Review

Long-term Drug Treatment for Obesity
A Systematic and Clinical Review

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IMPORTANCE Thirty-six percent of US adults are obese, and many cannot lose sufficient weight to improve health with lifestyle interventions alone.

OBJECTIVE To conduct a systematic review of medications currently approved in the United States for obesity treatment in adults. We also discuss off-label use of medications studied for obesity and provide considerations for obesity medication use in clinical practice.

EVIDENCE REVIEW A PubMed search from inception through September 2013 was performed to find meta-analyses, systematic reviews, and randomized, placebo-controlled trials for currently approved obesity medications lasting at least 1 year that had a primary or secondary outcome of body weight change, included at least 50 participants per group, reported at least 50% retention, and reported results on an intention-to-treat basis. Studies of medications approved for other purposes but tested for obesity treatment were also reviewed.

FINDINGS Obesity medications approved for long-term use, when prescribed with lifestyle interventions, produce additional weight loss relative to placebo ranging from approximately 3% of initial weight for orlistat and lorcaserin to 9% for top-dose (15/92 mg) phentermine plus topiramate–extended release at 1 year. The proportion of patients achieving clinically meaningful (at least 5%) weight loss ranges from 37% to 47% for lorcaserin, 35% to 73% for orlistat, and 67% to 70% for top-dose phentermine plus topiramate–extended release. All 3 medications produce greater improvements in many cardiometabolic risk factors than placebo, but no obesity medication has been shown to reduce cardiovascular morbidity or mortality. Most prescriptions are for noradrenergic medications, despite their approval only for short-term use and limited data for their long-term safety and efficacy.

CONCLUSIONS AND RELEVANCE Medications approved for long-term obesity treatment, when used as an adjunct to lifestyle intervention, lead to greater mean weight loss and an increased likelihood of achieving clinically meaningful 1-year weight loss relative to placebo. By discontinuing medication in patients who do not respond with weight loss of at least 5%, clinicians can decrease their patients' exposure to the risks and costs of drug treatment when there is little prospect of long-term benefit.

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Obesity (body mass index [BMI, calculated as weight in kilograms divided by height in meters squared] ≥30) is highly prevalent in the United States; 36% (>78 million) of US adults are estimated to be obese.[1] Almost all US health professionals in the United States treat patients with obesity and are well aware of its medical consequences.

Weight loss of 5% to 10% of initial weight, achieved through intensive lifestyle intervention, reduces cardiovascular disease (CVD) risk factors, prevents or delays the development of type 2 diabetes, and improves other health consequences of obesity.[2,3] Although improvements in some CVD risk factors can be seen with sustained weight loss as small as 3%, weight loss of 5% or more is generally considered to be clinically meaningful.[4,5] Even larger weight losses produce greater reductions in cardiometabolic risk.[6]

With intensive lifestyle treatments, a majority of obese participants in clinical trials lose 7% to 10% of their initial weight at 1 year.[5] However, results from these efficacy trials are far better than those attained by patients in primary care settings, where studies using low-intensity counseling have not demonstrated clinically meaningful mean weight loss.[7] Regardless of initial weight loss success, longer-term weight maintenance is difficult. With continued lifestyle treatment, weight regain can be ameliorated but not eliminated.[8] The need for constant vigilance to sustain behavior changes in the face of biologic and environmental pressures to regain weight emphasizes the challenges faced by even the most mo-

Table 1. Drugs With US Food and Drug Administration–Approved Indication for Obesity

Generic Drug (Proprietary Name[s]) Dose Frequency/d)	Mechanism of Action	Wholesale Price/mo, $[a]	1-y Weight Change Relative to Placebo, Mean (95% CI), kg[b]	Common Adverse Effects
Short-term approval[c]				
Phentermine 15-37.5 mg (Adipex-P, Fastin, Oby-Cap, Ionamin, Others; 1×)[d]	Noradrenergic causing appetite suppression	6-45	Not included	Insomnia, elevation in heart rate, dry mouth, taste alterations, dizziness, tremors, headache, diarrhea, constipation, vomiting, gastrointestinal distress, anxiety, and restlessness[e]
Diethylpropion 25 mg or 75 mg, SR (Tenuate, Tenuate Dospan, Tepanil; low dose, 3×; SR dose, 1×)[d]	Noradrenergic causing appetite suppression	47-120	Not included	Same as phentermine[e]
Phendimetrazine 17.5-70 mg or 105 mg, SR (Bontril; lower doses, 2-3×; SR dose, 1×)[f]	Noradrenergic causing appetite suppression	6-20	Not included	Same as phentermine[e]
Benzphetamine 25-50 mg (Didrex; 1-3×)[f]	Noradrenergic causing appetite suppression	20-50	Not included	Same as phentermine[e]
Long-term approval[c]				
Orlistat 60 mg (Alli) or 120 mg (Xenical; 3× within 1 h of a fat-containing meal)[g]	Lipase inhibitor causing excretion of approximately 30% of ingested triglycerides in stool	60 mg, 45 120 mg, 207	60 mg, −2.5 kg (−1.5 to −3.5) 120 mg, −3.4 kg (−3.2 to −3.6)	Oily spotting, flatus with discharge, fecal urgency, fatty oily stool, increased defecation, fecal incontinence[h]
Lorcaserin 10 mg (Belviq; 2×)[d]	Highly selective serotonergic 5-HT2C receptor agonist causing appetite suppression	240	−3.2 kg (−2.7 to −3.8)	Headache, dizziness, fatigue, nausea, dry mouth, cough, and constipation; and in patients with type 2 diabetes, back pain, cough, and hypoglycemia[h]
Phentermine plus topiramate-ER (Qsymia; 3.75 mg/23 mg for 2 weeks, increased to 7.5 mg/46 mg, escalating to a max of 15 mg/92 mg; 1×)[d]	Noradrenergic + GABA-receptor activator, kainite /AMPA glutamate receptor inhibitor causing appetite suppression	140-195	7.5 mg/46 mg, −6.7 kg (−5.9 to −7.5) 15 mg/92 mg, −8.9 kg (−8.3 to −9.4)	Paresthesias dizziness, taste alterations, insomnia, constipation, dry mouth, elevation in heart rate, memory or cognitive changes[h]

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; ER, extended release; GABA, γ-aminobutyric acid.

[a] Reference prices[9] as of March 8, 2013.

[b] Weight change data are relative to placebo using intent-to-treat analyses for each medication at 1 year. No studies for older noradrenergic agents met inclusion criteria for length of treatment, sample size, and attrition.

[c] Food and Drug Administration–approved for short-term (ie, a few weeks) or long-term use.

[d] Medications listed on Drug Enforcement Administration Schedule IV are associated with a lower risk of abuse than medications on Schedule III.

