango, small	½
Nectarine, small	1
Orange, small	½
Papaya	1 cup1
Peach, medium, fresh	½
Pear, large, fresh	½ cup
Pears, canned	⅓ cup
Pineapple, canned	¾ cup
Pineapple, fresh	2
Plum (2 inch diameter)	1 cup
Raspberries, raw	1 cup
Strawberries, raw	2
Tangerine, small	1¼ cup
Watermelon	
Avoid canned fruits packed in heavy syrup	
Dried fruit	
Apples	4 rings
Apricots	7 halves
Dates	2½
Figs	1½
Prunes	3 medium
Raisins	1 Tbsp
Fruit Juice	
Apple, grapefruit, orange, pineapple	½ cup (4 oz)
Cranberry, grape, prune.	⅓ cup

Table H-9: Dairy Group [240,241]

1 Dairy serving = 12 grams carbohydrate, 8 grams protein

Nutrition	Recommended Intake
Fat free/Low-fat Milk: 90 calories, 0-3 grams fat/serving	**Serving Size**
Milk (skim, or 1%)	1 cup
Evaporated milk, canned	½ cup
Buttermilk (skim or low-fat)	1 cup
Soy milk, (fat free or low-fat)	1 cup
Yogurt (fat free plain, low-fat flavored with nonnutritive sweetener and fructose)	1 cup (varies)
Non-dairy creamer	½ cup
Frozen yogurt (fat free or skim)	
Reduced Fat Milk: 120 calories, 5 grams fat/serving	
2 % milk	1 cup
Soy milk	1 cup
Yogurt, low-fat	1 cup
Cheese: Low-fat/fat free: 35 calories, 7 grams Protein, 0 grams Carbohydrate, 0-1 gram fat	
Cheese, fat free	1 oz
Cottage cheese, low-fat/fat free	¼ cup
Cheese: reduced fat: 55 calories, 7 grams Protein, 0 grams Carbohydrate, 3 grams fat	
Cheese	< 3 grams fat per ounce
Cottage cheese, 4.5%	¼ cup
Cheese: Medium Fat: 75 calories, 7 grams Protein, 0 grams Carbohydrate, 5 grams fat	
Feta, mozzarella, reduced-fat cheeses, string	<5 grams fat per ounce
Ricotta cheese	¼ cup
Cheese: High Fat: 100 calories, 7 grams Protein, 0 grams Carbohydrate, ≥8 grams fat	
American, Bleu, brie, cheddar, hard goat, monterey jack, queso and swiss	1 oz

Table H-10: Protein Group [240,241]

1 Protein serving = 0 grams carbohydrate, 7 grams protein;

1 oz unless otherwise stated

Nutrition
Very Lean Meats: 35 calories, 0-1 grams fat/serving
Chicken, turkey, white meat, no skin
Fish – fresh or frozen
Shellfish – clams, oysters, shrimp, squid, scallops, octopus, lobster
Tuna – canned in water (rinse to remove sodium)
Egg substitutes (¼ cup)
Beans, peas, lentils (cooked) - (contains 15 grams carbohydrate (½ cup)

Nutrition
Lean Meats: 55 calories, 3 grams fat/serving Chicken, turkey – dark meat, no skin Lean beef – round, sirloin, flank steak Lean pork – tenderloin, ham Low-fat luncheon meats with < 3 grams fat/serving) Salmon, tuna canned in oil
Medium Fat Meats: 75 calories, 5 grams fat/serving Beef, most cuts, prime cuts, short ribs Pork, chop, top loin Chicken, turkey (dark meat, with skin) Fried fish Egg Tempeh (¼ cup) Tofu (4 oz or ½ cup) Choose very lean and lean meats more often than medium fat meats.

Appendix I: Physical Activity and Exercise: Intensity and Duration

Table I-1: Examples of Moderate* Amounts of Activity [9]

Washing and waxing a car for 45-60 minutes	**Less Vigorous, More Time****
Washing windows or floors for 45-60 minutes	↓
Playing volleyball for 45 minutes	
Playing touch football for 30-45 minutes	
Gardening for 30-45 minutes	
Wheeling self in wheel-chair for 30-40 minutes	
Walking 1¾ miles in 35 minutes (20 min/mile)	
Basketball (shooting baskets) for 30 minutes	
Bicycling 5 miles in 30 minutes	
Dancing fast (social) for 30 minutes	
Pushing a stroller 1½ miles in 30 minutes	
Raking leaves for 30 minutes	
Walking 2 miles in 30 minutes (15 min/mile)	
Water aerobics for 30 minutes	
Swimming laps for 20 minutes	
Wheelchair basketball for 20 minutes	
Basketball (playing a game) for 15-20 minutes	
Bicycling 4 miles in 15 minutes	
Jumping rope for 15 minutes	
Running 1½ miles in 15 minutes (10 min/mile)	
Shoveling snow for 15 minutes	
Stair walking for 15 minutes	**More vigorous, less time**
*A moderate amount of physical activity is roughly equivalent to physical activity that uses approximately 150 calories of dietary energy per day or 1,000 calories per week. **Some activities can be performed at various intensities; the suggested durations correspond to expected intensity of effort.	

Table I-2: Duration of Various Activities to Expend 150 kcal for an Average 70 kg (154 lbs) Adult [103]

Intensity	Activity	Approximate Duration (in minutes)
Moderate	Volleyball, noncompetitive	43
Moderate	Walking, moderate pace (3 mph, 20 min/mile)	37
Moderate	Walking, brisk pace (4 mph, 15 min/mile)	32
Moderate	Table tennis	32
Moderate	Raking leaves	32
Moderate	Social dancing	29
Moderate	Lawn mowing (powered push mower)	29
Hard	Jogging (5 mph, 12 min/mile)	18
Hard	Field hockey	16
Very Hard	Running (6 mph, 10 min/mile)	13

Appendix J: Pharmacotherapy

Orlistat

Pharmacology

Orlistat is an irreversible inhibitor of pancreatic and gastric lipases. Inhibition of these enzymes prevents the hydrolysis of dietary fat (in the form of triglycerides) into absorbable free fatty acids. As a result, undigested triglycerides are eliminated in the feces.

Efficacy for acute weight loss

Two systematic reviews of 15 trials found that orlistat modestly increased weight loss compared with placebo in obese patients without obesity-associated conditions and obese adults with diabetes, dyslipidemia, or hypertension. [130,131] Mean differences in weight loss for orlistat-treated patients compared to placebo-treated patients were 2.9 kg and 3.4 kg after one year or longer. Weight loss was greater with 120 mg three times a day than 60 mg three times a day. The percentage of patients taking orlistat 120 mg three times a day losing ≥5% and ≥10% of their baseline body weight after one year ranged from 35% to 73% compared to 14% to 41% taking placebo. In each trial, each treatment group received identical life style intervention programs. An Agency for Healthcare Research and Quality (AHRQ) meta-analysis of 12 randomized control trials (RCTs) reported that after 12 months, patients taking orlistat lost an average of three pounds more than those taking placebo. The average percent change in body weight with orlistat was 8% compared to 5% with placebo in this study. [31]

Efficacy in weight maintenance

Four orlistat weight loss trials included a continuation phase to assess weight maintenance. A total of 1,159 patients entered these continuation phases. All four studies included an orlistat 120 mg three times a day treatment arm (three of the four studies also included 60 mg three times a day treatment arms). In two studies patients were re-randomized to placebo or orlistat for the maintenance phase and patients in the other two studies continued on their previously assigned treatment. Diets either remained unaltered or were increased by 200-300 kcal/day for those aiming to continue to lose weight. In all four studies, weight regain during the maintenance phase was similar for the orlistat and placebo groups, preserving the weight differential observed after the weight loss phase. [130,131]

Effect on secondary outcomes and obesity-associated conditions

There is no direct evidence that orlistat reduces cardiovascular morbidity or mortality. Orlistat has been shown to improve cardiovascular risk factors in some clinical trials, although the clinical significance of these changes is unclear and may vary for each patient. [130,131] Orlistat produced statistically significant improvements in glycemic control, cholesterol, and blood pressure; however, the clinical significance of these changes in cardiovascular risk factors may be small (see **Table J-1**). One RCT found that orlistat treatment for four years increased weight loss and significantly reduced the incidence of type 2 diabetes in patients with impaired glucose tolerance at baseline. [124]

Table J-1: Differences between Orlistat and Placebo in Secondary Obesity-Associated Conditions

Outcome	Number of studies (n)	Weighted Mean Difference or Risk Difference (orlistat – placebo)	95% Confidence Interval
Waist Cir., cm	9 (4631)	-2.06	-2.86, -1.26
SBP, mm Hg	13 (6965)	-1.52	-2.19, -0.86
DBP, mm Hg	12 (8322)	-1.38	-2.03, -0.74
Fasting glucose, mmol/L	5 (1678)	-1.03	-1.49, -0.57
Hemoglobin A_{1C}, %	5 (1678)	-0.38	-0.59, -0.18
TG,mmol/L	11 (4456)	-0.03	-0.12, 0.07
Tot. Chol., mmol.L	13 (5206)	-0.32	-0.37, -0.28
LDL Chol., mmol/L	13 (5206)	-0.26	-0.30, -0.22
HDL Chol., mmol.L	11 (4152)	-0.03	-0.04, -0.02
Adapted from Rucker et al. [131]			

Adverse effects

Orlistat treatment is associated with an increase in gastrointestinal compliant including diarrhea, flatulence, oily spotting, and bloating/abdominal pain/dyspepsia reported by 15% to 30% of patients. [131] Patients prescribed orlistat are instructed not to consume more than 30% of their daily calories from fat and their dietary fat intake is to be divided equally between their three meals in order to minimize their risk for gastrointestinal adverse events.

