Review Article

Drug Therapy

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OBESITY

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OVERWEIGHT and obesity are the most common nutritional disorders in the United States, affecting the majority of adults in the country. Given a normal body-mass index (defined as the weight in kilograms divided by the square of the height in meters) ranging from 18.5 to 24.9, 34 percent of the adult population is overweight (body-mass index, 25 to 29.9), and another 27 percent is obese (body-mass index, ≥30).[1] The prevalence of obesity has increased by more than 75 percent since 1980.[2] The prevalence of overweight in children and adolescents (defined as a body-mass index in the 95th percentile or higher for age and sex)[3] has more than doubled since 1976.[4]

Health care professionals should be concerned about overweight and obesity because of the well-established relations between excess body weight and such medical conditions as type 2 diabetes, hypertension, and osteoarthritis.[5] Evidence-based guidelines issued by the National Institutes of Health call for weight loss both in obese persons and in overweight persons with two or more risk factors for obesity-related diseases.[6]

Medications for the treatment of obesity are currently approved for use in adults who have a body-mass index of 27 or higher plus obesity-related medical conditions or a body-mass index of 30 or higher in the absence of such conditions.[7] In 1999, $321 million was spent in the United States on prescription medications to treat obesity.[8] Between 1996 and 1998, 2.5 percent of the adults in the United States — or about 4.6 million persons — reported having used such medications.[9] Approximately 10 percent of women and 3 percent of men with a body-mass index of 30 or higher have reported using weight-loss medications for obesity.[9] In this review we briefly examine nonpharmacologic approaches to promoting weight loss and give greater consideration to the use of medications as adjunctive therapy in the management of obesity.

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NONPHARMACOLOGIC APPROACHES TO WEIGHT LOSS

Although 29 percent of the men in the United States and 44 percent of the women describe themselves as trying to lose weight,[10] only about 20 percent report restricting caloric intake and increasing physical activity simultaneously, despite recommendations indicating that this combination is effective.[6] Many studies demonstrate that obese adults can lose about 0.5 kg per week by decreasing their daily intake to 500 to 1000 kcal below the caloric intake required for the maintenance of their current weight.[11] More severe caloric restriction, with the use of diets that are very low in calories, increases the rapidity of weight loss but not the rate of long-term success in maintaining a reduced weight.[6] Although adding exercise to caloric restriction minimally increases weight loss during the acute phase of weight loss, it appears to be the component of treatment that is most likely to promote long-term maintenance of a reduced weight.[12] Behavioral treatments help obese persons to develop adaptive thinking, eating, and exercise habits that enable them to decrease their weight and avoid regaining weight.[11] Persons who combine caloric restriction and exercise with behavioral treatment may expect to lose about 5 to 10 percent of preintervention body weight over a period of four to six months.[11] Although patients often perceive this "small" weight loss as insufficient,[13] it suffices to improve many obesity-related conditions.[14]

Unfortunately, improvements are not sustained if weight is regained; and for the vast majority of persons, weight loss is followed by a slow, inexorable climb to the preintervention body weight — or even higher.[15] Bariatric surgical treatments, such as gastric bypass, can induce long-term weight loss, but are appropriate only for selected patients with a body-mass index of at least 40 or a body-mass index of at least 35 along with obesity-related medical conditions.[6] Losing weight is difficult for most obese persons, yet long-term maintenance of a reduced weight is even more challenging.

HISTORY OF PHARMACOTHERAPY FOR OBESITY

For many years, obesity was approached as if it were either a moral failing or evidence of underlying psychopathology.[16] With the advent of behavioral treatments for obesity in the 1960s,[17] hope arose that modification of maladaptive eating and exercise habits would lead to sustained weight loss, and that time-limited programs would produce permanent changes in weight. Medications for the treatment of obesity were proposed as short-term adjuncts for patients, who would presumably then acquire the skills necessary to continue to lose weight, reach "ideal body weight," and maintain a reduced weight indefinitely. Unfortunately, such short-term approaches proved unsuccessful, and the history of many ill-fated weight-loss regimens is well documented.[18]

The field underwent a paradigm shift in 1992 with the publication of studies by Weintraub et al.[19-27] concerning the efficacy of the combination of behavioral treatment and two medications with different mechanisms of action — fenfluramine and phentermine. Those studies found that weight loss could be sustained for as long as three and a half years with continuing pharmacotherapy. Although the number of patients studied was small, the idea behind the approach — that obesity should be treated in the same manner as any other chronic disease that might be ameliorated through the long-term use of medication — differed dramatically from those of prevailing approaches. The new approach meshed well with the emerging realization that short-term treatments for obesity generally do not lead to sustained weight reduction and that patients are generally unwilling to continue behavioral treatment indefinitely.[11] Long-term use of weight-loss medications could be seen as a tool to help patients adhere to the dietary and behavioral changes necessary to maintain a reduced body weight.[28,29] Although the subsequent withdrawal from the market of fenfluramine (and dexfenfluramine) because of an association with valvular heart disease[30] had a dampening effect on the use of medications in the treatment of obesity, an important lesson remained: obesity could and should be approached as a chronic condition that requires continuing medical care. For a minority of obese patients who have substantially increased medical risk and for whom nonpharmacologic treatments alone prove unsatisfactory, weight-loss medications may be useful adjuncts to behavioral treatments.

