

Editor's Note: On February 13, 2020, the U.S. Food and Drug Administration (FDA) requested that the manufacturer of Belviq (lorcaserin) voluntarily withdraw this drug from the market because a safety clinical trial showed an increased occurrence of cancer that outweighed any potential weight loss benefits. See the FDA Drug Safety Communication (<https://www.fda.gov/drugs/drug-safety-and-availability/fda-requests-withdrawal-weight-loss-drug-belviq-belviq-xr-lorcaserin-market>).

Update on Office-Based Strategies for the Management of Obesity

MICHAEL ERLANDSON, MD; LAURIE C. IVEY, PsyD; and KATIE SEIKEL, DO, RD
Swedish Family Medicine Residency, University of Colorado School of Medicine, Littleton, Colorado

Obesity is a common condition that is associated with numerous medical problems such as cardiovascular disease, pulmonary disease, and diabetes mellitus. Primary care physicians have an important role in helping patients develop a successful weight loss plan to improve their overall health. Dietary strategies emphasizing reduced caloric intake, regardless of the nutrient composition, are important for weight loss. Behavioral interventions such as motivational interviewing and encouraging physical activity lead to additional weight loss when combined with dietary changes. Medication regimens for concomitant medical problems should take into account the effect of specific agents on the patient's weight. Persons with a body mass index of 30 kg per m² or greater or 27 kg per m² or greater with comorbidities who do not succeed in losing weight with diet and activity modifications may consider medication to assist with weight loss. Medications approved for long-term treatment of obesity include orlistat, lorcaserin, liraglutide, phentermine/topiramate, and naltrexone/bupropion. Physicians should consider referring patients for bariatric surgery if they have a body mass index of 40 kg per m² or greater. For those with obesity-related comorbid conditions, patients should be considered for adjustable gastric banding or other bariatric surgical approaches if they have a body mass index of 30 to 39.9 kg per m². The most commonly performed procedures for weight loss are Roux-en-Y gastric bypass, sleeve gastrectomy, and adjustable gastric banding. Bariatric surgery is the most effective intervention for weight loss in obese patients, and it leads to improvement in multiple obesity-related conditions, including remission of diabetes. (*Am Fam Physician*. 2016;94(5):361-368. Copyright © 2016 American Academy of Family Physicians.)

CME This clinical content conforms to AAFP criteria for continuing medical education (CME). See CME Quiz Questions on page 346.

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► Patient information: A handout on this topic is available at <http://www.aafp.org/afp/2016/0901/p361-s1.html>.

Scan the QR code below with your mobile device for easy access to the patient information handout on the AAFP mobile site.



Obesity is a pervasive problem confronting patients and their physicians. From 2011 to 2012, 69% of U.S. adults were overweight or obese.¹ Many common medical problems, such as diabetes mellitus, pulmonary disease, and cardiovascular disease, are related to obesity and can improve with weight loss.² The management of obesity continues to evolve with the approval of new treatments. This review will provide answers to some of the common clinical questions that physicians encounter when managing obesity in the outpatient setting.

What Is the Family Physician's Role in Screening for and Managing Obesity?

Physicians should screen all patients for obesity with measurement of body mass index (BMI) or waist circumference. Diet and behavioral interventions should be initiated in patients who are obese.

EVIDENCE SUMMARY

The U.S. Preventive Services Task Force (USPSTF) recommends that all persons 18 years and older be screened for obesity (*Table 1*^{1,3}), and that those with a BMI of 30 kg per m² or greater be offered intensive, multicomponent behavioral interventions.² The American Academy of Family Physicians recommends screening for obesity followed by intensive counseling and behavioral interventions, with at least one session per month for at least three months.⁴ Waist circumference may be an acceptable alternative in some persons because BMI may not account for the cardiovascular risk of central adiposity. Family physicians can assist patients in setting weight loss goals, improving nutrition, increasing physical activity, addressing barriers to change, and developing strategies to maintain long-term lifestyle changes. Behavior modifications can lead to clinically important weight loss of

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
BMI should be calculated for all patients 18 years and older, and those with obesity should be referred for intensive, multicomponent behavioral interventions.	B	2
Increased physical activity should be recommended for weight loss in combination with diet and behavioral modifications.	B	20
Physicians should consider medications for weight loss in patients with a BMI of 30 kg per m ² or greater, or 27 kg per m ² or greater who also have comorbidities and have unsuccessfully tried diet and lifestyle modification first.	C	26
Patients with a BMI of 40 kg per m ² or greater and those with a BMI greater than 35 kg per m ² who also have obesity-related comorbidities should be referred for consideration of bariatric surgery. Patients with a BMI greater than 30 kg per m ² who also have obesity-related comorbidities may be candidates for adjustable gastric banding.	B	36

BMI = body mass index.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort>.