Drug interactions

The absorption of fat soluble vitamins has been shown to be reduced with orlistat and may be a significant adverse effect for some patients. Patients should take a daily multivitamin that contains vitamins A, D, E, K, and beta carotene. Orlistat may reduce the absorption of levothyroxine, cyclosporine, warfarin and anticonvulsants. Orlistat dosing should be separated from levothyroxine by four hours and from cyclosporine by three hours. Monitoring of the appropriate parameters is recommended. (Xenical Package Label, 2013)

Phentermine/Topiramate Extended-Release

Pharmacology

A combination product of phentermine and topiramate extended-release (P/T ER) is commercially available; only the topiramate component is extended release.

Phentermine is a sympathomimetic amine similar in activity to amphetamine with anorectic or anorexigenic properties. Phentermine thus reduces appetite and decreases food intake through mediation of catecholamine release in the hypothalamus. Other metabolic effects may be involved in the impact on appetite and food intake.

Topiramate's mechanism of action for weight management is unknown. The appetite suppression and satiety enhancement characteristic of topiramate may be due to one or a combination of several effects

including augmentation of gamma-aminobutryate, modulation of voltage-gated ion channels, inhibition of AMPA/kainite excitatory glutamate receptors, or inhibition of carbonic anhydrase.

Efficacy for acute weight loss

Evidence of the efficacy of P/T ER was established by two 56-week RCTs comparing P/T plus a standard lifestyle program to placebo plus a standard lifestyle program. [128,129] The EQUIP trial enrolled patients with a body mass index (BMI) >35. Participants had a mean body weight of 115 kg to 118.5 kg and a mean BMI of 42. After a 4-week washout period, 1267 participants were randomized to placebo, P/T ER in daily doses of 3.75 mg/23 mg or 15 mg/92 mg. The CONQUER trial enrolled patients with a BMI of 27 to 45 plus at least two weight-related comorbidities. A total of 2487 patients with a mean body weight of 103 kg and BMI of 36.6 were randomized to daily placebo, P/T ER 7.5/46 or P/T ER 15/92. The primary outcome results from each trial using an intention-to-treat with last observation carried forward analysis are shown in **Table J-2**. In both trials, a higher proportion of subjects assigned to P/T ER realized a weight loss >5%. P/T ER combined with a standard lifestyle program resulted in weight loss deemed a substantial net benefit.

Table J-2: Results 52-Week Post-Randomization EQUIP and CONQUER [128,129]

	EQUIP			CONQUER		
Outcome	Placebo	P3.75/T23	P15/T92	Placebo	P7.5/T46	P15/T92
% Completing	53.0	61.0	66.4	57.0	69.0	64.0
Mean % weight loss BBW*	1.6	5.1	10.9	1.2	7.8	8.6
≥5% loss BBW*	12.3	44.9	66.7	21.0	62.0	70.0
≥10% loss BBW*	7.4	18.8	47.2	7.0	37.0	48.0
≥15% loss BBW*	3.4	7.3	32.3	NA	NA	NA
Mean weight loss	NA	NA	NA	1.4	8.1	10.2

*BBW = baseline body weight; NA = not available

Efficacy in weight maintenance

The one year extension trial of CONQUER was the SEQUEL trial. [163] Participants were eligible if they had been compliant with the CONQUER protocol and their study site was selected. Site selection was based on enrollment and retention rates; 36 of the 93 sites were invited to participate. The 676 participants remained in their original treatment assignment. The mean percent change in weight and actual weight after 108 weeks was -1.8% and -2.1 kg with placebo, -9.3% and -9.6 kg with P/T ER 7.5/46, and -10.5% and -10.9 kg with P/T ER 15/92, respectively. The proportion of participants who lost >5%, >10%, and >20% were 30%, 11.5%, and 2.2% in the placebo arm; 75.2%, 50.3%, and 9.2% in the P/T ER 7.5/46; and 79.3%, 53.9%, and 15.3% in the P/T ER 15/92 arm, respectively. All comparisons between active treatment and placebo were statistically significant. These findings support the continuation of P/T ER as part of a weight maintenance regimen.

Effect on secondary outcomes and obesity-associated conditions

All secondary outcomes and obesity-associated conditions with the exception of fasting blood glucose in EQUIP and CONQUER improved significantly in the P/T ER groups compared to placebo (**Table J-3**). An analysis of participants in CONQUER with dyslipidemia and/or hypertension found the changes in lipids and blood pressure were not significant between the groups when adjusted for weight loss. A greater proportion of patients assigned to P/T ER had improvements in their lipids and blood pressure due to greater weight loss occurring in more patients. [164] Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) improved significantly in all three treatment arms by the end of SEQUEL except the change in SBP in the placebo arm. These changes were not significant between the three treatment arms. The percent of subjects with a net change in antihypertensive medications decreased in both P/T ER groups and increased in the placebo group. Similar net changes in lipid lowering and diabetes medications were reported. In CONQUER pre-diabetics assigned to P/T ER 15/92 had a lower risk of developing diabetes compared to placebo.

Table J-3: Changes in Secondary Obesity-Associated Conditions: EQUIP and CONQUER [128,129]

Outcome	EQUIP			CONQUER		
	Placebo	P3.75/T23	P15/T92	Placebo	P7.5/T46	P15/T92
Waist circumference, cm	-3.1 (-4.0, -2.2)	-5.6 (-6.8, -4.3)	-10.9 (-11.8, -10.0)	-2.4	-7.6	-9.2
SBP, mm Hg	0.9 (-0.2, 2.1)	-1.8 (-3.4, -0.3)	-2.9 (-4.0, -1.8)	-2.4	-4.7	-5.6
DBP, mm Hg	0.4 (-0.40, 1.2)	-0.1 (-1.2, 1.0)	-1.5 (-2.4, -0.6)	-2.7	-3.4	-3.8
Fasting glucose, mg/dL	1.9 (1.0, 2.9)	0.8 (-0.5, 2.1)	-0.6 (-1.5, 0.4)	-2.3	-0.1	-1.3
Triglycerides, %	9.1 (4.7, 13.5)	5.2 (-2.4, 12.6)	-5.2 (-9.6, -0.8)	4.7	-8.6	-10.6
Cholesterol (chol), %	-3.5 (-4.7, -2.2)	-5.4 (-7.1, -3.7)	-6.0 (-7.3, -4.8)	-3.3	-4.9	-6.3
Low-density lipoprotein chol, %	-5.5 (-7.4, -3.7)	-7.7 (-10.3, -5.2)	-8.4 (-10, -6.5)	-4.1	-3.7	-6.9
High-density lipoprotein chol, %	0 (-1.6, 1.6)	0.5 (-1.7, 2.7)	3.5 (1.9, 5.1)	+1.2	+5.2	+6.8

*Mean change (95% confidence intervals)

Adverse effects

Serious adverse events were reported by 2.5% of subjects in each treatment group in EQUIP. One serious drug-related adverse drug event was reported in each of the P/T ER groups and two in the placebo arm. Serious adverse events in CONQUER were reported in 4%, 3%, and 5% of subjects assigned to placebo, P7.5/T46 ER and P15/T92 ER, respectively.

Adverse effects that were prevalent 1.5 times in the P/T ER treatment groups compared to placebo were paresthesia, dizziness, dysgeusia, insomnia, constipation and dry mouth. Other adverse effects to monitor for include an increase in heart rate, attention difficulty, and decreases in serum bicarbonate or potassium concentrations. Topiramate is associated with oral cleft abnormalities. The use of P/T ER is

contraindicated during pregnancy (FDA Category X). P/T ER is subject to a Risk Evaluation Mitigation Strategy (REMS) program. (See **Table J-6**)

Drug interactions

- Monoamine oxidase inhibitors – phentermine is contraindicated during or within 14-days following administration of an MAOI
- Oral contraceptives – a reduction in contraceptive efficacy is not anticipated but irregular bleeding (spotting) may be more frequent
- Antiepileptic drugs:
    - Phenytoin and carbamazepine decrease topiramate concentrations by 48% and 40%, respectively
    - Valproic acid in combination with topiramate has been associated with hyperammonemia with or without encephalopathy and hypothermia
    - Carbonic anhydrase inhibitors – increased severity of metabolic acidosis and increased risk of kidney stone formation
    - Central Nervous System (CNS) depressants including alcohol – concomitant use may increase sedation and other adverse effects
    - Non-potassium sparing diuretics – may potentiate potassium loss

Lorcaserin

Pharmacology

Lorcaserin is a selective agonist of serotonin 2_c (5-HT2_C) receptors. Lorcaserin's selectivity for the 5-HT2_C receptor is ~15-times and ~100-times greater than it is for 5-HT2_A and 5-HT2_B receptors, respectively. Drugs such as fenfluramine were nonselective and also activated 5-HT2_B receptors which are highly expressed in cardiac valvular tissue resulting in serious cardiac side effects and being subsequently pulled from the market. Further, activation of 5-HT2_A receptors can induce hallucinations.