MECHANISMS OF ACTION OF WEIGHT-LOSS DRUGS

Medications currently approved for weight loss in the United States (Table 1) fall into two broad categories: those that decrease food intake by reducing appetite or increasing satiety (appetite suppressants) and those that decrease nutrient absorption. A third category, medications that increase energy expenditure, includes ephedrine, which is not currently approved as a treatment for obesity in the United States, and other investigational compounds.[31]

Appetite-Suppressant Medications

Most appetite suppressants work primarily by increasing the availability of anorexigenic neurotransmitters — notably, norepinephrine, serotonin, dopamine, or some combination of these neurotransmitters — in the central nervous system.

Noradrenergic Agents

Noradrenergic drugs available in the United States include phentermine, diethylpropion, phendimetrazine, and benzphetamine (Table 1). Amphetamines are no longer recommended (and are not approved for use) for weight loss because of the potential for their abuse. Benzphetamine and phendimetrazine, which are classified as Schedule III drugs by the Drug Enforcement Administration (DEA), are considered by the DEA to have substantially greater potential for abuse than those on Schedule IV.

All of the above medications are approved by the Food and Drug Administration (FDA) for use of "a few weeks" only (generally presumed to be 12 weeks or less) for the treatment of obesity.[7] Few studies of their safety and efficacy have extended to six months or beyond.[28] Such studies show a consistent but moderate difference in weight loss (a difference of 2 to 10 kg) in comparisons with placebo.[32-37] Side effects of noradrenergic medications include insomnia, dry mouth, constipation, euphoria, palpitations, and hypertension.[7] Although the most widely used of these compounds, phentermine, was used in combination with fenfluramine, it has not been independently associated with valvular heart disease.[38] The only over-the-counter appetite-suppressant medication approved for the treatment of obesity, phenylpropanolamine, was recently withdrawn from the market because of concern about an association with hemorrhagic stroke in women.[39]

Serotonergic Agents

Serotonergic agents act by increasing the release of serotonin, inhibiting its reuptake, or both. Fenfluramine (Pondimin) and dexfenfluramine (Redux), medications that both stimulated serotonin release and inhibited its reuptake, were withdrawn from the market in the United States in 1997 because of associations with valvular heart disease and pulmonary hypertension. Their efficacy in controlled studies appeared similar to that of the noradrenergic agents.[28,40]

TABLE 1. MEDICATIONS APPROVED FOR THE TREATMENT OF OBESITY.*

GENERIC NAME	TRADE NAMES	MECHANISM OF ACTION	DOSAGE	WHOLESALE PRICE	DEA SCHEDULE†	POTENTIAL DRUG INTERACTIONS	CONTRAINDICATIONS‡
Benzphetamine	Didrex	Noradrenergic	25–50 mg 1–3 times/day	$1.19–$2.38/day	III	MAOIs, guanethidine, CNS stimulants, alcohol, sibutramine, tricyclic antidepressants	Hypertension, advanced cardiovascular disease, hyperthyroidism, glaucoma, agitated states, history of drug abuse
Phendimetrazine	Bontril, Plegine, Prelu-2, X-Trozine	Noradrenergic	17.5–70 mg 2–3 times/day or 105 mg sustained-release/day	$1.20–$5.25/day	III	Same as benzphetamine	Same as benzphetamine
Phentermine	Adipex-P, Fastin, Oby-Cap, others	Noradrenergic	18.75–37.5 mg/day	$0.67–$1.60/day	IV	Same as benzphetamine	Same as benzphetamine
Phentermine resin	Ionamin	Noradrenergic	15–30 mg/day	$1.75–$2.01/day	IV	Same as benzphetamine	Same as benzphetamine
Diethylpropion	Tenuate, Tenuate Dospan, Tepanil	Noradrenergic	25 mg 3 times/day or 75 mg sustained-release/day	$1.27–$1.52/day	IV	Same as benzphetamine	Same as benzphetamine
Sibutramine	Meridia	Mixed noradrenergic and serotonergic	5–15 mg/day	$2.98–$3.68/day	IV	SSRIs, MAOIs, centrally active anorexiants, sumatriptan, dihydroergotamine, dextromethorphan, meperidine, pentazocine, fentanyl, lithium, tryptophan	Uncontrolled hypertension, severe renal impairment, severe hepatic dysfunction, narrow-angle glaucoma, or history of substance abuse, coronary artery disease, congestive heart failure, arrhythmias, or stroke
Orlistat	Xenical	Lipase inhibitor	120 mg 3 times/day with or within 1 hr after fat-containing meals, plus a daily multivitamin	$3.56/day	Not scheduled	Cyclosporine	Chronic malabsorption syndromes, cholestasis

*Only sibutramine and orlistat are approved for long-term use; the others are approved only for short-term use (i.e., a few weeks). DEA denotes Drug Enforcement Administration, MAOI monoamine oxidase inhibitor, CNS central nervous system, and SSRI selective serotonin-reuptake inhibitor.