[e] Common adverse events for noradrenergic agents include those listed as common in Prescription Medications for the Treatment of Obesity[10] because adverse event frequency is not available in drug package inserts for these agents.

[f] Drug Enforcement Administration Schedule III medication.

[g] Orlistat is a non-Drug Enforcement Administration–scheduled drug.

[h] For orlistat, lorcaserin, and phentermine plus topiramate-ER, common adverse events are those listed in the drug package inserts[11-13] that are reported to occur more frequently than placebo and with more than 5% prevalence. See full prescribing information for all adverse effects, cautions, and contraindications.

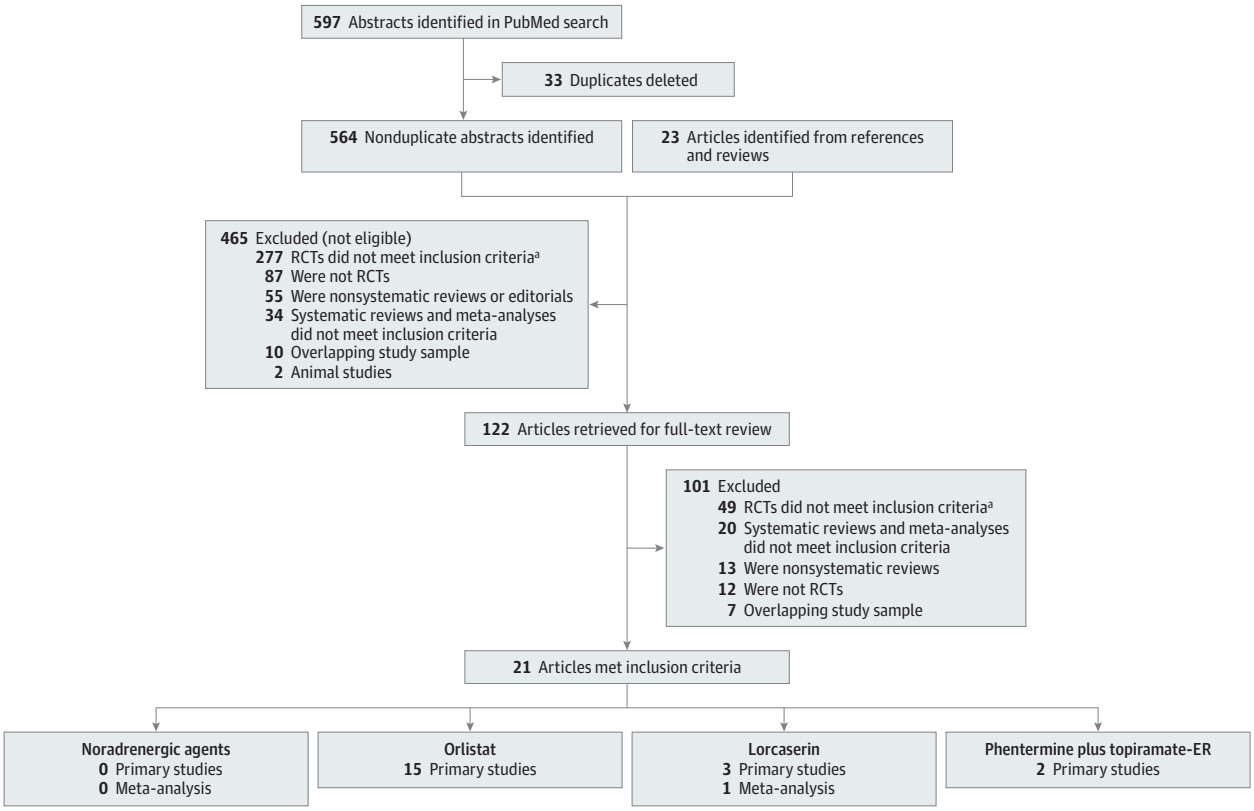
tivated patients who have achieved weight loss. Thus, there is a need for adjunctive therapies that can help patients who are not able to lose or sustain sufficient weight loss to improve health with lifestyle interventions alone.

This article systematically reviews the literature for long-term use of medications currently approved by the US Food and Drug Administration (FDA) for obesity treatment in adults (**Table 1**). We also discuss off-label use of medications approved for other purposes that have been studied for obesity treatment or drug-induced weight gain, and provide considerations for use of obesity medications in clinical practice.

Methods

A PubMed search was conducted from inception to September 15, 2013, to find long-term studies investigating drugs currently approved for use alone or in combination for an obesity or weight management indication using the terms *obesity*, *appetite* or *satiety*, and *drug* or *pharmacotherapy*; and *orlistat*, *phentermine*, *diethylpropion*, *phendimetrazine*, *benzphetamine*, *topiramate*, *Qsymia*, *Qnexa*, *lorcaserin*, or *Belviq*; and *clinical trial* or *meta-analysis*. Searches were restricted to human studies in English. The primary search resulted in 564 articles (**Figure**). Automated searches were supplemented by examination of expert recommendation reports and bibliographic references from included research studies, and searches of www.clinicaltrials.gov for each identified medication. Studies identified underwent review of the title, abstract, or both by each author to discard clearly nonrelevant articles as well as reports describing drugs that have been withdrawn from use (eg, sibutramine) or for which further development for an obesity indication has been abandoned (eg, fluoxetine). To be included, studies had to report randomized placebo-controlled clinical trials lasting a minimum of 1 year with a primary or secondary outcome of body weight change, study at least 50 participants per group at baseline, report at least 50% retention, and report results on an intention-to-treat basis. Re-

Figure. Identification of Manuscripts for Systematic Review



A PubMed search was conducted from inception to September 15, 2013, to find long-term (≥1-y) placebo-controlled randomized clinical trials and meta-analyses investigating drugs currently US Food and Drug Administration–approved alone or in combination for an obesity or weight-management indication. ER indicates extended release.

[a] Randomized controlled trials (RCTs) were excluded for the following reasons: nonapproved drug or drug combination, participants were children, not published in English, no placebo group, did not meet criteria for size, duration, or attrition, not an intention-to-treat analysis, or insufficient description of data analysis. Many studies had more than 1 exclusion criterion.

sults for randomized controlled trials meeting our inclusion criteria are reported in Table 1 and **Table 2**.

Medications approved for other purposes but tested for at least 52 weeks for obesity prevention or treatment were also reviewed nonsystematically.