In contrast, 5-HT2_C receptors are predominantly expressed in the CNS in the choroid plexus, prefrontal cortex, hippocampus, basal ganglia and are associated with control of mood, cognition and appetite although lorcaserin's exact mechanism of action to decrease food consumption and promote satiety is unknown. It is hypothesized that it does so by acting as an agonist on 5-HT2_C receptors in hypothalamic melanocortin system. Lorcaserin may also have an active role in regulating glucose tolerance and hepatic insulin sensitivity.

Efficacy for acute weight loss

Lorcaserin's efficacy was established in the three phase three trials: Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM), BLOOM-DM (diabetes mellitus), and Behavioral Modification and Lorcaserin Second Study for Obese Management (BLOSSOM). [125-127] The BLOOM trial enrolled patients with a BMI of 30-45 kg/m^2 or 27-45 kg/m^2 plus at least one weight-related comorbid condition; BLOOM-DM enrolled patients with type 2 diabetes, a HbA1c of 7%-10%,

and a BMI of 27-45 kg/m^2; and BLOSSOM enrolled patients with a BMI of 30-45 kg/m^2 or 27-29.9 kg/m^2 plus at least one weight-related comorbidity. All three trials used a randomized, placebo-controlled, parallel-group design and lasted at least one year. All participants received lifestyle modifications including moderate exercise and dietary instructions to reduce caloric intake plus placebo or lorcaserin. After one year patients assigned to lorcaserin 20 mg per day achieved greater weight loss than those assigned to placebo **(Table J-4)**.

Table J-4: Efficacy of Lorcaserin [125-127]

Outcomes MITT-LOCF*	BLOOM		BLOOM-DM		BLOSSOM	
	Placebo	Lorcaserin	Placebo	Lorcaserin	Placebo	Lorcaserin
% Completing	45.1	55.4	62.1	66.0	52.0	57.2
Mean % weight loss BBW**	2.2	5.8	1.5	4.5	2.8	5.8
≥5% loss BBW**	20.3	47.5	16.1	37.5	25.0	47.2
≥10% loss BBW**	7.7	22.6	4.4	16.3	9.7	22.6
Mean weight loss	2.2	5.8	1.6	4.7	2.9	5.8

**MITT-LOCF = Modified Intention to Treat - Last Observation Carried Forward*
***BBW = baseline body weight*

Efficacy in weight maintenance

Support for lorcaserin's role in maintaining weight loss is derived from the BLOOM study which included a second year with a primary endpoint of the proportion of patients who achieved ≥5% weight loss after the first year and maintained this reduction during the second year. At the start of the second year subjects initially assigned to lorcaserin were re-randomized to lorcaserin or placebo, while those originally assigned to placebo continued placebo. At the end of the second year, 50.3% of subjects assigned to placebo in year 2-only maintained their 5% weight loss compared to 67.9% taking lorcaserin years one and two.

Effect on secondary outcomes and obesity-associated conditions

The changes in secondary outcome measures and obesity-associated conditions in BLOOM, BLOOM-DM and BLOSSOM are shown in **Table J-5**. [125-127] In BLOOM, after one year subjects receiving lorcaserin demonstrated nearly twice the reduction in waist circumference than placebo, p<0.001. Changes in SBP and DBP were significant. Total cholesterol declined in the lorcaserin group and increased in the placebo group, p<.001. Low-density lipoprotein (LDL) cholesterol increased in both groups, but significantly more in the placebo group. Triglycerides declined in both groups, p<0.001. Significant improvements (p<0.001) favoring lorcaserin were noted in fasting glucose, fasting insulin (-3.33 uU/mL vs. -1.28 uU/mL), homeostasis model assessment of insulin resistance (HOMA-IR, -0.41 vs. -0.17) and A1C (-0.04% vs. 0.03%). Significant improvements in high-sensitivity C-reactive protein and fibrinogen also favored lorcaserin. The change in IWQOL-LITE® (Impact of Weight on Quality of Life-Lite questionnaire, 0-100,

with higher scores indicating a better quality of life) score favored lorcaserin (12.4 vs. 10.7, p<0.001). [125]

The secondary outcome measures in BLOOM-DM focused on lorcaserin's effect on glycemic control. Changes from baseline in glycemic measures demonstrate both lorcaserin treatment arms improved significantly compared to placebo in fasting glucose, A1C, and in the proportion of subjects achieving a A1C <7% or <6.5% at one year. HOMA-IR was significantly improved with the lorcaserin 20 mg/day. The same measures (excluding an A1C <6.5and HOMA-IR data not provided) improved significantly among subjects whose baseline A1C was <9%. Among subjects whose baseline A1C was >9%, only the change in fasting glucose between lorcaserin 20 mg/day and placebo was significant. BMI, waist and hip circumference, and heart rate were significantly reduced in both lorcaserin groups compared to placebo. High-density lipoprotein (HDL) cholesterol increased with lorcaserin 20 mg/day. Changes in SBP, DBP, and triglycerides were not significant. Only subjects taking lorcaserin 10 mg/day reported a significant improvement in IWQOL-Lite® score. [126]

Of the secondary outcome measures in BLOSSOM only changes in waist circumference, HDL cholesterol, and quality of life were significantly different for both doses of lorcaserin compared to placebo. SBP and DBP were reduced and heart rate declined ~1-2 bpm in each of the three treatment arms. The proportion of subjects who were able to decrease their net use of medications to treat or avoid increases in mediations to treat dyslipidemia favored lorcaserin 10 mg twice a day compared with placebo. More patients assigned to lorcaserin 10 mg twice a day were able to reduce their antihypertensive medications than those assigned to placebo. [127]

Table J-5: Changes in Secondary Obesity-Associated Conditions: BLOOM, BLOOM-DM, BLOSSOM [125-127]

Outcome, Mean LS Change (95% CI)	BLOOM		BLOOM-DM		BLOSSOM	
	Placebo	Lorcaserin	Placebo	Lorcaserin	Placebo	Lorcaserin
Waist circumference, cm	-3.9	-6.8	-3.3	-5.5	-4.1	-6.3
SBP, mm Hg	-0.8	-1.4	-0.9	-0.8	-1.2	-1.9
DBP, mm Hg	-0.6	-1.1	-0.7	-1.1	-1.4	-1.9
Fasting glucose, mg/dL	1.1	-0.8	-11.9	-27.4	NA	NA
Triglycerides, %	-0.14	-6.15	-4.8	-10.7	-0.9	-4.3
Cholesterol, %	0.57	-0.9	-0.1	-0.7	0.0	-0.7
LDL cholesterol, %	4.03	2.87	5.0	4.2	1.7	0.3
HDL cholesterol, %	-0.21	0.05	1.6	5.2	1.3	3.7

Adverse effects

Gastrointestinal disorders such as nausea, diarrhea, constipation and dry mouth were more common with lorcaserin 20 mg per day than with placebo. Fatigue, headache, and dizziness were other

complaints more common with lorcaserin 20 mg. The use of lorcaserin is contraindicated during pregnancy (FDA Category X).

Drug interactions

The use of selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI) was excluded in clinical trials with lorcaserin because of the theoretical risk for serotonin syndrome. In addition, there are no studies on the safety or efficacy of combining lorcaserin with other weight loss drugs such as phentermine, topiramate or orlistat. Lorcaserin should be used with caution with drugs that are cytochrome P450 (CYP) 2D6 substrates.