†Medications on DEA Schedule III are associated with a higher risk of abuse than those on Schedule IV, for which the potential for abuse is considered low.

‡If there is a sustained increase in blood pressure or pulse rate, either a reduction in the dose or discontinuation should be considered.

Selective serotonin-reuptake inhibitors are currently approved for a number of indications that are not related to obesity, including depression and obsessive–compulsive disorder. Some selective serotonin-reuptake inhibitors have induced weight loss in short-term studies, and fluoxetine (Prozac) (at a dose of 60 mg) has undergone considerable evaluation to determine its efficacy for weight loss.[41,42] Unfortunately, although patients who received fluoxetine for six months lost more weight than those who received placebo, steady regain occurred during the next six months despite the continuation of medication, eroding any difference between the treatment groups.[28] Sertraline (Zoloft), evaluated as an adjunct for weight maintenance after a very-low-calorie diet, showed a similar lack of long-term efficacy.[43]

Mixed Noradrenergic–Serotonergic Agents

Sibutramine (Meridia), an inhibitor of both norepinephrine reuptake and serotonin reuptake that also weakly inhibits dopamine reuptake (Fig. 1), is approved by the FDA for weight loss and weight maintenance in conjunction with a reduced-calorie diet.[7] Sibutramine is given in a dose of 10 to 15 mg once daily and may be given in a 5-mg dose to patients who do not tolerate the 10-mg dose. Unlike fenfluramine and dexfenfluramine, it does not induce serotonin release, and has not been implicated in the development of valvular heart disease.[44,45] Over a six-month period, subjects who follow a reduced-calorie diet and receive sibutramine typically lose 5 to 8 percent of their preintervention body weight, as compared with 1 to 4 percent among subjects who receive placebo.[46-49] Sibutramine-induced reductions in weight appear to be largely maintained for periods of up to one year and remain significantly greater than those observed in patients who receive placebo.[50] Published studies with up to two years of data are now available. The Sibutramine Trial of Obesity Reduction and Maintenance followed 605 European adults who took 10 mg of sibutramine daily for 6 months, after which 467 participants who had lost more than 5 percent of their preintervention body weight were randomly assigned to continue to receive sibutramine or to receive placebo for 18 months.[51] Although weight was regained in both groups during the second year of follow-up, weight losses were significantly greater among those who received sibutramine for the full two years of the trial. More than 25 percent of those who continued to take sibutramine maintained their reduced weight for the entire observation period. As in most studies of weight-loss medications, the large numbers of dropouts in both the study-drug group and the placebo group limit the generalizability of the findings.[51] By the end of the study, the dose of sibutramine had been increased to 20 mg, a dose higher than is approved in the United States, in 52 percent of the subjects taking the medication. However, 86 percent of the subjects who did not regain any of the weight they had lost were taking no more than 15 mg of sibutramine daily. Sibutramine may also increase weight loss and improve maintenance of reduced weight in subjects who have previously lost weight with a very-low-calorie diet.[52]

Side effects of sibutramine include increases in blood pressure and pulse; although these are usually mild, they lead to the discontinuation of sibutramine in up to 5 percent of patients.[47,48,50,51] In general, reductions in blood pressure in those who lose weight with sibutramine are less than the reductions in blood pressure seen with similar weight loss obtained with other treatments.[47] Adverse reactions also include dry mouth, headache, insomnia, and constipation.[45] Commensurate with weight loss, other metabolic risk factors improve; these include hyperlipidemia and hyperuricemia, as well as glycemic control and plasma insulin levels in patients with type 2 diabetes.[46,48,50,51,53]

Medications That Reduce Nutrient Absorption

The only FDA-approved medication for obesity that reduces nutrient absorption is orlistat (Xenical), which acts by binding to gastrointestinal lipases in the lumen of the gut, preventing hydrolysis of dietary fat (triglycerides) into absorbable free fatty acids and monoacylglycerols (Fig. 2). Patients who take 120 mg of orlistat with or up to one hour after meals excrete in the stool approximately one third of the dietary fat they ingest, thereby reducing calorie and fat intake. In double-blind, placebo-controlled trials, orlistat had moderate efficacy for weight loss in adults. Orlistat-treated subjects who completed trials lasting one year lost approximately 9 percent of their preintervention body weight, as compared with 5.8 percent among those who took placebo.[54]