5%, improved glucose tolerance, and reduction in other cardiovascular risk factors.²

Which Dietary Approaches Have Been Shown to Be Most Effective for Weight Loss?

Adherence to a diet with a deficit of 500 kcal per day, regardless of macronutrient composition, is most effective for weight loss. Simple and realistic diet modifications have the highest likelihood of success.

EVIDENCE SUMMARY

Various commonly used diet plans result in a similar degree of weight loss, regardless of the specific dietary composition of macronutrients (carbohydrate, protein, and fat).⁵ Adherence to calorie reduction is the most important factor; any diet in which caloric intake is less than caloric expenditure will lead to weight loss.⁶ A deficit of at least 500 kcal per day can be achieved with intake of 1,200 to 1,500 kcal for women and 1,500 to 1,800 kcal for men. Very low-calorie diets (800 kcal or less per day) should be avoided unless the patient is under close supervision with high-intensity lifestyle interventions.⁷

Diet plans with multiple components can be overwhelming and lead to poor adherence. A simpler approach using a single dietary adjustment may produce weight loss similar to more complex plans. For example, encouraging a patient to increase dietary fiber intake produces comparable adherence and weight loss to encouraging compliance with the many goals of the American Heart Association diet. Similarly, more permissive goals, such as adding more vegetables and standing more, lead to greater improvement in life-

Table 1. Weight Classifications

<i>Classification</i>	<i>Body mass index (kg per m²)</i>	<i>Prevalence (%)</i>	<i>Waist circumference</i>
Underweight	< 18.5	NA	—
Normal weight	18.5 to 24.9	NA	Male < 40 in (102 cm) Female < 35 in (89 cm)
Overweight	25 to 29.9	33.6	—
Class 1 obesity	30 to 34.9	20.4	Male ≥ 40 in
Class 2 obesity	35 to 39.9	8.1	Female ≥ 35 in
Class 3 obesity	≥ 40	6.4	

NA = not available.

Information from references 1 and 3.

WHAT IS NEW ON THIS TOPIC: OBESITY

Using a single dietary adjustment may produce weight loss similar to more complex plans. For example, encouraging a patient to increase dietary fiber intake produces comparable adherence and weight loss to encouraging compliance with the many goals of the American Heart Association diet.

style behaviors than restrictive approaches that instruct patients to avoid certain foods.⁸ Although different diets with similar caloric intake can result in comparable weight loss, a higher-quality diet of nutrient-dense foods (e.g., vegetables, fruits, whole grains) that are rich in fiber, vitamins, and minerals will produce greater results.⁹ The 2015-2020 Dietary Guidelines for Americans reinforce the need to make healthier food and beverage choices by consuming nutrient-dense foods from all food groups and limiting intake of added sugars, saturated fats, and sodium.¹⁰

Which Behavioral Interventions Are Helpful for Weight Loss?

The USPSTF recommends that patients who are obese be referred to intensive, multicomponent behavioral interventions with 12 to 26 sessions per year.² Interventions that have been proven effective include motivational interviewing, worksite interventions, and exercise.

EVIDENCE SUMMARY

Motivational interviewing involves assessing a patient's motives for change and acting as a supportive partner

to empower them in the process (*Table 2*).^{11,12} Multiple studies have shown that motivational interviewing can modestly enhance the effects of a weight-loss program (−3.3 lb [−1.5 kg]; 95% confidence interval [CI], −4.4 to −2.0 lb [−2.0 to −0.9 kg]), and it can be readily used by primary care physicians.¹³ This technique can also indirectly have beneficial effects on other cardiovascular risk factors, such as activity and cholesterol levels.¹⁴

Worksite interventions are gaining in popularity, and family physicians can encourage patient participation. A systematic review found that worksite nutrition and physical activity programs achieve modest improvements in weight (−2.8 lb [−1.3 kg]; 95% CI, −4.6 to −1.0 lb [−2.1 to −0.5 kg]) over six to 12 months.¹⁵ Another study evaluated the effect of worksite incentive programs in which participants received regular education about a healthful diet and exercise.¹⁶ Participants received monetary rewards for meeting weight loss goals and lost an average of 2.2 lb (1.0 kg).