Table J-6: Recommended Dosage for Select Obesity Pharmacotherapies

Drug	Usual Dosage Range	Comments
Orlistat	120 mg three times daily	• Taken with or within 1 hour of each meal containing fat • Omit dose if a meal is skipped or a meal contains no fat • Must take once daily multivitamin (containing fat soluble vitamins A, D, E and K) at least 2 hours prior to orlistat **Cautions** • Increased gastrointestinal events (adverse effects) when orlistat is taken with diet high in fat (greater than 30% total daily calories from fat) • Orlistat is FDA Category X and is contraindicated for use during pregnancy • It is not known if orlistat is secreted in human breast milk. Orlistat should not be taken by mothers who are nursing. **Drug Interactions** • Cyclosporine's whole blood concentrations may be reduced (possibly resulting in a decrease in the immunosuppressive action of cyclosporine; monitor and adjust as necessary). Take cyclosporine 2 hours before or after orlistat. More frequent monitoring of cyclosporine levels should be considered. • May decrease absorption of some fat soluble vitamins (A, D, E, and K). Levels of vitamin D and beta-carotene may be low in obese patients compared with non-obese subjects. The supplement should be taken 2 hours before or after orlistat. • Patients taking warfarin should be monitored closely and warfarin dose adjusted accordingly. • Levothyroxine: monitor for changes in thyroid function • Anticonvulsant efficacy may be affected; monitor for changes in seizure frequency or severity.
Phentermine / topiramate	Phentermine 7.5 mg / topiramate 46 mg each morning; maximum dose 15	**Dose Titration** • One phentermine 3.75 mg/topiramate 23 mg extended-release capsule in each morning for 14 days; then increase to 7.5 mg/46 mg each morning for an additional 12 weeks. • If a weight loss of 3% of baseline body weight is not achieved increase the dose to 11.25 mg/69 mg each morning for 14 days; then increased

Drug	Usual Dosage Range	Comments
	mg/92 mg each morning.	to 15 mg/92 mg (maximum dose) daily. • If after 12 weeks on 15 mg/92 mg the patient has not lost at least 5% of baseline body weight, discontinue phentermine/topiramate, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment • The 3.25 mg/23 mg and 11.25 mg/69 mg formulations are for titration purposes only • Discontinue use of phentermine 15 mg/topiramate 92 mg gradually by taking a dose every other day for at least 1 week prior to stopping the medication altogether, due to the possibility of precipitating a seizure **Dose in Patients with Renal Impairment** • The dose for patients with an estimated creatinine clearance using the Cockcroft-Gault equation of <50 ml/min (moderate to severe renal impairment) should not exceed 7.5 mg/46 mg once daily • Phentermine/topiramate has not been studied in patients with end-stage renal disease on dialysis and should be avoided in this patient population **Doses in Patients with Hepatic Impairment** • A dose adjustment is not necessary in patients with mild hepatic impairment (Child-Pugh score 5-6) • The dose for patients with moderate hepatic impairment (Child-Pugh 7-9) should not exceed 7.5 mg/46 mg once daily • Phentermine/topiramate has not been studied in patients with severe hepatic impairment (Child-Pugh 10-15) and should be avoided in this patient population **Adverse Effects** • Paresthesia • Dizziness • Insomnia • Constipation • Dry mouth • Increased heart rate • CNS – loss of attention and concentration, memory, and word finding difficulties **Monitoring:** • Weight • Blood pressure (orthostatic) and/or signs/symptoms of hypotension in patients taking antihypertensives or other medications that can lower blood pressure • Resting heart rate • Serum bicarbonate, especially if patient is taking another carbonic anhydrase inhibitor • Serum potassium, especially if patient is taking another carbonic anhydrase inhibitor • Glucose and/or signs/symptoms of hypoglycemia in patients with diabetes • Mood (symptoms of depression) and sleep disorders

Drug	Usual Dosage Range	Comments
		• Pregnancy tests in women of reproductive potential • The prescribing information for phentermine/topiramate states under Warnings and Precautions that "*women of reproductive potential obtain a negative pregnancy test before treatment and monthly thereafter and that they use effective contraception*." The Healthcare Provider Counseling Tool for Females of Reproductive Potential provided by the REMS program states "*pregnancy testing is recommended before initiating treatment with Qsymia and monthly during treatment" and that the provider "Advise patients to undergo pregnancy testing before starting treatment with Qsymia and monthly thereafter. Discuss with patients whether pregnancy testing should be performed in the office or with a home pregnancy test".* **Contraindications** • Pregnancy - FDA Category X. Contraindicated because weight loss is not beneficial during pregnancy and may result in fetal harm. Topiramate is associated with cranial-facial fetal abnormalities. **Risk Evaluation and Mitigation Strategy (REMS)** • Phentermine/topiramate is subject to a REMS program to inform prescribers and female patients of the reproductive risks. See product label for additional information. Glaucoma – secondary angle closure. • Hyperthyroidism • Monoamine oxidase inhibitor (MAOI) use – concurrent or within 14 days **Warnings and Precautions** • Increased heart rate – the phentermine/topiramate combination can cause an increase in resting heart rate. The clinical significance of the increase is unclear, especially in patients with cardiovascular or cerebrovascular disease. The combination has not been studied in patients with recent or unstable cardiac or cerebrovascular disease and use is not recommended in these patients. • Suicidal behavior and ideation – because the combination includes topiramate, an antiepileptic drug, this warning has been extended to the combination product. • Acute myopia and secondary angle closure glaucoma • Mood and sleep disorders – see Adverse Events for additional information • Cognitive impairment – patients should exercise caution when operating hazardous machinery • Metabolic acidosis – hyperchloremic, non-anion gap, metabolic acidosis has been reported. Reduce the dose or discontinue if metabolic acidosis is persistent. Use with caution in patients taking a carbonic anhydrase inhibitor. • Elevation in creatinine – if persistent, either discontinue or reduce the dose • Potential hypoglycemia in type 2 diabetics on anti-diabetic therapy – weight loss may increase the risk of hypoglycemia necessitating a

Drug	Usual Dosage Range	Comments

		decrease in the dose of anti-diabetic medications
		• Potential hypotension in patients treated with antihypertensive medication – weight loss may result in a reduction in blood pressure and possibly hypotension necessitating a decrease in the dose of antihypertensive medications
		• CNS depression with concomitant CNS depressants including alcohol
		• Potential seizures with abrupt withdrawal of topiramate – regardless of seizure history. It is recommended that patients taking the 15 mg/92 mg dose have their dose tapered prior to discontinuation
		• Patients with renal impairment – adjust dose based on estimated creatinine clearance. See Dosage and Administration
		• Patients with hepatic impairment – adjust dose for patients with moderate hepatic impairment. See Dosage and Administration
		• Kidney stones – topiramate has been associated with kidney stone formation. Concurrent use of other drugs that inhibit carbonic anhydrase or a ketogenic diet may increase the risk
		• Oligohydrosis and hyperthermia – has been reported with the use of topiramate. Caution patients to monitor for this adverse effect
		• Hypokalemia – inhibition of carbonic anhydrase or use of a non-potassium sparing diuretics may increase risk
		Drug-Drug Interactions
		• MAIO – phentermine is contraindicated during or within 14-days following administration of an MAOI
		• Oral contraceptives – a 16% reduction in AUC of ethinyl estradiol and a 22% increased AUC of norethindrone were reported. A reduction in contraceptive efficacy is not anticipated but irregular bleeding (spotting) may be more frequent.
		• Antiepileptic drugs
		  • Phenytoin and carbamazepine decrease topiramate concentrations by 48% and 40%, respectively
		  • Valproic acid in combination with topiramate has been associated with hyperammonemia with or without encephalopathy and hypothermia
		  • Carbonic anhydrase inhibitors – increased severity of metabolic acidosis and increased risk of kidney stone formation
		  • CNS depressants including alcohol – concomitant use may increase sedation and other adverse effects
		  • Non-potassium sparing diuretics – may potentiate potassium loss

Lorcaserin	10 mg twice a day	**Dosage and Administration** • One 10 mg tablet by mouth twice a day without regard to meals • Discontinue if 5% weight loss is not achieved by week 12 as it is unlikely that a meaningful weight loss will be achieved and sustained with continued treatment **Dose in Patients with Renal Impairment** • Dose adjustment is not required in mild renal impairment. • Lorcaserin should be used with caution in patients with moderate

Drug	Usual Dosage Range	Comments
		renal impairment • Use is not recommended in patients with severe renal impairment or end stage renal disease **Doses in Patients with Hepatic Impairment** • No dose adjustment is required for patients with mild (Child-Pugh score 5-6) to moderate (Child-Pugh score 7-9) hepatic impairment • Lorcaserin has not been studied in patients with severe hepatic impairment and should be used with caution in such patients **Adverse Effects (common)** • Nausea, diarrhea, constipation, dry mouth, vomiting • Fatigue • Headache • Dizziness **Monitoring:** • Weight • Blood pressure (orthostatic) and/or signs/symptoms of hypotension in patients taking antihypertensives or other medications that can lower blood pressure • Pregnancy tests in women of child-bearing potential as deemed necessary by provider and patient • Glucose and/or signs/symptoms of hypoglycemia in patients with diabetes • Signs and symptoms of valvulopathy • Signs and symptoms of depression, suicidal thought or behavior, cognitive impairment, or changes in mood **Contraindications** • Pregnancy – FDA Category X. Contraindicated because weight loss is not beneficial during pregnancy and may result in fetal harm. **Warnings and Precautions** • Serotonin syndrome or neuroleptic malignant syndrome-like reactions are theoretically possible since lorcaserin is a serotonergic drug. Concomitant use with a serotonergic or anti-dopaminergic drug or MAOI has not been studied. Extreme caution is advised if lorcaserin is combined with these types of drugs. • Valvular heart disease, regurgitant, primarily affecting the mitral and/or aortic valves has been reported with other agonists of 5-HT_{2B} receptors. Lorcaserin has demonstrated selectivity for 5-HT_{2C} receptors. Lorcaserin has not been studied in patients with congestive heart failure and should be used with caution. Combining lorcaserin with other serotonergic and dopaminergic drugs that are potent 5-HT_{2B} agonists and are known to increase the risk for cardiac valvulopathy (e.g., cabergoline). • Cognitive impairment in the form of impaired attention and memory, confusion, somnolence and fatigue has been reported. Patients should be cautioned when operating machinery and driving until they are know who lorcaserin affects them. • Psychiatric disorder reactions including euphoria, hallucinations and