Orlistat has also been found to slow the rate of regain of weight during a second year of use; orlistat-treated subjects regained less weight during the second year than placebo-treated subjects did (a regain of 35.2 percent vs. 62.4 percent, a difference of about 2.5 kg).[55-57] In these long-term studies, orlistat-treated patients also had moderate decreases in diastolic blood pressure, insulin levels while fasting, and total cholesterol and low-density lipoprotein cholesterol, with a small cholesterol-lowering effect that was independent of weight loss. Orlistat induced small reductions in body weight in patients with type 2 diabetes that were nevertheless significantly greater than those that occurred in such patients who received placebo (losses of 6.2 kg vs. 4.3 kg); orlistat also led to improvement in glycosylated hemoglobin

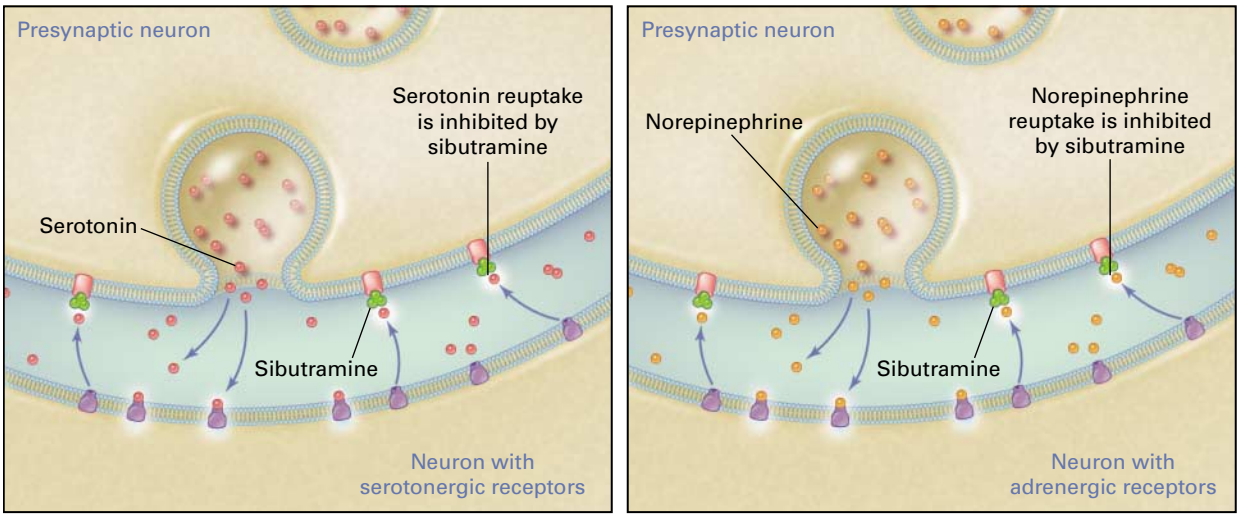

Figure 1. Mechanisms of Action of Sibutramine.
Sibutramine and its active metabolites inhibit the reuptake of serotonin and norepinephrine, thereby prolonging the actions of these neurotransmitters at their postsynaptic receptors.

values and a decreased requirement for sulfonylurea drugs.[58] Orlistat appears to have similar efficacy regardless of whether it is prescribed in a primary care or a specialized treatment setting.[59]

Side effects of orlistat include flatulence with discharge, fecal urgency, fecal incontinence, steatorrhea, oily spotting, and increased frequency of defecation. These side effects are usually mild to moderate, and generally decrease in frequency with ongoing treatment. However, such side effects lead to discontinuation in nearly 9 percent of patients, as compared with a rate of discontinuation of 5 percent among patients treated with placebo.[7,54] Orlistat also decreases absorption of fat-soluble vitamins, primarily vitamin D, an effect that can be counteracted by daily administration of a multivitamin at least two hours before or after a dose of orlistat.[7]

DIETARY SUPPLEMENTS AND HERBAL PREPARATIONS

Unlike prescription and over-the-counter medications, dietary supplements are not prospectively reviewed for safety or efficacy by the FDA, which takes action only if a dietary supplement is shown to present "a significant or unreasonable risk."[60] Producers of a dietary supplement cannot claim that it treats a disease (including obesity) but may claim that it reduces the risk of a disease in a population.[60]

Allison and colleagues[61] critically reviewed the published literature on herbal and dietary supplements for which claims have been made about the promotion of weight loss: chitosan, chromium picolinate, conjugated linoleic acid, ephedra alkaloids (ma huang), and garcinia cambogia. They found that most such reports were based on poorly designed trials that lacked randomization, blinding, or control groups. Although some dietary supplements have mechanisms of action that could plausibly lead to weight loss or have shown promising results in small-scale studies in humans or animals, Allison et al. found that there were insufficient data to provide evidence of either the safety or the efficacy of any of these compounds as agents promoting weight loss. Herbal compounds containing ephedra alkaloids and caffeine are the only types for which there are data from randomized, double-blind, placebo-controlled trials indicating efficacy in promoting weight loss.[61-63] However, all such studies have been short-term (six months or less).