Increasing physical activity is an important part of any weight loss plan. The National Institute for Health and Care Excellence recommends 45 to 60 minutes per day of moderate-intensity exercise to prevent obesity and 60 to

Table 2. Motivational Interviewing Techniques

Technique	Example	Rationale
Ask permission to discuss behavior-change topic	"Would it be okay if we talked about your weight today?"	When patient gives permission, he or she is more open to the conversation
Show empathy	"Losing weight is very challenging."	Aids in building rapport, particularly in difficult discussions
Scale motivation (0 = low to 10 = high)	"On a scale of 0 to 10, with 10 being the highest, how motivated are you to try to lose weight?"	Assesses motivation to change; if very low, the patient may not be ready for change; if high, additional intervention strategies may be successful
Scale confidence (0 = low to 10 = high)	"On a scale of 0 to 10, with 10 being the highest, how confident are you that you can lose weight?"	Identifies need for interventions to overcome obstacles
Inquire about the scores on above scales	"Why did you choose 3 instead of 2? What would help you move from 3 to 4?"	Further the conversation on thinking about behavior change
Use decisional balance technique (explore pros and cons of change vs. no change)	"What are the pros of losing weight?" "What are the pros of not losing weight?" "What are the cons of losing weight?" "What are the cons of not losing weight?"	Helps patient and physician understand barriers to and motivators for change
Listen for change talk and reinforce it; let the patient take ownership by generating ideas for change	Patient: "I think I could try to walk more." Physician: "That's a fantastic idea that will help you move toward your goal."	Provides encouragement and helps promote confidence in patients

Information from references 11 and 12.

90 minutes per day to avoid regaining weight.¹⁷ The U.S. Department of Health and Human Services recommends 150 to 300 minutes of moderate-intensity activity or 75 to 150 minutes of vigorous activity per week.¹⁸ Exercise alone is not as beneficial for weight loss as it is when combined with a behavioral weight-management program.¹⁹ A 2006 Cochrane review showed modest weight loss with exercise alone (−1.1 to −8.8 lb [−0.5 to −4.0 kg]), but the effect was not as significant as when exercise was combined with dietary modification (−7.5 to −39.0 lb [−3.4 to −17.7 kg]).²⁰

What Is the Role of Medications in the Treatment of Obesity?

Medications approved for long-term treatment of obesity include orlistat (Xenical), lorcaserin (Belviq), liraglutide (Saxenda), phentermine/topiramate (Qsymia), and naltrexone/bupropion (Contrave). Medications prescribed for concomitant conditions should be optimized to increase the chance of weight loss.

EVIDENCE SUMMARY

Pharmacotherapeutic options for treating obesity have expanded in recent years. Medications should be considered only for patients who have not achieved weight loss goals with diet and lifestyle changes, and after an extensive discussion of the risks and benefits. All of the agents discussed below have been approved by the U.S. Food and Drug Administration for long-term weight management in conjunction with a reduced-calorie diet and increased physical activity in patients with a BMI of 30 kg per m² or greater, or 27 kg per m² or greater who have comorbid conditions such as hypertension, diabetes, or dyslipidemia²¹⁻²⁵ (Table 3²¹⁻³²). Despite their indication for long-term therapy, the optimal duration of treatment is unclear; the available evidence was limited to one to two years. Relatively high rates of attrition in studies also raise concern about the utility of these agents in ongoing treatment. Multiple sympathomimetic agents, including phentermine, are approved for short-term treatment (less than 12 weeks), but these agents are