Drug	Usual Dosage Range	Comments
		dissociation were observed following supratherapeutic doses of lorcaserin. Patients should be monitored for signs of the emergence or worsening of depression including suicidal thoughts or behavior. • Potential risk of hypoglycemia in patients with type 2 diabetes on anti-diabetic therapy**.** Hypoglycemia was been reported following weight loss in type 2 diabetic patients taking lorcaserin. Adjustment in a patient's diabetes medication may be needed to avoid hypoglycemia. • Priapism is a potential effect of 5-HT2C receptor agonists. Use with caution in patients who have conditions that predispose them to priapism or patients taking a phosphodiesterase type 5 inhibitor. • Heart rate decrease was noted to be greater in patients treated with lorcaserin than placebo in clinical trials. Use with caution in patients with bradycardia or a history of heart block greater than first degree. • Hematological changes including decrease in red and white blood cells were reported in clinical trials • Prolactin elevation – lorcaserin moderately elevates prolactin concentrations. Patients who develop signs or symptoms of excess prolactin should have their prolactin concentrations measured. • Pulmonary hypertension has been associated with other centrally-acting weight loss serotonergic drugs. Due to the low incidence of this disease, the clinical trial experience with lorcaserin is deemed inadequate to determine whether exposure increases the risk for pulmonary hypertension. **Drug-Drug Interactions** • Use of SSRIs and SNRIs was excluded in clinical trials because of theoretical risk for serotonin syndrome • There are no studies on the safety or efficacy of combining lorcaserin with other weight loss drugs such as phentermine, topiramate or orlistat • Use with caution with drugs that are CYP 2D6 substrates whose exposure can be increased
For complete drug information, review the manufacture's prescribing information: Xenical, 1999, revised September 2, 2005 and January 2012; QSYMIA, July 2012, revised April 2013; and BELVIQ June 2012.		

Off-label Pharmacotherapy

Several drugs have been used off-label as long-term treatment for weight loss. [242,243] Below is a list of some of these medications.

Topiramate (Monotherapy)

Weight loss was noted as a side effect when topiramate was used to treat epilepsy. A mean of 3.9 kg is lost at three months and 5.9 kg at 1 year although the amount of weight loss tends to be greater in those with a higher BMI. Studies which have identified greater weight loss with increasing dose have reported a ceiling effect at a dose of 192 mg/day. [244]

A meta-analysis that included 3320 obese patients from 10 studies (19 treatment arms) comparing topiramate (64 mg – 400 mg/day as a weight loss agent) to placebo over periods of 16 to 60 weeks found the mean weight loss experienced by patients taking topiramate was 5.34 kg (95% CI, -6.12 to -4.56 kg) greater than with placebo. The amount of weight lost was a function of both dosage and duration of exposure. Topiramate's effect on A1C was included in four trials: patients with diabetes had a mean reduction in A1C of -0.43% (-0.57 to -0.25%). Safety data were available for 6620 patients. The risk of study withdrawal due to an adverse event was greater for topiramate treated patients (OR 1.95, 95% CI, 1.64-2.29) and was associated with higher dosage. This same dose-related pattern was observed with the other common adverse events including paresthesias, taste perversion, psychomotor impairment, hypoesthesia, difficulty concentrating, anorexia, memory impairment and nervousness. [245]

Metformin

Modest weight loss has been well-documented with the use of metformin when used to treat patients with diabetes, pre-diabetes, metabolic syndrome, and polycystic ovarian syndrome. [46,246-250] It has also been shown to cause weight loss in non-diabetic patients with antipsychotic-induced weight gain. [251] In diabetic patients, reductions have persisted for ten years or more and the most important influence on both weight loss and maintenance is adherence to metformin therapy. [252] There is insufficient evidence for the use of metformin for weight loss in patients without the aforementioned conditions. [253] Metformin is generally safe, though the risk of lactic acidosis (boxed warning) must be considered, particularly in patients with dehydration, renal insufficiency or those receiving acute loads of intravenous contrast media for radiologic procedures. Approximately 10% of patients will experience gastrointestinal side effects.

Glucagon-Like Peptide-1 Receptor Agonists *(exenatide, liraglutide)*

A Cochrane review of 17 randomized controlled trials involving 6899 participants and typically lasting 26 weeks showed weight loss of 2.87 kg and 3.24 kg for exenatide and liraglutide, respectively in patients with type 2 diabetes. [254] Nausea is common and tends to subside with continuation of therapy. For both these agents, the risk of inducing pancreatitis is a concern as well as a boxed warning of thyroid tumors. A new drug application for liraglutide as a chronic weight loss medication has been submitted to the Food and Drug Administration (FDA).

Bupropion

Bupropion, as monotherapy, has been noted to cause weight loss when used in patients with depression or those seeking to abstain from tobacco.[255] In three studies, [256-258] patients taking daily bupropion 300-400 mg combined with naltrexone lost around 5 kg more than those taking placebo. A new drug application for the combination of naltrexone sustained release (SR)/bupropion SR has been submitted to the FDA for approval as a weight loss drug. Bupropion has a black box warning for suicidality and is contraindicated in patients with a seizure disorder, bulimia, or anorexia.

Amphetamines/Stimulants *(mixed amphetamine salts, lisdexamfetamine, methylphenidate, others)*

Weight loss in children prescribed stimulants is considered a treatment-limiting adverse event. No studies have been published with weight loss as a desired outcome in obese adults. All of these medications have concerns and/or boxed warnings for abuse/dependence and cardiovascular/central nervous system side effects.

Testosterone Replacement Therapy

Testosterone replacement therapy has been advocated to achieve weight loss in hypogonadal obese men. [259] However, two systematic reviews showed that while lean body mass increased, there was no difference in body weight vs. placebo. [260,261] Similarly, testosterone supplementation in eugonadal men (total testosterone 350-400 ng/dL or higher) leads to no improvement in weight loss).

Human Chorionic Gonadotropin

Human chorionic gonadatropin (HCG) has no role in weight loss therapy, is ineffective and has serious safety concerns. A meta-analysis published in 1995 reviewed the use of intramuscular HCG in 24 studies to include 14 randomized controlled trials. [262] The authors concluded that HCG was no more effective than placebo or diet alone for weight loss, fat-redistribution, or sense of well-being. Since 1995, there have been no further trials evaluating intramuscular HCG. To date, there are no studies demonstrating efficacy of HCG drops, pellets, and lozenges or HCG injections (in the absence of severe calorie restriction) over placebo or alternate therapy. Serious adverse events, to include deep vein thrombosis and pulmonary embolism have been reported. [263]

Cyanocobalamin (Vitamin B-12)

Vitamin B-12 has a very limited role in promoting weight loss. Based on theoretical extrapolation of the actions of vitamin B-12 at the cellular level, it is sometimes used to promote weight loss. There are no studies evaluating weight loss with Vitamin B-12 injections, tablets, sublingual pills, or drinks. Conversely, B-12 deficiency has been associated with weight loss, particularly after bariatric surgical procedures. [264] No weight loss should be anticipated as a result of the use of exogenous vitamin B-12. Risks of injection might be anticipated if that route is chosen. In patients with normal renal function, a hypervitaminosis state is unlikely.

Thyroid Hormones

Several small studies have evaluated the association between weight loss and use of levothyroxine and liothronine replacement in hypothyroid patients.[265] Normalization of the hypothyroid state is associated with small losses of weight (typically less than 1 kg), which are not durable beyond 12-24 months. Normalization of the hyperthyroid state is associated with weight gain of approximately 7 kg. Treatment of euthyroid patients to hyperthyroid levels has not been reported outside of control groups in early phase clinical trials. The risks associated with hyperthyroidism—particularly cardiac, ocular, and neuopsychiatric—make intentional creation of a hyperthyroid state highly inadvisable for weight loss.

Appendix K: Bariatric Surgery

The performance of bariatric surgery has increased over the last decade, corresponding with a number of factors, not the least of which is the growing epidemic problem of morbid obesity in the United States. The other major factor that has led to its growing acceptance is the advent of minimally invasive techniques to perform bariatric operations. Irrespective of surgical approach, these are major operative procedures done for a population with significant co-morbidities. All surgical candidates should have adequate physiological reserve to withstand a major operative procedure.