Ephedrine is an adrenergic agent with thermogenic and appetite-suppressant properties.[49] In the United States, ephedrine is approved for nonprescription use for mild asthma and upper respiratory symptoms. Ephedrine in combination with caffeine, aspirin, or both, has been found in controlled trials to produce greater weight losses than placebo for periods of up to one year, although most studies have been short-term.[31,64-67] Ma huang (*Ephedra sinica*) is a botanical source of ephedra alkaloids often included in dietary supplements sold for the purpose of promoting weight loss. Dietary supplements containing ephedra alka-

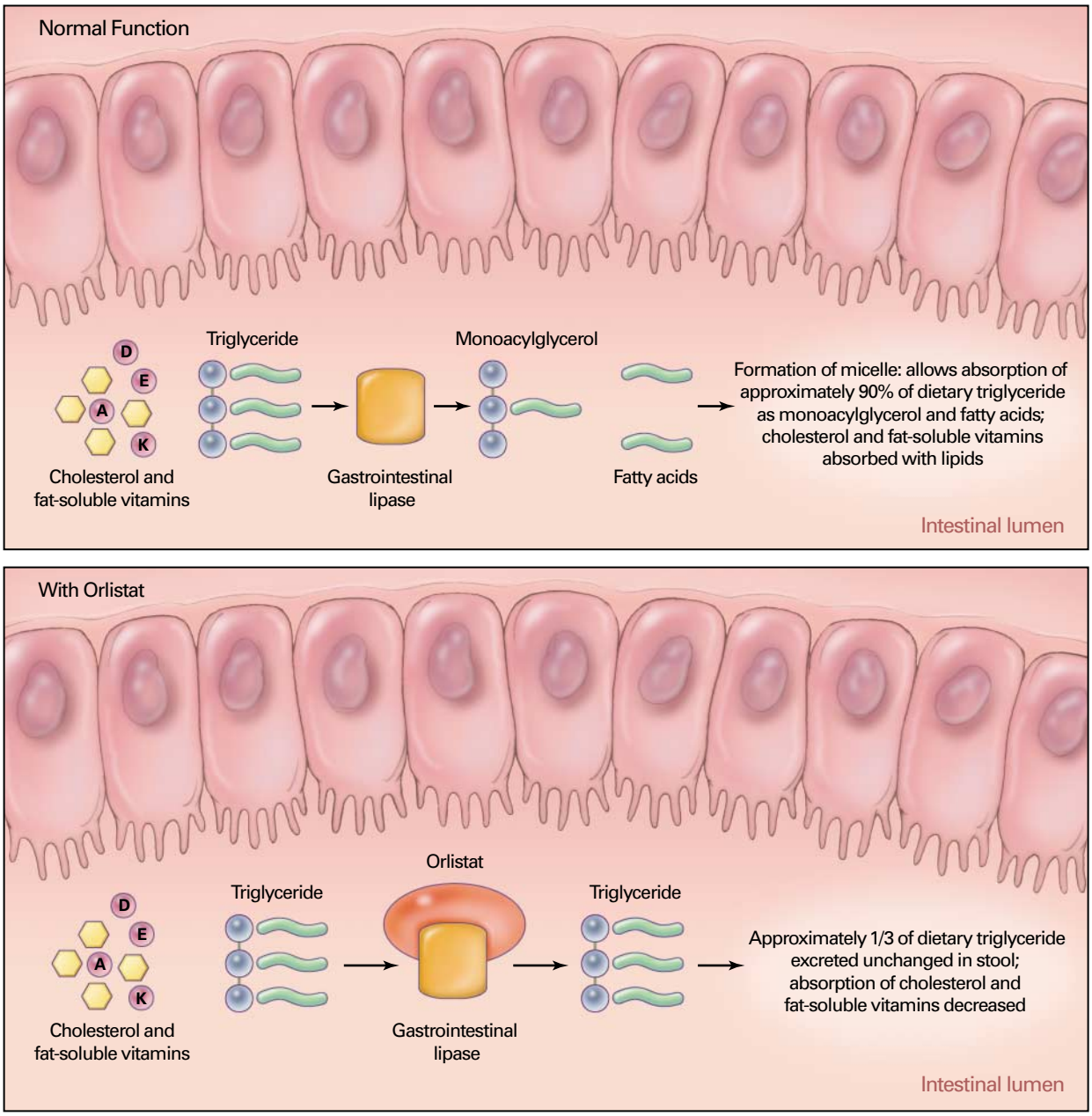

Figure 2. Inhibition of Fat Absorption by Orlistat.

loids frequently contain a dosage that differs substantially from that indicated on the product label.[68] Case reports concerning ephedra alkaloids (often in combination with caffeine) have noted serious cardiovascular and central nervous system events, including hypertension, cardiac arrhythmia, stroke, seizure, myocardial infarction, and sudden death.[69] However, the incidence of such events among persons who take ephedra alkaloids at the recommended doses has not been established.[70] Because of the unpredictable amounts of active ingredients and the potential for harmful effects, the National Institutes of Health guidelines state that herbal preparations are not recommended as part of a weight-loss program.[6]

WEIGHT-LOSS MEDICATIONS CURRENTLY IN CLINICAL TRIALS

Medications Approved by the FDA for Indications Other Than Obesity

A number of medications with different mechanisms of action are currently in clinical trials to evaluate their safety and efficacy in obese patients.