Results

Included studies are reported in Table 2, **Table 3**, and **Table 4**. No studies for older noradrenergic agents (phentermine, diethylpropion, phendimetrazine, and benzphetamine) met inclusion criteria for length of treatment, sample size, or attrition. Fifteen trials[14-28] reporting intention-to-treat data from 5006 adults treated with orlistat and 4555 with placebo appeared to meet study entry criteria for orlistat, although data for absolute weight change were not ascertainable from 2 trials.[26,28] Multiple meta-analyses[34-38] for orlistat 120 mg have been carried out that included most of these identified studies and found similar pooled 1-year weight loss results, but none met all of the criteria for study inclusion. Pooled, sample size-weighted estimates and 95% CIs for weight loss at 1 year were calculated from the primary studies. There were no meta-analyses identified for orlistat 60 mg. Pooled, sample size-weighted estimates and 95% CIs for weight loss at 1 year were calculated from the primary studies of 452 adults treated with orlistat and 449 with placebo reported in the 2 primary studies[18,20] that met criteria for inclusion. One meta-analysis[39] reported results from 3350 patients treated with lorcaserin (10 mg twice daily) and 3288 with placebo reported in the 3 articles[29-31] meeting study criteria for lorcaserin; results are reported from this meta-analysis. There were no meta-analyses identified for phentermine plus topiramate–extended release (ER). However, pooled data from 3 groups of adult participants in the phase III studies for change in weight that met inclusion criteria[32,33] (488 treated with phentermine 7.5 mg plus topiramate-ER 46 mg; 1479 treated with phentermine 15 mg plus topiramate-ER 92 mg; and 1477 treated with placebo) were obtained from the integrated summary of efficacy submitted by Vivus, Inc to the FDA as part of their new drug application.[40,41] No studies, and therefore no meta-analyses, for any of the noradrenergic medications met inclusion criteria. Results from a quantitative analysis of the extant clinical trials by Haddock et al[42] are reported in the text. Primary studies meeting inclusion criteria for each medication were also reviewed for their effect on health outcomes other than weight loss.

Medications currently approved by the FDA for obesity treatment are listed in Table 1. All are considered indicated for adults with a BMI at least 30 and all but benzphetamine and diethylpropion are

Table 2. Studies Included in Systematic Review for Long-term Pharmacotherapy of Obesity Using Orlistat

Source (Location)	Participant Characteristics[a]	No. Randomized		Dosage/d		Lifestyle Intervention Program	Attrition, %[b]
		Intervention	Placebo	Intervention	Placebo		
Hollander et al,[14] 1995 (United States)	49% Women, BMI 28-40, DM-2, clinically stable on oral sulfonylureas only, 70% treatment adherent in placebo run-in	163	159	120 mg, 3×	3×	Caloric reduction 500 kcal/d	21
Sjostrom et al,[15] 1998 (Europe)	83% Women, BMI 28-47, 75% treatment adherent in placebo run-in	345	343	120 mg, 3×	3×	Caloric reduction 600-900 kcal/d	21
Davidson et al,[16] 1999 (United States)	84% Women, BMI 30-43, 75% treatment adherent in placebo run-in	668	224	120 mg, 3×	3×	Caloric reduction 500-900 kcal/d, behavior modification with exercise counseling, food diary	34
Finer et al,[17] 2000 (United Kingdom)	88% Women, BMI 30-43, 70% treatment adherent in placebo run-in	114	114	120 mg, 3×	3×	Caloric reduction 600-900 kcal/d	39
Hauptman et al,[18] 2000 (United States)	78% Women, BMI 30-44, 75% treatment adherent in placebo run-in	60 mg, 213 120 mg, 210	212	60 mg, 3× 120 mg, 3×	3×	Maintain 1200-1500 kcal/d, exercise, food diary, educational video	33
Lindgarde,[19] 2000 (Sweden)	64% Women, BMI 28-38, DM-2 treated only with metformin or sulfonylurea, hypercholesterolemia and/or hypertension, complete a placebo run-in	190	186	120 mg, 3×	3×	Caloric reduction 600-900 kcal/d, exercise, self-help weight control education	14
Rossner et al,[20] 2000 (Europe)	82% Women, BMI 28-43, 75% treatment adherent in placebo run-in	60 mg, 242 120 mg, 244	243	60 mg, 3× 120 mg, 3×	3×	Caloric reduction 600 kcal/d, food diaries, counseling by dietitian	28
Broom et al,[21] 2002 (United Kingdom)	78% Women, BMI ≥28, untreated hypertension, impaired glucose tolerance or dyslipidemia, complete a 2-wk placebo run-in; withdrawn if <60% drug adherence	265	266	120 mg, 3×	3×	Caloric reduction 600-900 kcal/d, food diary	35
Hanefeld and Sachse,[22] 2002 (Germany)	51% Women, BMI ≥28, DM, HbA_{1C} 6.5%-11% treated with diet alone or sulfonylurea, complete a 4-wk placebo run-in; withdrawn if <75% drug adherence	195	188	120 mg, 3×	3×	Caloric reduction 600 kcal/d, diet diary	31
Miles et al,[23] 2002 (Canada; United States)	48% Women, BMI 28-43, DM-2, HbA_{1C} 7.5%-12%, receiving oral hypoglycemic medication, complete a 2-wk screening phase	255	261	120 mg, 3×	3×	Caloric reduction 600 kcal/d, exercise counseling	40
Krempf et al,[24] 2003 (France)	86% Women, BMI ≥28, without DM or other significant medical condition, complete a 2-wk placebo run-in	346	350	120 mg, 3×	3×	20% Energy-reduced diet increased 10% if weight stable, food diary	≤39[c]
Torgerson et al,[25] 2004 (Sweden)	55% Women, aged 30-60 y, BMI ≥30, nondiabetic glucose tolerance	1650	1655	120 mg, 3×	3×	Caloric reduction 800 kcal/d, lifestyle intervention	16
Berne,[26] 2005 (Sweden)	45% Women, aged 30-75 y, BMI 28-40, DM-2, HbA_{1C} 6.5%-10% treated only with metformin or sulfonylurea, complete a 2-wk diet run-in	111[d]	109[d]	120 mg, 3×	3×	Caloric reduction 600 kcal/d, diet/exercise counseling, self-management education	14

(continued)

Table 2. Studies Included in Systematic Review for Long-term Pharmacotherapy of Obesity Using Orlistat (continued)

Source (Location)	Participant Characteristics[a]	No. Randomized		Dosage/d		Lifestyle Intervention Program	Attrition, %[b]
		Intervention	Placebo	Intervention	Placebo		
Swinburn et al,[27] 2005 (Australia and New Zealand)	57% Women, aged 40-70 y, BMI 30-50, DM-2 treated only with oral agents, HbA_{1C} 6.5%-10%, hypercholesterolemia and/or hypertension, complete a placebo run-in	170	169	120 mg, 3×	3×	Reduced-fat diet and exercise counseling	21
Derosa et al,[28] 2012 (Italy)	49% Women, BMI ≥30, DM-2, HbA_{1C} >8.0%	126	128	120 mg, 3×	3×	Caloric reduction 600 kcal/d, behavior modification, exercise counseling	8

Abbreviations: BMI, body mass index; DM, diabetes mellitus; DM-2, diabetes mellitus type 2; HbA_{1c}, hemoglobin A_{1c}.