There is no consensus regarding the necessary requirements for patients considering bariatric surgery. Numerous insurance companies mandate enrollment in a structured weight loss program for a prescribed period of time before patients can be considered for these procedures. There is no evidence supporting this practice, either as a legitimate preoperative criterion or as an effective means to prepare patients for surgery. [266] These preoperative diets are also not associated with improved outcomes after bariatric surgery. Similarly, although often required preoperatively, no evidence supports routine preoperative assessment by mental health providers. [267,268] As with all general surgical procedures, a complete history and physical is required and the preoperative evaluation should include a review of the assessment elements noted in the Screening and Assessment section of this CPG **(Box 2)**.This includes identification of problematic eating patterns that may require further assessment or management. A history of obstructive sleep apnea, asthma, and current and historical levels of diabetic and hypertensive control should be investigated. Although nearly all obese patients have shortness of breath, if shortness of breath is severe, a cardiopulmonary evaluation is warranted to identify any potential contraindications to surgery. Smokers should be encouraged to quit and abstain from smoking. Patients that have active, untreated addictions to drugs or alcohol should not be referred for bariatric surgery.

An integrated lifestyle program for the patient should be in place, both prior to and after the surgical procedure, to provide ongoing guidance and support. The support includes necessary dietary regimen, appropriate physical activity, patient education, behavioral treatment and social support. Adherence to restricted diet, physical activity and lifestyle changes is essential to long-term maintenance of weight loss after surgery. Patients should receive preoperative nutritional counseling to ensure they understand postoperative dietary requirements and the need for lifestyle alteration. Many patients suffer from clinical depression pre-operatively. Occasionally, depression persists post-operatively or patients who were not previously depressed become depressed post-operatively and thus require treatment. In addition, lifelong medical surveillance after bariatric surgery should include monitoring for changes in the status of chronic health conditions and procedure-specific complications such as nutritional deficiencies.

While evidence to support absolute contraindications for bariatric surgery is lacking, expert consensus states that women who are pregnant or who are considering pregnancy in the next 18-24 months should not be considered candidates for bariatric surgery. [269] Other relative contraindications to bariatric surgery that are supported only by expert consensus include conditions that compromise anesthesia or wound healing, lack of patient's ability to follow pre- and postoperative instructions,

general high risk surgical conditions, and reduced life expectancy for reasons unrelated to obesity. [270] Consultation with the bariatric surgery team should be performed to discuss all possible contraindications for surgery or a successful result.

Most Common Types of Bariatric Procedures Performed in the US

Currently, the two most common procedures done in the United States (US) are Roux-en-Y gastric bypass and the adjustable gastric band. The Roux-en-Y procedure (done open or more commonly via a laparoscopic approach) involves creation of 30 ml gastric pouch which empties into a roux limb of jejunum. A variable distance downstream from this anastomosis, another anastomosis is created with the biliary limb to form a common channel which travels to the cecum. This operation therefore provides a restrictive component, in that early satiety is produced with a small volume of food, with over-distention of the pouch resulting in nausea and vomiting, thus prompting dietary compliance. It also provides for a mal-absorptive component, which is directly related to the length of the "common channel" of small intestine traveling to the cecum. With the adjustable gastric band procedure, a silastic inflatable band is placed around the cardia of the stomach. A reservoir port placed under the skin is subsequently injected with saline to expand or desufflate the band to create more or less restriction to food postoperatively. The adjustable gastric band may be considered a reversible form of the previously popular vertical banded gastroplasty. Multiple post-operative band adjustments are often required. The gastric band is a purely restrictive operation as there is no malabsorptive component.

Sleeve gastrectomy is increasingly performed in the US. It is a partial gastrectomy that can be performed laparoscopically in which most of the stomach is removed without bypassing the intestines; hence it is a type of restrictive operation. Additionally, it may provide further benefit through its effects on gut hormones. It is generally a safer procedure than Roux-en-Y gastric bypass. Less commonly performed operations (in the US) include biliopancreatic diversion with duodenal switch, vertical band gastroplasty, gastric plication, and the i-band which involve gastric plication in combination with an adjustable gastric band. In broad terms, more technically challenging operations (with increased risks of complications), involve greater durable weight loss than more technically simple procedures (i.e. biliopancreatic diversion/duodenal switch/Roux-en-Y gastric bypass weight loss > sleeve gastrectomy > bands).

Mortality Risk

Bariatric procedures have complications and there is a risk for mortality from these procedures. The rate of mortality varies according to the type of procedure performed and is approximately 0.1% for gastric banding, 0.5% for Roux-en-y gastric bypass, and 1.1% for biliopancreatic diversion. [137] One retrospective cohort study of 16,155 Medicare beneficiaries found mortality rates to be greater in those aged 65 years or older compared with younger people (4.8% vs. 1.7% at 30 days; 6.9% vs. 2-3% at 90 days; and 11.1% vs. 3.9% at 1 year; $P<0.001$). [271] More recent data from Longitudinal Assessment of Bariatric Surgery Consortium demonstrated 30 day mortality for laparoscopic adjustable gastric banding, laparoscopic Roux-en-Y gastric bypass and open Roux-en-Y gastric bypass of 0% of 1109 patients, 0.2% of 2975 patients, and 2.1% of 437 patients, respectively. [272] Advanced age, male gender, and BMI > 50 kg/m^2 have consistently been associated with higher mortality risk from these operations. [273-276] The

Bariatric Outcomes Longitudinal Database 30-day mortality rate for 81,751 patients undergoing Roux-en-Y surgery was 0.15%. Risk factors significantly associated with 30-day mortality were increasing BMI, increasing age, and male gender. Other factors associated with increased risk were the presence of congestive heart failure, liver disease, and pulmonary hypertension. [277]

Morbidity Risk

In terms of morbidity, adverse events occur in about 10-20% of cases. [271,274] Operative and postoperative complications are common and vary with the type of bariatric procedure performed. The following is a list of some common complications of bariatric surgery:

1. Stricture of gastrojejunostomy: The rate of gastrojejunal anastomotic stricture ranges from 1-31% across multiple series after Roux-en-y gastric bypass. The complication occurs more frequently following the laparoscopic than the open gastric bypass. Anastomotic stricture presents with dysphagia, vomiting, and/or food intolerance. This problem is generally addressed by endoscopic pneumatic balloon dilation. Multiple follow-up dilations may be required, but surgical revision is rarely required. Most surgeons are comfortable performing this procedure approximately two to three weeks after surgery and this complication rarely develops before that time.

2. Gastrointestinal bleeding: Gastrointestinal bleeding occurs in approximately 1-2% of patients after Roux-en-y gastric bypass and usually occurs from one of the various staple lines in the immediate post-operative time period. Pre-operative identification of the site of staple line bleeding may be nearly impossible. The gastric pouch and anastomotic staple lines are easily identified with upper endoscopy. The jejunojejunostomy may be as far as 150cm distal to the gastrojejunostomy making this anastomosis less accessible by endoscopy. As with most gastrointestinal bleeding, endoscopic therapy is the preferred method of management and should be performed with the knowledge of the operating surgeon. Fortunately most staple line bleeding in the immediate post-operative time period usually stops with conservative care alone. Bleeding can also occur from the gastric remnant staple line, which is usually not accessible through normal endoscopy. Many surgeons consider transfusion requirements in excess of 4-6 units of packed red blood cells as an indication for operative intervention if endoscopy is not revealing. Under these circumstances, the patient should be referred to a center with experienced bariatric surgeons. Bleeding can later occur in conjunction with a marginal ulcer.

3. Marginal ulcer: Marginal ulcers are peptic ulcerations that occur at the gastro-jejunal anastomosis. They are felt to be ischemic in nature. Almost all of these patients will heal with a course of proton-pump inhibition. Follow-up endoscopy should be performed to document resolution. When refractory to medical treatment, the anastomosis might require revision. Marginal ulcer bleeding can be severe but usually responds to endoscopic intervention.

4. Bowel obstruction: As with any operation, adhesive bowel obstructions may occur as a result of gastric bypass. Laparoscopic gastric bypass has a relatively high rate of internal hernia resulting

in bowel obstructions. The most common site of intestinal obstruction occurs in “Petersons Space” which is between the roux limb going to the gastric pouch and the transverse mesocolon. Bowel obstruction occurs less frequently with the open approach due to associated adhesion formation.

As with any obstruction, the presenting symptoms include vomiting, abdominal distension and pain. Internal hernias can present more insidiously with intermittent symptoms such as cramping and abdominal pain that resolves spontaneously. A high index of suspicion is needed to make the diagnosis. Oftentimes, radiographic studies may appear normal, especially with high obstructions. A high index of suspicion is required with the diagnosis usually being made at either formal laparotomy or laparoscopy. Partial bowel obstructions require admission and intravenous (IV) fluid hydration with initial conservative care. Gastrografin small bowel studies may be helpful in the localization of a transition point (point of obstruction) and predicting the future need for operative intervention. Most partial obstructions resolve with IV fluid resuscitation and naso-gastric tube decompression. Complete bowel obstructions require emergent surgery.