Table 3. Medications Approved for the Long-Term Treatment of Obesity

Medication	Maintenance dosing	Mechanism of action	Weight loss relative to placebo	Study duration	Adverse effects
Liraglutide (Saxenda)	0.6, 1.2, 1.8, 2.4, or 3 mg per day subcutaneously	Glucagon-like peptide-1 inhibitor	1.2 mg: 4.6 lb (2.1 kg) 1.8 mg: 6.2 lb (2.8 kg) 2.4 mg: 7.7 lb (3.5 kg) 3 mg: 9.7 to 13 lb (4.4 to 5.9 kg)	20 to 56 weeks	Abdominal pain, constipation, decreased appetite, diarrhea, dizziness, fatigue, headache, hypoglycemia, increased lipase levels, nausea, vomiting
Lorcaserin (Belviq)	10 mg two times per day	5-HT _{2C} receptor agonist	7 lb (3.2 kg)	One to two years	Back pain, constipation, cough, dizziness, dry mouth, fatigue, headache, hypoglycemia, nausea
Naltrexone/bupropion (Contrave)	Two 8/90-mg tablets two times per day	Opioid antagonist/aminoketone antidepressant	16 mg: 7.7 lb 32 mg: 10.4 to 10.8 lb (4.7 to 4.9 kg)	56 weeks	Constipation, diarrhea, dizziness, dry mouth, headache, insomnia, nausea, vomiting
Orlistat (Xenical)	60 or 120 mg three times per day	Lipase inhibitor	60 mg: 5.5 lb (2.5 kg) 120 mg: 7.5 lb (3.4 kg)	One to four years	Fecal incontinence, fecal urgency, flatus, increased defecation, oily stool
Phentermine/topiramate (Qsymia)	7.5/46 mg per day 15/92 mg per day	Sympathomimetic/antiepileptic	7.5/46 mg: 14.8 lb (6.7 kg) 15/92 mg: 19.6 lb (8.9 kg)	56 to 108 weeks	Constipation, dizziness, dry mouth, dysgeusia, insomnia, paresthesia,

*—All are contraindicated during pregnancy.
Information from references 21 through 32.

not reviewed here. Physicians should consider the effect that medications prescribed for concomitant conditions may have on a patient's weight (Table 4).^{3,33}

Orlistat, a reversible inhibitor of gastrointestinal lipase, is a common first choice for therapy because of its long history and lack of systemic effects due to limited absorption. It is taken as a 60- to 120-mg capsule three times per day during or up to one hour after a fat-containing meal. Patients should take a daily multivitamin containing fat-soluble vitamins while using orlistat.²¹ A systematic review showed an average weight loss of 7.5 lb (3.4 kg; 95% CI, 7.1 to 7.9 lb [3.2 to 3.6 kg]) and 5.5 lb (2.5 kg; 95% CI, 3.3 to 7.7 lb [1.5 to 3.5 kg]) greater than placebo for the 120-mg and 60-mg doses, respectively.²⁶ Benefits also include a reduction in multiple cardiovascular risks, including blood pressure, lipid levels, and blood glucose levels. Gastrointestinal symptoms such as oily stool, flatus, fecal urgency, and fecal incontinence are the most common adverse effects limiting long-term use. These symptoms are more severe in patients con-

suming greater than the recommended dietary fat intake (30% of total calories).^{21,26}

Lorcaserin is a serotonin 5-HT_{2C} receptor agonist administered as a 10-mg tablet twice per day. It should not be used in combination with other serotonergic medications because of concern for serotonin syndrome, and should be discontinued if 5% weight loss has not been achieved in the first 12 weeks of therapy.²² A systematic review showed a mean weight loss of 7.1 lb (3.2 kg; 95% CI, 6.0 to 8.4 lb [2.7 to 3.8 kg]) greater than placebo.²⁶ Its mechanism of action is more specific to the 5-HT_{2C} receptor to minimize the risk of valvulopathy that occurs with other serotonergic weight-loss medications. Serial echocardiography performed in multiple trials revealed no short-term increase in valvulopathy.³⁴

Liraglutide is a glucagon-like peptide-1 receptor agonist that is administered subcutaneously and leads to weight loss when used for diabetes. Dosing for weight loss starts at 0.6 mg per day and is increased in weekly intervals to the full dosage of 3 mg per day, higher than the 1.8-mg dose used for diabetes. Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 syndrome, and it may affect the absorption of other medications via delayed gastric emptying.²³ Randomized trials of 3 mg of liraglutide have shown weight loss of 9.7 to 13.0 lb (4.4 to 5.9 kg) greater than placebo, with improved maintenance of weight loss.²⁷⁻²⁹

Phentermine/topiramate is a combination sympathomimetic and antiepileptic that is started at a dosage of 3.75 mg/23 mg per day for 14 days, after which the dose escalates to a maximum of 15 mg/92 mg. It should be discontinued if 5% weight loss is not achieved in the first 12 weeks of use at the maximum dose. When discontinuing, phentermine/topiramate should be tapered gradually because of the risk of seizure. Women of child-bearing age should use contraception and have regular pregnancy testing during treatment because of the risk of fetal toxicity.²⁴ A systematic review showed a mean weight loss of 19.6 lb (8.9 kg; 95% CI, 18.3 to 20.7 lb [8.3 to 9.4 kg]) greater than placebo with the 15-mg dose, and another trial showed sustained weight loss through two years of follow-up.^{26,30}