[a] All participants were adults. BMI was calculated as weight in kilograms divided by height in meters squared.

[b] Attrition for each study was calculated from the total number of participants who were randomized to receive treatment.

[c] Attrition available only at 18 mo.

[d] Allocation to intervention or placebo group was unclear for 1 participant.

Table 3. Studies Included in Systematic Review for Long-term Pharmacotherapy of Obesity Using Lorcaserin or Phentermine Plus Topiramate-ER

Source (Location)	Participant Characteristics[a]	No. Randomized		Dosage/d		Lifestyle Intervention	Attrition, %[b]
		Intervention	Placebo	Intervention	Placebo		
Lorcaserin							
Smith et al,[29] 2010 (United States)	83% Women, BMI 30-45 or BMI 27-29.9 with an obesity-related comorbid condition	1595	1587	10 mg, 2×	2×	Caloric reduction 600 kcal/d, standardized nutritional and exercise counseling	50
Fidler et al,[30] 2011 (United States)	80% Women, BMI 30-45 or BMI 27-29.9 with an obesity-related comorbid condition	801 1602	1601	10 mg, 1× 10 mg, 2×	2×	Caloric reduction 600 kcal/d and exercise counseling, diet diary	45
O'Neil et al,[31] 2012 (United States)	54% Women, BMI 27-45, DM-2 treated with metformin or sulfonylurea, HbA_{1C} 7%-10%	95 256	252	10 mg, 1× 10 mg, 2×	2×	Caloric reduction 600 kcal/d; nutritional and exercise counseling	34
Phentermine plus topiramate-ER							
Allison et al,[32] 2012 (United States)	83% Women, BMI ≥35, fasting glucose ≤110mg/dL, triglycerides ≤200 mg/dL with ≤1 lipid-lowering drug, BP ≤140/90 mm Hg with ≤2 antihypertensive drugs	241 Starting dose 512 top dose	514	3.75 mg/23 mg Starting dose 15 mg/92 mg top dose	1×	Self-help weight control manual, caloric reduction 500 kcal/d, monthly progress reviews	40
Gadde et al,[33] 2011 (United States)	70% Women, BMI 27-45 and ≥2 weight-related comorbidities, no lower BMI limit for participants with DM-2 (16% of cohort)	498 Recommended dose 995 top dose	994	7.5 mg/46 mg Recommended dose 15 mg/92 mg top dose	1×	Standardized lifestyle counseling, caloric reduction 500 kcal/d	31

Abbreviations: BMI, body mass index; DM, diabetes mellitus; DM-2, diabetes mellitus type 2.

[a] All participants were adults. BMI was calculated as weight in kilograms divided by height in meters squared.

[b] Attrition for each study was calculated from the total number of participants who were randomized to receive treatment.

also approved for patients with a BMI of 27 or greater plus at least 1 weight-related comorbidity such as hypertension or type 2 diabetes.

Noradrenergic Activation

Four centrally acting noradrenergic agents (phentermine, diethylpropion, phendimetrazine, benzphetamine) are FDA-approved for short-term (usually considered ≤12 weeks) management of obesity. All were approved before the necessity of long-term treatment for obesity was established. In addition, none were required to meet the current efficacy benchmarks for weight loss relative to placebo (mean weight loss ≥5% more than that of the placebo group or proportion of drug-treated participants who lose ≥5% of initial weight is ≥35% and approximately double the proportion who lose ≥5% in the placebo group at 1 year).[43] Limited treatment duration for these noradrenergic agents was a requirement added in 1973 because of concerns about abuse potential and transient efficacy.[43] No trials of these 4 medications met our criteria for inclusion (dura-

Table 4. One-Year Weight Change in Studies Included in Systematic Review for Long-Term Pharmacotherapy of Obesity[a]

	1-y Change							
	Loss Relative to Baseline Weight, kg		Loss Relative to Baseline Weight, %		≥5% Loss of Baseline Weight, %		≥10% Loss of Baseline Weight, %	
Source	Intervention	Placebo	Intervention	Placebo	Intervention	Placebo	Intervention	Placebo
Orlistat								
Hollander et al,[14] 1995	−6.2	−4.3	−6.2	−4.3	48.8	22.6	17.9	8.8
Sjostrom et al,[15] 1998	−10.3	−6.1	−10.2	−6.1	68.5	49.2	38.8	17.7
Davidson et al,[16] 1999	−8.8	−5.8	−8.8	−5.8	65.7	43.6	38.9	24.8
Finer et al,[17] 2000	−3.3	−1.3	−8.5	−5.4	35	21	28	17
Hauptman et al,[18] 2000	60 mg, −7.1 120 mg, −7.9	−4.1	60 mg, −7.1 120 mg, −7.9	−4.2	60 mg, 48.8 120 mg, 50.5	30.7	60 mg, 24.4 120 mg, 28.6	11.3
Lindgarde,[19] 2000	−5.6	−4.3	−5.9	−4.6	54.2	40.9	19.2	14.6
Rossner et al,[20] 2000	60 mg, −8.5 120 mg, −9.4	−6.4	60 mg, −8.6 120 mg, −9.7	−6.6	60 mg, NA 120 mg, NA	NA	60 mg, 31.2 120 mg, 38.3	18.8
Broom et al,[21] 2002	−5.8	−2.3	−5.8	−2.3	55.6	24.3	19.7	11
Hanefeld and Sachse,[22] 2002	−5.3	−3.4	−5.4	−3.6	51.3	31.6	NA	NA
Miles et al,[23] 2002	−4.7	−1.8	−4.6	−1.7	39.0	15.7	14.1	3.9
Krempf et al,[24] 2003	−6.3	−3.3	−6.3	−3.6	65.9	46.4	32.9	24.5
Torgerson et al,[25] 2004	−10.6	−6.2	NA	NA	72.8	45.1	41	20.8
Berne,[26] 2005	NA	NA	−5.0	−1.8	45.9	11	13.5	2.8
Swinburn et al,[27] 2005	−4.7	−0.9	NA	NA	NA	NA	NA	NA
Derosa et al,[28] 2012	NA	NA	NA	NA	NA	NA	NA	NA
Lorcaserin								
Smith et al,[29] 2010	−5.8	−2.2	−5.8	−2.2	47.5	20.3	22.6	7.7
Fidler et al,[30] 2011	10 mg 1×, −4.7 10 mg 2×, −5.8	−2.9	10 mg 1×, −4.7 10 mg 2×, −5.8	−2.8	10 mg 1×, 40.2 10 mg 2×, 47.2	25.0	10 mg 1×, 17.4 10 mg 2×, 22.6	9.7
O'Neil et al,[31] 2012	10 mg 1×, −5 10 mg 2×, −4.7	−1.6	10 mg 1×, −5 10 mg 2×, −4.5	−1.5	10 mg 1×, 44.7 10 mg 2×, 37.5	16.1	10 mg 1×, 18.1 10 mg 2×, 16.3	4.4
Phentermine plus topiramate-ER								
Allison et al,[32] 2012	NA	NA	3.75 mg/23 mg, −5.1 15 mg/92 mg, −10.9	−1.6	3.75 mg/23 mg, 44.9 15 mg/92 mg, 66.7	17.3	3.75 mg/23 mg, 18.8 15 mg/92 mg, 47.2	7.4
Gadde et al,[33] 2011	7.5 mg/46 mg, −8.1 15 mg/92 mg, −10.2	−1.4	7.5 mg/46 mg, −7.8 15 mg/92 mg, −9.8	−1.2	7.5 mg/46 mg, 62 15 mg/92 mg, 70	21	7.5 mg/46 mg, 37 15 mg/92 mg, 48	7

Abbreviation: NA, not available.