5. Obstructions about the distal intestinal anastomosis with Roux-en-Y gastric bypass: Acute “gas bloat” of the distal bypassed stomach may rarely occur and usually is associated with obstruction about the distal anastomosis. This is a surgical emergency in that if the distal stomach is not vented, gastric necrosis, perforation and death may rapidly ensue. Patients present with epigastric fullness and “hiccups.” Diagnosis is suggested by a large gas bubble in the right upper quadrant on plain films. The distal gastric remnant is decompressed via tube gastrostomy.

6. Complications of the LapBand: Although this procedure is associated with fewer acute peri-operative complications, it has its own set of potential problems. As with any prosthesis, there can be migration of the band caudal or cephalad, as well as into the esophagus or stomach. With erosion into the lumen of the stomach, removal may be accomplished endoscopically. Patients may also present with severe food intolerance which may be related to the degree of band inflation. A certain degree of such intolerance is necessary, however, in order for the action of the band to allow for weight loss. There have been reports of significant esophageal dilation and promotion of gastroesophageal reflux but these are seen less frequently using the pars flaccida technique of insertion. In most cases, deflating the band will correct these problems if the patient has not lost the desired weight; conversion to a Roux-en-y gastric bypass may be required for lack of adequate weight loss.

7. Deep venous thrombosis and anastomotic leak: The two major complications associated with any bariatric procedure in the immediate post-operative period are deep venous thrombosis (DVT)/pulmonary embolism and acute anastomotic leak (not applicable in band patients). While chemical prophylaxis is indicated in these high risk patients for DVT, it is no substitute for early ambulation. Anastomotic leak may rapidly progress to sepsis and death. The earliest sign of a leak is tachycardia. These patients require expeditious return to the operating room for wide

external drainage of the leak. Insertion of internal stents covering the anastomotic leak may greatly enhance recovery.

Suicide Risk

Suicide appears to be increased following bariatric surgery. Tindle et al. found that the suicide rate following bariatric surgery performed in Pennsylvania was 13.7 per 10,000 men and 5.2 per 10,000 women compared to the age- and sex-matched suicide rates in the US of 2.4 per 10,000 men and 0.7 per 10,000 women. [278] A systematic review of 28 studies involving 23,885 patients revealed a suicide rate of 4.1 per 10,000 person years. [279] Adams et al. found rates of death caused by all non-disease states such as accidents and suicide to be increased; suicide alone was not statistically increased. [151] However, most studies investigating the relationship between bariatric surgery and suicide did not include comparison groups that controlled for the presence and degree of obesity. [278] Nonetheless, because depression is not uncommon after bariatric surgery, increased vigilance for suicidal ideation and other risk factors for suicide (e.g., alcohol and other substance use disorder) is warranted. [280,281]

Nutritional Concerns

All patients should be followed regularly and closely for potential nutritional deficiencies. In its evidence-based clinical practice guideline for endocrine and nutritional management of the post-bariatric surgery patient, the Endocrine Society has provided a strong recommendation, based on moderate quality evidence, for periodic clinical and biochemical monitoring for micro- and macronutritional deficiencies after bariatric surgery. This recommendation includes a suggested detailed schedule of 16 laboratory tests, e.g., complete blood count, liver function tests, glucose, creatinine, and electrolytes. [282] In general, those having a malabsorptive component have the greatest risk for nutritional deficiency. Of these, biliopancreatic diversion, with or without duodenal switch, results in the most malabsorption since approximately 60% of the small intestine is bypassed thereby reducing surface absorption. Furthermore, the markedly reduced mixing of bile and pancreatic enzymes results in fat and protein malabsorption, respectively. This procedure is uncommonly performed in the US. However, the most common procedure, Roux-en-Y gastric bypass is a restrictive procedure that also has a malabsorptive component due to similar processes as described above. Even purely restrictive procedures, e.g., laparoscopic adjustable gastric banding, can result in deficiencies since the volume of food intake is markedly reduced. Hence, purely restrictive procedures require augmentation with a minimum of a multivitamin. Furthermore, all post-operative patients should receive an average of 60-120 g of protein daily, particularly in those receiving malabsorptive procedures. [282]

Specifically after Roux-en-Y gastric bypass, several nutritional deficiencies are common and supplementation at higher than the usual recommended daily dose may be required. Typical doses of elemental calcium are 1200-1200mg daily, preferably as calcium citrate which is better absorbed in the absence of gastric acid. The optimal dose of vitamin B12 is not known. While all forms of delivery have been shown to be effective, poor absorption is common and sublingual or IM injection may be required. Iron deficiency is common and typically all patients receive prophylactic therapy in conjunction with vitamin C to enhance absorption. Women with ongoing menstrual losses should receive a higher dose.

Folate and B-complex vitamins are usually supplied in the form of a complete multivitamin. Fat soluble vitamin status should be monitored by clinical and laboratory methods and though not as common as in biliopancreatic diversion procedures, deficiencies may occur. Thiamine deficiency can also occasionally occur typically associated with intractable vomiting after surgery.

All patients should be monitored routinely by an experienced team to detect nutritional deficiencies. Though purely restrictive procedures tend not to have selective nutritional deficiencies, due to poor dietary tolerance or reduced intake, monitoring may be required. The American Association of Clinical Endocrinologists/The Obesity Society/American Society for Metabolic &Bariatric Surgery and the Endocrine Society have both issued recommendations for post-operative monitoring for various surgical procedures.[282,283] See **Table K-1** below for Endocrine Society recommendations.

All bariatric procedures can lead to deficiencies in iron, vitamin B12, folate and calcium during subsequent pregnancies. These deficiencies can result in maternal complications, such as severe anemia, and in fetal complications including neural tube defect, intrauterine growth restriction, and failure to thrive. Nutrient supplementation following bariatric surgery and close supervision before, during, and after pregnancy can help prevent nutrition-related complications and improve maternal and fetal health. Therefore, women who have undergone weight loss surgery and subsequently become pregnant need to receive intensive nutritional follow-up by providers with expertise in clinical nutrition.

TABLE K-1: Schedule for Clinical and Biochemical Monitoring of the Post-Bariatric Surgery Patient [282]*

	Preoperative	1 month	3 months	6 months	12 months	18 months	24 months	Annually
Complete blood count	X	X	X	X	X	X	X	X
LFTs	X	X	X	X	X	X	X	X
Glucose	X	X	X	X	X	X	X	X
Creatinine	X	X	X	X	X	X	X	X
Electrolytes	X	X	X	X	X	X	X	X
Iron/ferritin	X			X[a]	X[a]	X[a]	X[a]	X[a]
Vitamin B12	X			X[a]	X[a]	X[a]	X[a]	X[a]
Folate	X			X[a]	X[a]	X[a]	X[a]	X[a]
Calcium	X			X[a]	X[a]	X[a]	X[a]	X[a]
Intact PTH	X			X[a]	X[a]	X[a]	X[a]	X[a]
25-D	X			X[a]	X[a]	X[a]	X[a]	X[a]
Albumin/prealbumin	X			X[a]	X[a]	X[a]	X[a]	X[a]
Vitamin A	X						Optional	Optional
Zinc	X			Optional	Optional		Optional	Optional
Bone mineral density and body composition	X				X[a]		X[a]	X[a]
Vitamin B1			Optional	Optional	Optional	Optional	Optional	Optional

Data indicate the suggested schedule for laboratory monitoring after bariatric surgery. LFT, Liver function tests.

[a] Examinations should only be performed after RYGB, BPD, or BPD/DS. All of them are considered as suggested for patients submitted to restrictive surgery where frank deficiencies are less common.