Bupropion (Wellbutrin) is an atypical antidepressant that is chemically unrelated to tricyclic agents or selective serotonin-reuptake inhibitors. It is a relatively weak inhibitor of the reuptake of norepinephrine, serotonin, and dopamine and has structural similarities to diethylpropion.[7] After it was noted in studies concerning depression that bupropion was associated with small weight losses, trials evaluating the use of sustained-release bupropion in the treatment of obesity were initiated and are currently being conducted.[71,72] Bupropion is contraindicated in patients with seizure disorders.[7]

In several clinical trials studying the safety and efficacy of topiramate (Topamax), a novel antiepileptic agent, for seizure control[73] or affective disorders,[74] reduced food intake and weight loss were noted. Trials of the safety and efficacy of topiramate in obese patients who do not have seizures, including patients with binge eating disorder[75] or hypothalamic obesity,[76] are ongoing. Adverse effects of topiramate include kidney stones and central nervous system symptoms, such as paresthesias, dizziness, fatigue, and somnolence.[77]

Metformin (Glucophage), a medication that inhibits hepatic glucose production and improves sensitivity to insulin, is approved by the FDA for the treatment of type 2 diabetes. Metformin not only reduces hyperglycemia but has also been noted to prevent weight gain or even to induce small weight losses in adults.[78,79] Metformin is being studied in overweight, nondiabetic adults and children to determine its effects on body weight, insulin resistance, and related medical conditions.[80-82] Metformin may cause nausea, flatulence, bloating, and diarrhea at the beginning of treatment, and approximately 5 percent of adults cannot take the drug at any dose because of such side effects.[83] The most serious side effect of metformin is lactic acidosis, which is estimated to occur at a rate of 3 cases per 100,000 patient-years of exposure, primarily in patients with renal insufficiency, congestive heart failure, pulmonary disease, or liver disease, which are contraindications to its use.[84]

Investigational Medications

Levels of leptin, a hormone secreted by adipocytes, reflect the lipid content of the total body of a nonfasting person.[85] In a few children, severe, early-onset obesity has been associated with an inability to produce functional leptin protein.[86] Treatment of a leptin-deficient girl with recombinant human leptin induced a dramatic reduction in body weight (a loss of 16.4 kg) and changes in body composition.[87] Less dramatic changes have been observed in adults with sufficient leptin levels who are treated with recombinant human leptin. A dose-dependent decrease in body weight and fat was observed, and the greatest weight loss (a mean [±SD] loss of 7.1±8.5 kg) occurred in eight persons who took leptin in a daily dose of 0.3 mg per kilogram of body weight for 24 weeks.[88] Pain and induration at the injection site, especially at higher doses, led to discontinuation in some patients. Ongoing studies are evaluating both different formulations of leptin[89] and leptin-replacement therapy during low-calorie dieting.[90] It remains unknown whether treatment with leptin will be beneficial in persons without mutations in the leptin gene.

Other medications that are currently in clinical trials to determine their ability to induce weight loss include ciliary neurotrophic factor,[91] a neuroactive cytokine that exerts its effects through a receptor whose mode of signal transduction is similar to that of the leptin receptor; a peptide analogue of the human growth hormone fragment 177-191[92]; and agonists of the β_3-adrenergic and cholecystokinin-A receptors.[93]

STRATEGIES FOR USE OF MEDICATIONS IN THE TREATMENT OF OBESITY

Because obesity is a chronic condition, pharmacotherapy should be initiated with the expectation that long-term use will most likely be needed.[28] Numerous studies indicate that, just as blood pressure may increase when antihypertensive drugs are discontinued, regaining of weight is extremely likely when weight-loss medications are discontinued.[28,52] Therefore, careful consideration of the known (and possible) risks of long-term medical therapy must be weighed against potential improvements in the patient's risk of obesity-related disease. National Institutes of Health guidelines recommend that pharmacotherapy should be initiated only in patients with a body-mass index of at least 30 in the absence of obesity-related medical conditions or a body-mass index of at least 27 in the presence of such conditions.[6]

Approved prescription medications for weight loss appear to have similar efficacy in controlled studies. Other than weight loss during the first few weeks of drug treatment, no predictors of responsiveness in an individual patient or class of patients have been established. Therefore, an empirical choice of a specific medication should be based on consideration of underlying medical conditions or contraindications to particular drugs, concurrent medications, need for monitoring, approval for long-term use, cost, and the preference of the patient. National Institutes of Health guidelines suggest that nonpharmacologic therapies should be attempted for six months and

that weight-loss drugs should be considered if weight loss is unsatisfactory (e.g., less than 0.45 kg per month).[94] In addition, behavioral treatment combined with pharmacotherapy may result in better outcome than drug treatment alone.[6,95] An evidence-based algorithm representing an overall approach to the treatment of obesity is shown in Figure 3. A practical guide designed to assist physicians in treating obese patients in the primary care setting is available.[94]