[a] Results for weight change are reported from intention-to-treat analyses, generally with the last observation carried forward. Some results reported in the studies (eg, for follow-up intervals other than 1 year) are not included.

tion, size, and attrition), although a meta-analysis with shorter-term outcomes has been published.[42] These centrally acting agents reduce appetite by increasing activation of adrenergic and dopaminergic receptors.[44]

Phentermine, despite its approval by the FDA for short-term use, is frequently prescribed off label for longer periods.[45,46] Phentermine is by far the most widely prescribed obesity medication in the United States, with 25.3 million prescriptions dispensed to an estimated 6.2 million users between 2008-2011.[46] Although it has a long history of use, there are few controlled trials of phentermine monotherapy for 6 months or more, and studies describing the effect of phentermine monotherapy on weight and CVD risk factors for more than 1 year are limited to case reports and case series. A meta-analysis of 6 studies ranging from 2 to 24 weeks[42] found that patients using 15 to 30 mg per day of phentermine had a mean additional weight loss, relative to placebo, of 3.6 kg, with mean total weight loss of 6.3 kg. The longest published placebo-controlled trial of phentermine lasted 36 weeks in 108 obese women treated with phentermine 30 mg per day either continuously or intermittently (alternating months) and found similar weight loss in the continuous (12.2 kg) and intermittent (13.0 kg) groups vs 4.8 kg with placebo. However, attrition was 41% and data were presented only for individuals who completed the trial, which is likely to overstate efficacy.[47] Among individuals who completed the trial, transient symptoms of central nervous system stimulation such as insomnia, irritability, and anxiety did not differ between participants receiving continuous (24%) vs intermittent (27%) therapy, compared with 8% for participants taking placebo. Several short-term placebo-

controlled studies of phentermine have shown elevations in pulse or smaller decreases in pulse, blood pressure, or both, than would be expected given the degree of weight loss.[3]

Diethylpropion has a similar adverse effect and weight loss profile to phentermine, but is much less frequently prescribed, with approximately 1 million prescriptions dispensed between 2008 and 2011.[46] A meta-analysis of 9 small studies ranging from 6 to 52 weeks[42] found that patients using diethylpropion 75 mg per day had a mean additional weight loss relative to placebo of 3.0 kg, with a mean total weight loss of 6.5 kg.

Phendimetrazine, despite the paucity of randomized controlled trials,[42] is prescribed 3 times more frequently than diethylpropion for obesity treatment, with more than 3 million phendimetrazine prescriptions estimated to have been filled between 2008 and 2011.[46] In the analyses of participants who completed 2 small 12-week trials,[48,49] it appears to have similar weight loss to other noradrenergic drugs.

Benzphetamine is less commonly prescribed for obesity treatment than the other noradrenergic drugs[46] and there are few data from controlled trials evaluating its safety or efficacy.[42]

Common adverse effects of noradrenergic drugs are shown in Table 1. Because these medications were approved prior to the requirements for long-term trials with adequate power to ascertain clinical end points, an adverse effect of noradrenergic obesity drugs on CVD events cannot be excluded, which is of concern given their known effect on heart rate and blood pressure.

Gastrointestinal Lipase Inhibition

Orlistat is a gastrointestinal lipase inhibitor which, when taken 3 times per day during or up to 1 hour after meals, leads to the excretion of approximately 30% of ingested fat. It is available in prescription (120 mg) and over-the-counter (60 mg) strengths. Orlistat 120 mg is FDA approved for use in adults and adolescents aged 12 to 16 years. The mean 12-month weight reduction attributable to orlistat 120 mg taken 3 times per day is modest: among adults participating in behavioral weight control programs and prescribed a lower-fat diet (≈30% of calories from fat) and a multivitamin, participants taking orlistat lost on average 3.4 kg (≈3.1% of initial weight) more than participants taking placebo (Table 1 and Table 2). Two trials[18,20] of orlistat 60 mg taken 3 times per day met study criteria for inclusion; the pooled estimate from these studies indicates 2.5 kg greater weight loss than placebo at 12 months.

Among the orlistat 120-mg trials examined (Table 2 and Table 4), the percentage of participants in the treatment group who achieved clinically meaningful (≥5%) weight loss at 1 year ranged from 35% to 73% and the proportion losing at least 10% ranged from 14% to 41%, with weight loss of at least 5% and at least 10% at 1 year significantly greater for participants taking orlistat than for placebo. At the end of a second year of treatment when a weight-maintenance diet was prescribed, participants taking 120 mg of orlistat had lost approximately 3.3 kg (≈3.3% of initial weight) more, and participants taking 60 mg of orlistat had lost approximately 2.5 kg (≈2.5% of initial weight) more than those given placebo.[15,16,18,20] Because of its weight loss–related and weight loss–independent[50] actions, treatment with 120 mg of orlistat is associated with significant improvements in cardiovascular risk factors including decreases in total and low-density lipoprotein cholesterol, fasting glucose, and systolic and diastolic blood pressures after 1 year of treatment.[51,52]

Data from the XENDOS trial of 3305 patients treated for as long as 4 years (attrition at 4 years, 48% for the orlistat group and 66% for the placebo group) found, in an intention-to-treat approach, that orlistat use decreased body weight over 4 years by 2.7 kg (≈2.4% of initial body weight) more than placebo and significantly decreased risk for developing type 2 diabetes from 9.0% with placebo to 6.2% with orlistat.[25] Because orlistat leads to obligate increases in undigested stool triglycerides, it may cause considerable gastrointestinal adverse effects (Table 1)[11] that may be decreased by coadministration of fiber-containing supplements.[53] These adverse effects may cause patients who do not reduce their fat intake to discontinue therapy. Indeed, despite being FDA-approved in 1999 for indefinite treatment of obesity, among those prescribed orlistat 120 mg clinically, fewer than 10% take it for at least 1 year and less than 2% of patients are prescribed the medication for 2 years.[46,54]