Naltrexone/bupropion is a combination opioid antagonist and antidepressant. It is given as a single 8-mg/90-mg dose and is titrated from one tablet per day to two tablets two times per day over four weeks. It carries a boxed warning for increased suicidality, and is contraindicated in patients with uncontrolled hypertension or seizure disorder, and in those who are receiving long-term opioid therapy.²⁵ Naltrexone/bupropion has a greater effect

Contraindications*	Approved by U.S. Food and Drug Administration
Personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2	2014
—	2012
Abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptics; anorexia nervosa; bulimia; long-term opioid use; seizure disorder; uncontrolled hypertension; use of a monoamine oxidase inhibitor within 14 days	2014
Cholestasis, chronic malabsorption syndrome	1999
Glaucoma, hyperthyroidism, use of a monoamine oxidase inhibitor within 14 days	2012

Table 4. Common Medications that Contribute to Weight Gain or Loss

Medication type	Promote weight gain	Weight neutral/variable	Promote weight loss
Antidepressants	Amitriptyline, doxepin, imipramine, mirtazapine (Remeron), nortriptyline (Pamelor), paroxetine (Paxil), phenelzine (Nardil)	Citalopram (Celexa), desvenlafaxine (Pristiq), duloxetine (Cymbalta), escitalopram (Lexapro), fluoxetine (Prozac), sertraline (Zoloft), venlafaxine	Bupropion (Wellbutrin)
Antipsychotics	Chlorpromazine, clozapine (Clozaril), olanzapine (Zyprexa), paliperidone (Invega), quetiapine (Seroquel), risperidone (Risperdal)	Aripiprazole (Abilify), haloperidol, ziprasidone (Geodon)	—
Cardiovascular agents	Amlodipine (Norvasc), atenolol, felodipine, metoprolol, nifedipine, propranolol	Angiotensin-converting enzyme inhibitors	—
Diabetic agents	Insulin, meglitinides, sulfonylureas, thiazolidinediones	Dipeptidyl peptidase-4 inhibitors	Alpha-glucosidase inhibitors, glucagon-like peptide-1 agonists, metformin, pramlintide (Symlin), sodium glucose cotransporter-2 inhibitors
Hormones	Estrogens, steroids	—	Progestins, testosterone
Hypnotics	Diphenhydramine (Benadryl)	Benzodiazepines, trazodone	—
Mood stabilizers	Lithium	Oxcarbazepine (Trileptal)	—
Seizure medications	Carbamazepine (Tegretol), gabapentin (Neurontin), pregabalin (Lyrica), valproate (Depacon)	Lamotrigine (Lamictal), levetiracetam (Keppra), phenytoin (Dilantin)	Felbamate (Felbatol), topiramate (Topamax), zonisamide (Zonegran)

Adapted with permission from Obesity Medicine Association. Obesity algorithm. <http://obesitymedicine.org/obesity-algorithm> [registration required]. Accessed July 24, 2015, with additional information from reference 33.

on weight loss than either agent alone.³⁵ The Contrave Obesity Research I and II trials showed a weight reduction of 10.4 to 10.8 lb (4.7 to 4.9 kg) greater than placebo.^{31,32} In the Contrave Obesity Research I trial there was a 50% completion rate, and 29.8% of participants experienced nausea; however, there was no increased risk of depression or suicidality.³¹

Which Patients Should Be Referred for Bariatric Surgery?

Patients with a BMI of 40 kg per m² or greater, or 30 kg per m² or greater who have obesity-related comorbidities should be offered referral for consideration of bariatric surgery. Adjustable gastric banding is most appropriate for patients with a BMI of 30 to 34.9 kg per m².