Identification of Patients with a Response to Treatment

Although the mean weight loss attributable to medications for obesity is less than 5 percent, individual patients do have more robust responses. As compared with placebo, pharmacotherapy more than doubles the percentage of patients in whom a weight loss of 5 or 10 percent is achieved.[6,28] Identification of patients with a response would enable the risks and costs of drug treatment to be concentrated among those who are most likely to benefit. In addition to preintervention body weight,[51] success during the first month of therapy usually predicts ultimate weight loss.[6,28] Therefore, in patients without a weight loss of at least 2.0 kg during the first four weeks of treatment, adherence to the medication, diet, and exercise recommendations should be reassessed and the possible need for an adjustment in the dosage should be considered. If there continues to be minimal response to the medication, the clinician should consider discontinuing it or substituting another medication.[28] For none of the currently available medications does the dose need to be tapered before treatment is stopped.[6]

Pharmacotherapy for the Prevention of Weight Regain

A major area of promise for pharmacotherapy is in enhancing weight maintenance in those who have lost weight by a variety of methods.[28] Because almost all nonsurgical obesity treatments lead to weight loss for the first four to six months followed by regain, pharmacotherapy can be instituted either to enhance weight loss during the active weight-loss phase or to prevent later regain. Although longer-term studies suggest that weight-loss medications can decrease the rate of regain,[51,52,56,57] it is important to note that data on the safety and effectiveness of use for more than two years are not available for any FDA-approved weight-loss medication.

Off-Label Use of FDA-Approved Medications

Use of FDA-approved medications in a manner inconsistent with labeling is considered off-label use, a common practice in medicine. Prudent physicians should inform patients whenever they prescribe medications to be used in a manner that is not consistent with FDA labeling and should discuss the paucity of data on safety and efficacy and obtain the patient's consent for such use. Whenever possible, patients who wish to use medications in such a manner should be encouraged to participate in clinical trials.[28]

Intermittent Use

Several small, short-term studies have described good results with the intermittent use (e.g., in alternating months) of appetite-suppressant weight-loss drugs.[18] One fairly large study found that the safety and efficacy of intermittent use of sibutramine (12 weeks of the drug alternating with 12 weeks of placebo) were similar to those of continuous sibutramine treatment.[96] An increase in the rate of side effects just after drugs are stopped or restarted has been noted in other studies.[25,34] Further studies of the intermittent use of such medications would help to answer questions about the effectiveness of this approach.

Drug Combinations

Treatment in which drugs of different therapeutic classes are combined in order to enhance efficacy or reduce adverse effects is common in the treatment of chronic diseases. It is possible that combination drug treatments for obesity will eventually be developed that are both safe and effective. However, in the absence of data from large trials, clinicians must exercise great caution in recommending unproven therapeutic combinations. For the most part, only case series[97-99] and preliminary studies[100-102] have examined the use of combinations of medications to enhance weight loss. A study in which orlistat was added to sibutramine treatment after one year of sibutramine alone found no enhancement of weight loss.[103] At present, using more than one drug in combination for the treatment of obesity cannot be recommended outside clinical trials.[6]

Treatment of Children and Adolescents

In general, the only children and adolescents who should be considered for pharmacotherapy are those with a body-mass index in the 95th percentile or higher for their age and sex plus an obesity-related medical condition that may be remediable by a reduction of weight. In selected populations of children 6 to 12 years old, intensive, family-based behavioral treatment programs have been found to have a favorable effect on children's weight for as long as 10 years.[104] In contrast, there have been no long-term (i.e., at least one year), randomized, double-blind, placebo-controlled trials involving children (defined, for FDA regulatory purposes, as persons less than 16 years of age) that have demonstrated the safety and effectiveness of weight-loss medications. The safety and effectiveness of orlistat and sibutramine for children and adolescents have not been established.[7] Med-