Serotonin Receptor Activation

Lorcaserin is a selective serotonin 2C ($5HT_{2c}$) receptor agonist that was anticipated to recapitulate the weight loss effects of fenfluramine without its adverse cardiac effects.[55] Lorcaserin 10 mg taken twice daily was FDA approved in 2012 on the basis of 2 large randomized, placebo-controlled trials in nondiabetic patients (BLOOM[29] [N=3182; 50% attrition] and BLOSSOM[30] [N=4004; 45% attrition]) along with a third smaller trial in adults with type 2 diabetes (BLOOM-DM[31] [N=603; 34% attrition]). In these trials, participants received low-intensity nutritional and exercise counseling. Lorcaserin decreased body weight modestly, by approximately 3.2 kg (≈3.2% of initial body weight) more than placebo.[39] However, significantly more patients treated with lorcaserin 10 mg twice daily than placebo lost at least 5% (BLOOM [47% vs 20%], BLOSSOM [47% vs 25%], BLOOM-DM [37% vs 16%]) or at least 10% (BLOOM [23% vs 8%], BLOSSOM [23% vs 10%], BLOOM-DM [16% vs 4%]) of their initial weight.

Reduction in body weight below baseline in the only study[29] with data from participants who took lorcaserin for 2 years had average weight loss of 5.6 kg vs 2.4 kg among participants receiving placebo. Blood pressure, total cholesterol, low-density lipoprotein cholesterol, and triglycerides also decreased significantly more in participants treated with lorcaserin.[12] Among patients with diabetes, lorcaserin treatment led to lower body weight and improved glycated hemoglobin concentrations.[31] Adverse effects (Table 1) include headache, nausea, fatigue, and dizziness.[12] Although neither incidence of valvulopathy nor hypertension was statistically greater during lorcaserin than placebo treatment, both were numerically somewhat more prevalent and the FDA has requested that a post-approval trial to assess the long-term cardiovascular effects of lorcaserin be conducted.[56]

Combination Therapy

Phentermine plus topiramate-extended release (ER) is the first FDA-approved combination drug for obesity, combining low-dose phentermine with a nonstandard dose of the antiepileptic medication topiramate-ER (Table 1). Phentermine plus topiramate-ER is administered as a once-daily capsule in 4 fixed-dose combinations: 3.75 mg phentermine plus 23 mg topiramate (starting dose); 7.5 mg phentermine plus 46 mg topiramate (recommended dose); 11.25 mg phentermine plus 69 mg topiramate (titration dose); and 15 mg

phentermine plus 92 mg topiramate (top dose). Dosage is increased over 14 days to 7.5 mg phentermine plus 46 mg topiramate, with additional titration to the top dose if weight loss is inadequate.[13]

Phentermine plus topiramate-ER was recommended for approval based largely on 2 phase 3 clinical trials (EQUIP[32] and CONQUER[33]). All groups received a low-intensity lifestyle program. All underwent dose titration over 4 weeks to an assigned dose followed by 52 weeks taking drug or placebo.

The EQUIP[32] trial (N=1267) randomized adults without diabetes and with BMI of at least 35 to placebo, to phentermine 3.75 mg plus topiramate-ER 23 mg (starting dose), or to phentermine 15 mg plus topiramate-ER 92 mg (top dose); 40% of participants withdrew. For participants given the top dose vs placebo, mean 1-year weight loss was 10.9% vs 1.6% of initial weight, weight loss of at least 5% of initial weight was 67% vs 17%, and weight loss of at least 10% of initial weight was 47% vs 7%.

The CONQUER[33] trial (N=2487) randomized a higher-risk sample of adults with BMI of 27 to 45 plus at least 2 obesity-associated comorbid conditions, to placebo or phentermine plus topiramate-ER; 31% of participants withdrew. One-year mean weight loss was 8.1 kg (7.8%) with the recommended dose and 10.2 kg (9.8%) with the top dose vs 1.4 kg (1.2%) with placebo. In addition, 62% taking the recommended dose and 70% taking the top dose lost at least 5% of initial weight vs 21% for placebo; and 37% taking the recommended dose and 48% taking the top dose lost at least 10% of initial weight vs 7% for placebo. Many CVD risk factors improved with active drug treatment at recommended or top dose.[57] At CONQUER sites selected for high enrollment and retention, the SEQUEL[58] trial (an extension to CONQUER) continued to treat 78% of CONQUER participants who had completed the initial 56-week trial for a total of 108 weeks. Of these participants, 84% completed their second year of treatment with sustained weight loss of 9.3% at the recommended dose and 10.5% at the top dose, vs 1.8% for placebo, and continued differences in many CVD risk factors. In addition, there was a significantly lower incidence of progression to type 2 diabetes in the top-dose group (0.9%) vs placebo (3.7%).

An area of considerable concern, given that most users of obesity medications are women of reproductive age, is the potential for oral clefts in the offspring of women who become pregnant while taking topiramate (Supplement, eTable).[59] A risk evaluation and mitigation strategy was developed to minimize the likelihood of pregnancy in women with reproductive potential that includes clinician training, dispensing only via certified pharmacies, and supplying patient information regarding risks and the necessity of using effective contraception.[60] Women with childbearing potential should have a negative pregnancy test prior to starting phentermine plus topiramate-ER and be tested monthly thereafter.[60] A small increase in resting heart rate has been observed in the clinical trials of phentermine plus topiramate-ER at higher doses, with more patients on top-dose (56.1%) than placebo (42.1%) having increases of more than 10 beats per minute, leading to some concerns regarding its potential long-term effect on CVD events.[61] Phentermine plus topiramate-ER was approved with a requirement for a postmarketing trial of to assess long-term cardiovascular safety.[56] The labeling recommends against prescription in patients with recent or unstable cardiac or cerebrovascular disease, and suggests regular monitoring of resting heart rate.[13]

Other Medications Studied Off Label for Obesity Prevention or Treatment

Medications that are FDA approved for other conditions and found to result in weight loss have been tested as potential obesity treatments. Some, such as fluoxetine, were found to promote weight loss for as long as 6 months, but not longer term.[62] Bupropion, a norepinephrine and dopamine reuptake inhibitor, was tested as monotherapy for as long as 1 year as a weight loss medication. A pooled analysis of 3 studies ranging from 6 to 12 months showed additional weight loss relative to placebo of 2.8 kg in patients receiving 400 mg per day of bupropion, with total weight loss of 4.4 kg.[35]

Metformin, increasingly used off label in patients with prediabetes and other insulin-resistant states, produces small sustained weight losses of about 2% relative to placebo.[63,64] Metformin improves insulin sensitivity, has a good safety profile, and long-term clinical experience. Because weight loss attributable to metformin is small, its usefulness as monotherapy for obesity treatment is limited, but its salutary effects on body weight make it a good choice when other indications warrant its prescription. Metformin has also been used to prevent or ameliorate weight gain with atypical antipsychotic agents and mood stabilizers. A meta-analysis examining the effect of medications for attenuation of antipsychotic weight gain found an approximate 3 kg additional weight loss relative to placebo attributable to metformin.[65]

Zonisamide, an antiepileptic medication, also induces weight loss. A 12-month randomized controlled trial of 225 adults, with 97% follow-up, found that a 400 mg dose led to significantly greater weight loss than placebo (6.8% vs 3.7%), as well as a greater proportion losing at least 5% and at least 10% of initial weight.[66] However, adverse effects were limiting.