EVIDENCE SUMMARY

Family physicians have a key role in identifying and counseling patients who may qualify for bariatric surgery (Table 5).³⁶⁻³⁸ Patients who have been unsuccessful with extensive lifestyle and medical therapy and who meet criteria for operative intervention based on BMI should be referred for a surgical evaluation. An extensive preoperative assessment of comorbidities and surgical

risk, as well as a willingness to comply with the long-term management and follow-up requirements, is crucial. Candidates for bariatric surgery include those with a BMI of 40 kg per m² or greater, regardless of comorbidities, or a BMI of 30 kg per m² or greater who have at least one severe obesity-related comorbidity, such as type 2 diabetes, hypertension, hyperlipidemia, obstructive sleep apnea, nonalcoholic fatty liver disease, debilitating arthritis, or impaired quality of life. There is increasing evidence for the use of bariatric surgery in patients with a BMI of less than 35 kg per m², and the adjustable gastric band system has been approved for use in patients with a BMI of 30 to 34.9 kg per m² who have obesity-related conditions.³⁶

How Effective Is Bariatric Surgery?

Bariatric surgery is more effective than diet, behavioral modifications, and pharmacotherapy in the management of obesity, and it leads to improvement in numerous obesity-related comorbidities.

EVIDENCE SUMMARY

Gastric bypass is the most common weight loss procedure worldwide. However, sleeve gastrectomy is being

Table 5. Summary of Common Bariatric Procedures

Procedure	Percentage of excess weight lost	Indications	Complications	Mechanism
Adjustable gastric banding	44	BMI \geq 40 kg per m ² , \geq 35 kg per m ² with comorbidities, or \geq 30 kg per m ² with diabetes mellitus or metabolic syndrome	Band erosion or slippage, need for revision or removal, reservoir leakage	Restrictive; silicone band placed around gastric fundus, inflates/deflates to adjust
Roux-en-Y gastric bypass	67	BMI \geq 40 kg per m ² , or \geq 35 kg per m ² with comorbidities	Anastomotic leak, delayed gastric emptying, dumping syndrome, gastric dilation, hernia, nutritional deficiencies, obstruction, staple line failure, stoma narrowing	Restrictive and malabsorptive; \leq 50-mL gastric pouch anastomosed to Roux limb 30 to 50 cm distal to bypass a portion of small bowel
Sleeve gastrectomy	56	BMI \geq 40 kg per m ² , or \geq 35 kg per m ² with comorbidities	Gastric leakage, vomiting	Restrictive; size of stomach is reduced to 25% with pylorus intact

BMI = body mass index.

Information from references 36 through 38.

performed with increasing frequency.³⁹ A 2014 Cochrane review found that surgery, regardless of the procedure, resulted in greater weight loss than nonsurgical treatment.³⁷ However, follow-up was limited to one to two years in most studies. The most weight loss occurs with gastric bypass, followed by sleeve gastrectomy and gastric banding.³⁸ Bariatric surgery is relatively safe, with an overall 30-day mortality rate of 0.08%, a complication rate of 17%, and a reoperation rate of 7%.⁴⁰ Bariatric procedures have been proven effective in reducing many obesity-related conditions, including all-cause mortality, myocardial infarction, and stroke.^{41,42} Surgery leads to a greater rate of diabetes remission than medical treatment, and the term metabolic surgery is increasingly used when referring to these procedures.⁴³ Bariatric surgery has also been shown to improve hypertension, dyslipidemia, sleep apnea, and health-related quality of life.^{37,44,45}

Data Sources: A PubMed search was completed in Clinical Queries using the key terms obesity, pharmacotherapy, bariatric surgery, diet, and behavioral modification. The search included meta-analyses, randomized controlled trials, clinical trials, and reviews. Also searched were the Agency for Healthcare Research and Quality evidence reports, the Cochrane database, the National Guideline Clearinghouse, Essential Evidence Plus, and UpToDate. Search dates: July 2015 through April 2016.

This review updates a previous article on this topic by Rao.⁴⁶

The Authors

MICHAEL ERLANDSON, MD, is an assistant clinical professor in the Department of Family Medicine at the Swedish Family Medicine Residency, University of Colorado School of Medicine, Littleton.

LAURIE C. IVEY, PsyD, is director of behavioral health at the Swedish Family Medicine Residency, University of Colorado School of Medicine.

KATIE SEIKEL, DO, RD, is a second-year resident at the Swedish Family Medicine Residency, University of Colorado School of Medicine.

Address correspondence to Michael Erlandson, MD, Swedish Family Medicine Residency, 191 E. Orchard Rd., Ste. 200, Littleton, CO 80121 (e-mail: michael.erlandson@healthonecares.com). Reprints are not available from the authors.

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