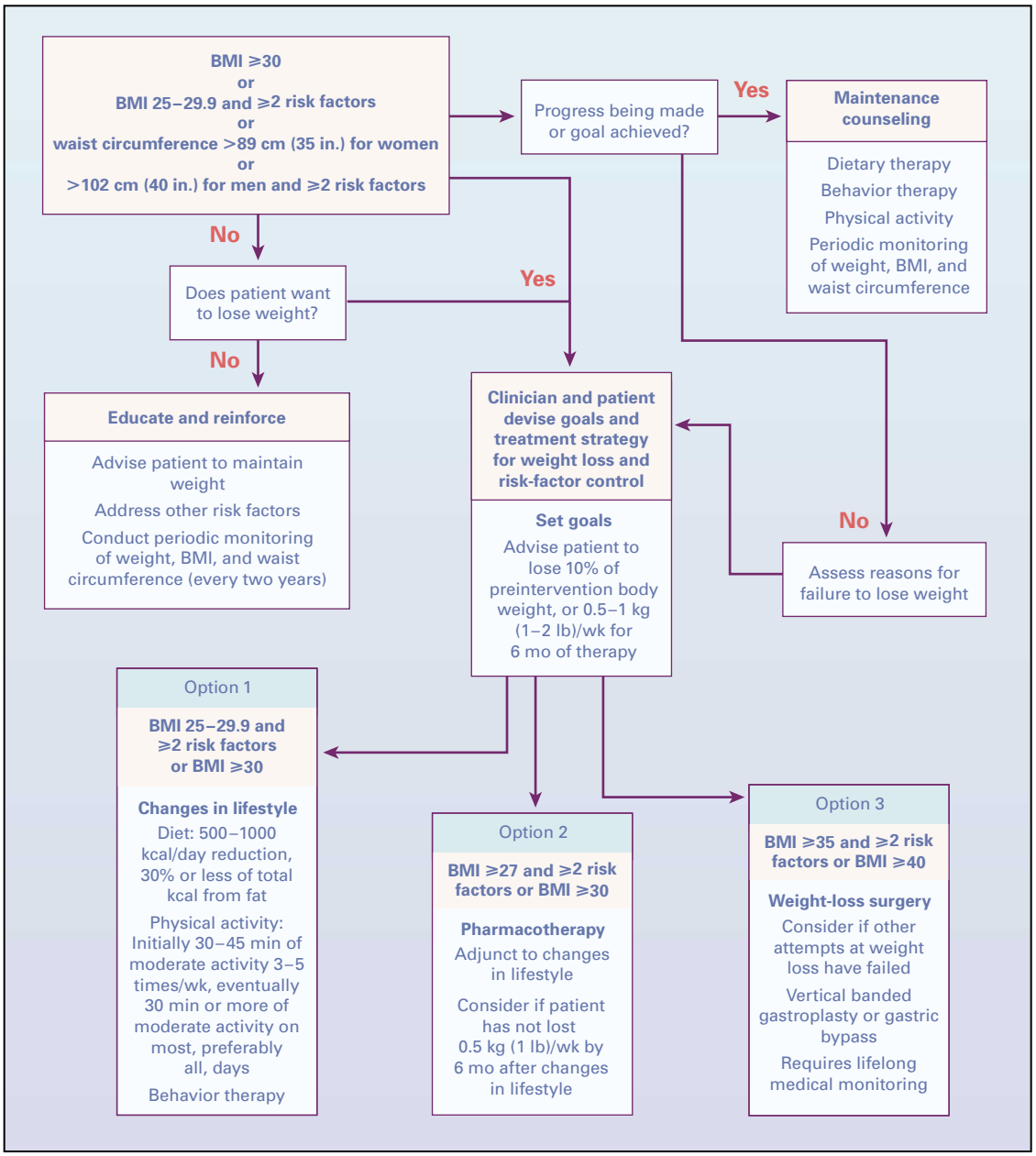

Figure 3. Evidenced-Based Algorithm for the Treatment of Obesity.
Adapted from the National Institutes of Health.[94] BMI denotes body-mass index.

ications that are currently in clinical trials involving children include orlistat,[105] sibutramine,[106] ephedrine–caffeine,[107] and metformin.[82] In addition, octreotide (a somatostatin agonist) is being evaluated in children and adolescents with the hypothalamic obesity syndrome.[108] Further studies are needed before pharmacotherapy outside clinical trials can be recommended for younger patients.

SUMMARY

Obesity is a serious and prevalent disorder whose effective management requires ongoing care. Cur-

rently approved prescription medications for weight loss, although moderate in their efficacy, can help carefully selected obese patients lose weight and can reduce the rate of regain. Behavioral interventions to improve diet and increase physical activity are considered the primary means to promote and maintain weight loss. Weight-loss medications should be considered as an adjunct only for patients who are at substantial medical risk because of their obesity and in whom nonpharmacologic treatments have not resulted in sufficient weight loss to improve health or to prevent regain. The safety and efficacy of weight-loss medications beyond two years of use have not been established. In addition, although some risk factors for obesity-related disease are improved with the use of weight-loss medications, the long-term effect of such medications on morbidity and mortality has not been determined.

In many ways, the current state of treatment for obesity is similar to the state of the treatment of hypertension several decades ago.[18] Few medications were available, their efficacy was limited, and predictors of response were lacking. Just as research into the underlying causes and consequences of hypertension has led to dramatic improvements in its treatment, advances in our understanding of energy balance will most likely lead to more effective treatments for obesity in the future. With such understanding, we can hope not only to develop safe and effective ways to help obese persons to achieve and maintain a healthy weight but also to understand how to prevent the development of obesity in those who are at risk.

Supported by a grant (ZO1 HD-00641) from the National Institute of Child Health and Human Development (to Dr. Jack A. Yanovski). The opinions expressed herein are those of the authors and do not necessarily reflect the views of the National Institutes of Health, the Public Health Service, or the Department of Health and Human Services.

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