Pramlintide is a synthetic analogue of human amylin, which is administered subcutaneously at meal times as an adjunct to insulin for patients with type 1 and type 2 diabetes. A meta-analysis[67] of 8 studies in patients with type 2 diabetes and obese nondiabetic populations found additional weight loss relative to placebo of approximately 2.2 kg for both groups. One study,[68] evaluating pramlintide in combination with phentermine vs pramlintide alone, found significantly greater weight loss with combination therapy, although diastolic blood pressure and heart rate increased despite greater weight loss with the combination.

Drugs in Late-Phase Clinical Trials for Obesity Treatment

A proprietary formulation of naltrexone-sustained release (SR) 32 mg plus bupropion-SR 360 mg, which was recommended for FDA approval as an antiobesity agent in December 2010,[69] is currently undergoing late-phase safety trials to assess its cardiovascular consequences.[70] Three randomized controlled trials (COR-1,[71] N=1742; COR-II,[72] N=1496; and COR-BMOD,[73] N=793 [all called Contrave Obesity Research; COR-BMOD {behavioral modification}]) suggest efficacy—approximately 4 to 5 kg more weight loss with naltrexone-SR 32 mg plus bupropion-SR 360 mg than with placebo at 1 year, and with 48% to 66%, vs 16% to 42% of placebo-treated participants, losing at least 5% of initial body weight and 25% to 42%, vs 6% to 20% losing at least 10% of initial body weight at 1 year, varying with intensity of the lifestyle intervention.

The glucagon-like peptide-1 receptor agonists (GLP-1RA), injectable incretins approved for treatment of type 2 diabetes, are known to produce weight loss. A meta-analysis of the effect of GLP-1RA on

body weight found a placebo-subtracted weight reduction of approximately 3% at 6 to 12 months[74] and studies in obese patients without diabetes have found additional weight loss relative to placebo at 6 to 12 months of 3.5 to 5.8 kg.[75,76] Both liraglutide[77] and exenatide[78] are in late-phase clinical trials as obesity treatments. A recently completed phase 3 trial[79] evaluating liraglutide 3.0 mg per day vs placebo for weight maintenance in 422 nondiabetic overweight and obese patients (72% retention) who successfully lost at least 5% of initial weight during a 4- to 12-week dietary run-in, found that weight decreased an additional 6.2% in the active treatment group over the ensuing 56 weeks, a placebo-subtracted difference of −6.1%. Both groups received face-to-face lifestyle counseling throughout the trial. Participants taking liraglutide were more likely both to maintain their initial weight loss (81% vs 49%) and to lose at least 5% (51% vs 22%) or at least 10% (26% vs 6%) additional weight than participants taking placebo during follow-up, suggesting a potential role for liraglutide in augmenting weight loss or ameliorating regain after initial weight loss achieved through lifestyle intervention. Recently, concerns have emerged regarding an increased risk of pancreatitis and pancreatic cancer with GLP-1RA,[80] although additional research is necessary to determine causality and clinical significance.

Discussion

Rational Use of Medications in Obesity Management

The scientific literature on drug treatment for obesity is limited, particularly for studies conducted before the requirement for registration of all clinical trials, by short intervention periods, high attrition, inadequate description of methods, and data analyses that used biased approaches to deal with missing data[81] or concentrated on results of those completing the trial.

Orlistat, lorcaserin, and phentermine plus topiramate-ER, when used as an adjunct to lifestyle intervention, all increase the likelihood that a patient will achieve a clinically meaningful (≥5%) 1-year weight loss. Because obesity contributes to many diseases, medications to help patients lose weight and sustain weight loss could potentially lead to improvements in multiple domains. Weight loss achieved through lifestyle modification and bariatric surgery has been shown to result in many such improvements; however, one cannot extrapolate from these studies to assume similar benefits will be attributable to weight loss attained with medications. Once established, obesity, like hypertension or dyslipidemia, requires long-term treatment. Therefore, medications for obesity treatment must be viewed through the lens of long-term use when evaluating their safety and efficacy.

A lesson from the withdrawal of previous antiobesity drugs is that uncommon but serious adverse effects may become apparent only when a drug is used in larger populations or for longer periods of time than in preapproval trials.[82] Given that more than one-third of the US adult population is obese, there is great potential exposure to any obesity medication. Because weight stigma is prevalent in the population and thinness is valued, misuse of medications for cosmetic purposes is also a concern, particularly among women.[83] However, untreated obesity confers risk; thus, the adverse effects of medication must be weighed against the health benefits that may result from successfully treated obesity, including improvements in feeling, functioning, and obesity-related comorbidities.[84]

Obesity drugs that are approved for long-term use result, on average, in additional weight loss relative to placebo ranging from approximately 3% for orlistat and lorcaserin to 9% for phentermine plus topiramate-ER at 1 year. Mean total weight loss can be 1% to 5% greater than these placebo-subtracted values, and varies based on factors including patient population and intensity of concomitant lifestyle intervention. However, it is only for those who lose weight successfully that a drug's benefits might conceivably exceed its risks. Unfortunately, there are few consistent pretreatment predictors for response to a given medication. Most studies have shown that initial weight loss response at 12 weeks predicts later weight loss at 1 year and afterward.[56,85,86] Therefore, if a patient does not lose at least 5% of initial weight after 12 weeks of therapy (after assessment for adherence and, where appropriate, an increase in dosage), that patient is more likely than those achieving this threshold to be exposed to the risks and costs of drug treatment when there is little prospect of long-term benefit.

Depending on the medication used, dose, patient population studied, and intensity of concomitant lifestyle intervention, from 30% to more than 60% of drug-treated patients may not achieve a 5% weight reduction at 12 weeks.[40,85,87] In such cases, the clinician should assess the balance of benefits and risks, consider discontinuing the medication, and reevaluate treatment options, including intensification of behavioral strategies, use of a medication with a different mechanism of action, reassessment and management of medical or other contributory factors, or referral for evaluation for bariatric surgery if otherwise appropriate. The recommendation to discontinue a drug therapy with insufficient weight loss after an adequate trial is included in the labeling for both lorcaserin and for phentermine-topiramate-ER.[12,13] The FDA labels have a 12-week threshold of less than 3% weight loss for discontinuation or escalation of recommended-dose phentermine plus topiramate-ER (7.5 mg/46 mg) and a 12-week threshold of less than 5% for discontinuation of both top-dose phentermine plus topiramate-ER (15 mg/92 mg) and for lorcaserin. No discontinuation recommendations based on weight loss are included in the product labels for orlistat or the noradrenergic drugs, although the latter are approved only for short-term use.