**Table 2, p. 4827. Used with permission.*

RYGB = Roux-en-Y gastric bypass; BPD = biliopancreatic diversion; BPD/DS = biliopancreatic diversion with duodenal switch

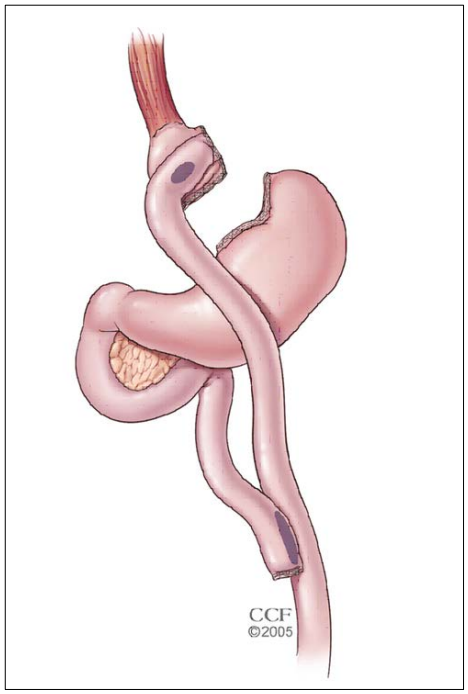
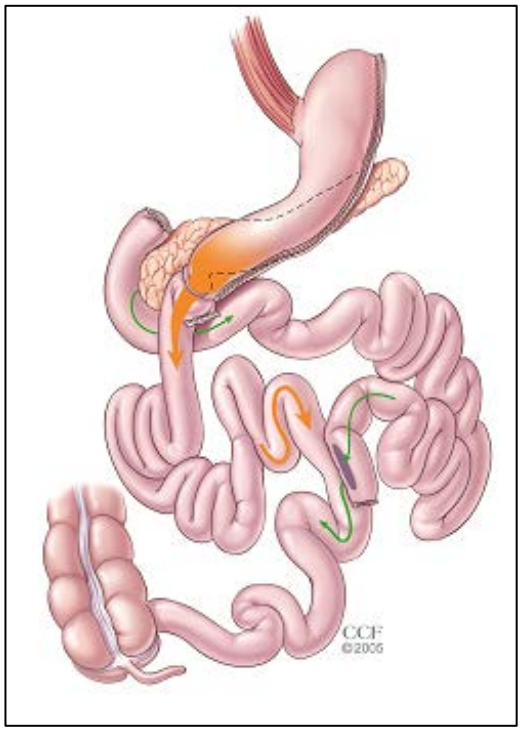


Figure K-1: Roux-en-Y Gastric Bypass
The stomach is either divided or stapled closed. A limb of jejunum is brought to the resultant pouch. The length of this limb is usually about 75 cm, however, in the long-limb variation of this procedure the limb may be as long as 150 cm. All operations involving duodenal/small intestinal bypass are associated with iron deficient anemia, calcium, B12, folate, micronutrient vitamin and mineral deficiencies without appropriate supplementation. Supplements are taken life-long following these procedures.

Figure K-2: Biliopancreatic Diversion or Duodenal Switch
These operations add significant nutrient malabsorption to the gastric restrictive component typical of the gastric bypass. The biliopancreatic diversion operation is similar to the gastric bypass but the intestinal limb is very long. Approximately 100 to 150 cm of small bowel is in contact with both the biliopancreatic secretions as well as food. The major advantage of these operations is that weight loss results irrespective of a patient's eating habits. A common side effect of the operation is malodorous flatus. The duodenal switch procedure is similar to the biliopancreatic diversion except that the duodenum is capped and is bypassed along with the small bowel. Rather than create a pouch, the gastric remnant is a sleeve along the lesser curve and about four times the size of the gastric bypass pouch. This operation has the advantage of retaining the pylorus, minimizing problems related to dumping syndrome and marginal ulcer. Sleeve gastrectomy involves only the conversion of the stomach to a tube as seen in the diagram, without intestinal bypass.



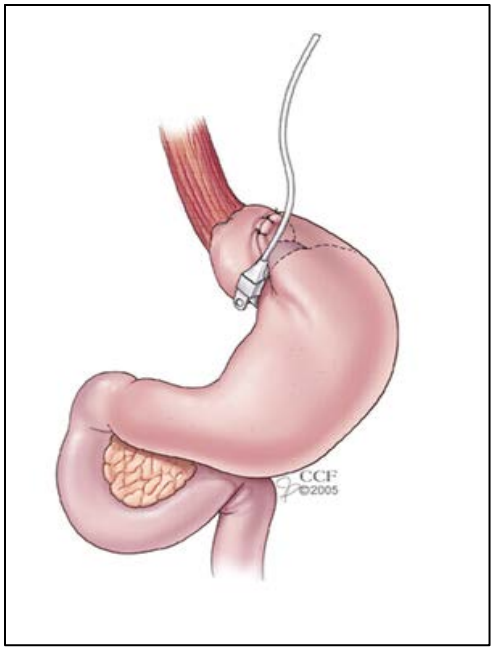
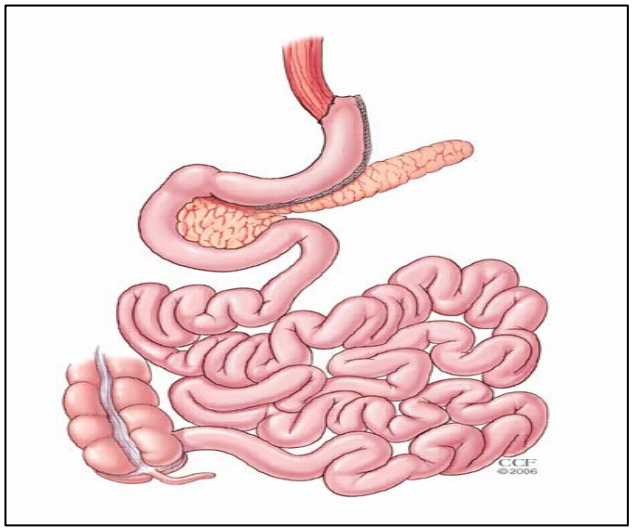


Figure K-3: Adjustable Gastric Banding Procedure
An inflatable band is placed around the proximal stomach by a laparoscopic approach. A reservoir is placed in a subcutaneous location that enables the band to be inflated or deflated depending on what the patient's requirements are.

Figure K-4: Sleeve Gastrectomy
Sleeve gastrectomy is technically easier to perform than Roux-en-Y gastric bypass. Approximately 80% of the stomach is removed and the remaining "sleeve" is dramatically reduced in volume. Though it is a restrictive procedure, gut motility may be affected and gut hormones may be involved producing benefits.



Appendix L: Participant List

Arianna Aoun, MS, RD, CSR, LD Clinical Dietitian Renal/Obesity Louis Stokes Cleveland VA Medical Center Cleveland, OH	Raymond Batz, DO, MPH CDR, MC, USN Family Medicine/Aerospace Medicine 2d Marine Aircraft Wing, Marine Corps Air Station, Cherry Point Havelock, NC
Ronny Bigham, PA MAJ, SP, USA Inter-service Physician Assistant AMEDD Center and School Joint Base Fort Sam Houston, TX	Carla Cassidy, MSN, ANP Clinical Quality Program Specialist Office of Quality, Safety and Value Department of Veterans Affairs Washington, DC
Y. Sammy Choi, MD(Co-Chair) Clinical Investigation Service Womack Army Medical Center Fort Bragg, NC	Elmer Combs, PhD, RN** US Army Public Health Command Aberdeen Proving Ground, MD
Ernest Degenhardt, MSN, FNP-BC Chief, Office of Evidence Based Practice Clinical Performance Assurance Directorate US Army Medical Command Ft. Sam Houston, TX	Michael Goldstein, MD (Co-Chair) Preventive Medicine Office of Patient Care Services VHA National Center for Health Promotion and Disease Prevention Durham, NC
Edwin Earl Gaar, MD, FACS Chief of Surgery Robley Rex VA Medical Center Professor of Surgery, Academic Advisory Dean University of Louisville School of Medicine Louisville, Kentucky	Navjit Goraya, MD Washington DC VAMC Washington, DC
Pennie Lou Pearson Hoofman, PhD LTC, MSC, USA Lyster Army Health Center Fort Rucker, AL	Sophia Hurley, MSPT Project Manager, National Telephone Lifestyle Coaching Pilot VHA National Center for Health Promotion and Disease Prevention Office of Patient Care Services Durham, NC
Elizabeth Liebner, PT CPT, USAF, BSC Peterson AFB, CO 80941	Belinda Millner, RN Fort Belvoir Community Hospital Fort Belvoir, VA

Kenneth Jones, PhD National Program Director for Weight Management VHA National Center for Health Promotion and Disease Prevention Durham, NC	Theresa Newlin, FNP, FPC-BC LTC, AN, USA Keller Army Community Hospital West Point, NY
M. Eric Rodgers, PhD, FNP, BC Clinical Quality Program Specialist Office of Quality, Safety and Value Department of Veterans Affairs Glendale, CO	Connie Scott, MSM, RD CDR, MSC, USN Navy and Marine Corps Public Health Center Portsmouth, VA
James Sebesta, MD COL, MC, USA General Surgeon Madigan Army Medical Center Joint Base Lewis McCord, WA	Robert Selvester, MD LCDR, MC, USN Family Practice Naval Air Station Corpus Christi Corpus Christi, TX
Todd Semla, MS, PharmD, BCPS, FCCP, AGSF National PBM Clinical Pharmacy Program Director Pharmacy Benefits Management Department of Veterans Affairs Hines, IL	Mamie Shell, RN-BC, CCM Case Management/Discharge Planning Naval Medical Center Portsmouth Portsmouth, VA
Leilani Siaki, PhD, FNP-BC LTC, AN, USA Nurse Researcher Madigan Army Medical Center Joint Base Lewis McCord, WA	Marjory Waterman, MN, RN CPG and Medical Management Coordinator Office of Evidence Based Practice Clinical Performance Assurance Directorate US Army Medical Command Joint Base Fort Sam Houston, TX
Darrell Zaugg, DO MAJ, USAF, MC Family Practice/Psychiatry Ramstein Air Base, Germany	

** Left the Work Group following the first face-to-face meeting.

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