In 2011, approximately 2.74 million patients were estimated to use obesity drugs in the United States,[46] a small number given the high prevalence of obesity. Barriers to the initiation or sustained use of obesity medications include costs, safety concerns, perception of limited efficacy, and reluctance to view obesity as a disease requiring medical treatment.[46,88] Studies with medications approved for long-term use have demonstrated improvements, compared with placebo, in patients' progression to diabetes and in many CVD risk factors. It should be noted, however, that no weight loss medication (or behavioral treatment[89]) has been shown to have a favorable effect on cardiovascular morbidity and mortality, and the Endocrinologic and Metabolic Drugs Advisory Committee has recommended to the FDA that all new medications reviewed for an obesity indication undergo premarket testing to ensure that they do not increase CVD events.[90]

As recommended by the US Preventive Services Task Force, physicians should offer or refer their patients with obesity for high-intensity multicomponent behavioral interventions.[4] Comprehen-

sive lifestyle interventions not only help patients to make the critical dietary and physical activity changes necessary for successful weight loss, but lead to better weight loss than provision of medication alone.[91] It is reasonable to advise patients who, during their lifetimes, have not previously participated in a comprehensive lifestyle intervention program, preferably of high-intensity, to do so prior to initiating obesity medication because a substantial proportion will respond to lifestyle treatment alone with clinically meaningful weight loss.[5] Effective treatment can be provided in primary care settings, specialized weight management clinics, community-based programs, through referral to a nutrition professional, via telephonically or electronically delivered interventions, or through commercial programs that are evidence based.[5] Once this criterion has been met, however, there are no data to support requirements for an arbitrary length of treatment failure with behavioral intervention prior to prescription of obesity drugs,[92] particularly for patients who have a history of multiple unsuccessful attempts to lose weight or sustain weight loss.

Although adding medications as a rescue strategy only for patients who do not lose weight after several months of behavioral treatment is attractive in theory, the nonrandomized addition of orlistat for nonresponders to an intensive lifestyle intervention did not suggest benefit.[93] Clinical trials examining the efficacy of medications as rescue therapy are needed. An intermittent strategy for use of obesity drugs (eg, taking medication during alternating months) has been reported to have efficacy in a few small trials,[47,94,95] but the benefits from this approach with newer medications and in broader populations are unknown. Similarly, the usefulness of adding obesity medications after successful weight loss achieved through lifestyle intervention in order to help patients improve or sustain their weight loss long term[79,96] appears promising and deserves further study, including evaluating both continuous and intermittent administration.

The goal of obesity medication use is to improve a patient's health and quality of life. Therefore, clinicians may wish to consider factors other than BMI alone when deciding whether or not to add an obesity medication to a patient's weight management regimen.[84,92,97] For example, a patient with a BMI of 30 who has prediabetes and knee osteoarthritis may warrant greater consideration of adjunctive obesity medication use; for a patient with a similar BMI but no elevation in cardiometabolic risk or other obesity-related conditions, the balance of benefits to risks may be less favorable. It is also possible, however, that obesity medications that elevate pulse, blood pressure, or both could actually increase risk in patients at highest risk for CVD.[82] Initial choice of a specific medication can be influenced by demographic factors such as sex and age, concomitant medications and medical conditions, drug efficacy, response to treatment, adverse effect profile, availability of long-term safety data, and cost. For women with reproductive potential, the increased likelihood of weight loss of 10% or more along with improvements in existing comorbid conditions with phentermine plus topiramate-ER must be weighed against the teratogenic risk of the topiramate component and the need for monthly pregnancy testing. Similarly, extreme caution should be used when considering prescribing lorcaserin to patients taking a selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor due to the potential for serotonin syndrome. Phentermine has the advantage of low cost and many years of clinical experience, but its long-term use is considered off label, long-term effects on CVD outcomes are unknown, and most use has been a few months or less.[46] There are even fewer data for long-term safety and efficacy of the other noradrenergic agents. Orlistat has a reasonably good safety profile, but modest weight loss and unpleasant gastrointestinal adverse effects limit its acceptability to patients. Medications used off label for weight loss have not been sufficiently tested for long-term safety and efficacy to be recommended outside of clinical trials.

Many patients with obesity take multiple medications, some of which are associated with significant weight gain. It is helpful to evaluate patients' medication regimens for drugs that may be contributing to weight gain and to consider adding or substituting drugs with weight-neutral or weight-loss potential where medically appropriate, such as bupropion for depression[98] or smoking cessation, topiramate for mood stabilization, or metformin for diabetes or prediabetes.[2] Clinicians should be aware of the need to monitor patients using antihypertensive therapy or taking diabetes medications that can cause hypoglycemia when initiating treatment with drugs that may cause weight loss. Medication adjustment may be necessary to decrease the risks of hypotension or hypoglycemia, particularly during the initial period of more rapid weight loss.

Because combination pharmacotherapy for obesity deploys medications with differing mechanisms of action, it offers the prospect of overcoming the counterregulatory mechanisms that become manifest in the weight-reduced state. Combination therapy may also allow prescription of lower doses of each medication to minimize adverse effects.[99] The first combination medication for obesity treatment has been approved, and others are in development.[99] Unfortunately, there are few studies examining the safety and efficacy of many of the drug combinations for obesity currently being prescribed. A survey of bariatric physicians found that 65% reported prescribing combinations of medications off label to treat obesity, including 20% who prescribed 5-hydroxytryptophan/carbidopa plus phentermine.[100] Use of nonapproved drug combinations for obesity treatment should be limited to clinical trials, and patients should be informed when drugs are being used off label alone or in combination.

Our systematic review was limited to currently approved medications with at least 1 year of data from studies with relatively large sample sizes, and we did not systematically review drugs used off label or drugs in development. Even the included studies are frequently limited by their high attrition rates. Many were efficacy rather than effectiveness trials and thus may not reflect patient outcomes in real-world clinical settings. Additionally, there were few longer-term data (>2 y) from controlled trials of drugs used for obesity treatment to provide information on long-term risks and benefits.

New drugs for obesity treatment provide additional options for weight management. For carefully selected patients who respond with clinically meaningful weight loss accompanied by improvements in feeling, functioning, CVD risk factors, or other obesity-related comorbid conditions, obesity drugs may be useful adjuncts to lifestyle treatment. However, no obesity medication has been shown to reduce cardiovascular morbidity or mortality. Additional studies are needed to determine the long-term health effects of obesity medications in large and diverse patient populations.

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