Keeping weight-loss drugs in perspective
If you’re dangerously overweight, diet pills may help—but not without major lifestyle changes.

Diet drugs have gotten a lot of press lately. In January 2006, a federal advisory panel recommended that the FDA make available, over the counter, a popular prescription weight-loss medication, orlistat (Xenical). The FDA usually takes the panel’s advice, but approval of the new orlistat (which would be called Alli) is not a sure thing. Many question the drug’s effectiveness in a broader setting; others worry about its side effects. Considerable excitement surrounds rimonabant (Acomplia), a new type of weight-loss drug that works by blocking the same receptors in the brain that cause the “munchies” in marijuana users. Rimonabant reduces weight, quiets food cravings, and improves cholesterol and other risk factors for heart disease, including waist circumference.

We certainly need new weight-loss solutions. Two-thirds of adults in the United States are overweight or obese and at risk for several major medical conditions as well as for premature death. Even modest weight loss can reduce these risks. But as most of us know, losing weight can be extremely difficult, and keeping it off even more so. Most people who shed pounds regain them within five years. Little wonder that there’s intense interest in drugs to boost weight-loss efforts.

But the reasons for weight problems are complex. Genetic makeup, hormones, brain chemistry, environmental influences, and psychosocial pressures all contribute. No pill can melt away fat or keep off the pounds. And the drugs currently prescribed for weight loss don’t do the job by themselves. But for people whose health is at risk and who are struggling to reduce through diet and exercise, drug therapy may increase the odds of success. Experts agree that weight-loss drugs, which all have side effects, are not for the mildly overweight or those who just want to lose a few pounds to improve their appearance.

Recent history of weight-loss drugs
Over the past few years, researchers have learned a lot about the biological causes of weight disorders. They’ve identified dozens of genes and begun to discover how these genes influence the many systems that affect weight. Weight-loss drugs can temporarily manipulate these systems. For example, sibutramine (Meridia) and phentermine (Adipex-P, others) suppress appetite, while orlistat reduces fat absorption. Some 100 new drugs are currently in the testing phase.

Weight medications have a history of failure and safety concerns. In the 1950s and 1960s, dieters took amphetamines to quell their appetites and boost their metabolisms—until it was discovered that the pills were addictive and caused paranoia. The combination of fenfluramine and phentermine—popularly known as fen-phen—was widely used in the mid-1990s, until it and another drug, dexfenfluramine, were linked to heart valve disease and subsequently withdrawn from the market. (Phentermine alone is still used.)

Until sibutramine was approved in 1997 for long-term use in obesity, the FDA had required that most such medications be prescribed for no longer than three months. Both sibutramine and orlistat are approved for use up to one year, but physicians, at their discretion, may prescribe them for longer. Sibutramine is considered effective and safe for up to two years, although it can increase blood pressure and thus requires monitoring. Orlistat, which inhibits the body’s ability to absorb fats, can interfere with the absorption of fat-soluble vitamins. Moreover, there’s

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little safety data on the use of weight-loss drugs beyond two years.

On the other hand, these medications have a role to play in medical treatment, especially now that obesity is recognized as a metabolic disease and not a failure of desire or willpower, as was once thought. Clinicians are finding that obesity, like other chronic conditions, is often easier to manage with a judicious use of medications.

Who should take them?

One way to minimize the risks of these drugs is to prescribe them only for people who need them for health reasons: those who have obesity-related conditions such as type 2 diabetes or hypertension, or those at high risk for developing such disorders. Guidelines issued by the National Institutes of Health (NIH) advise that weight-loss drugs be given only to people with a body mass index (BMI) of 30 or more, or—in the case of those with weight-related health problems—a BMI of 27 or more. The use of diet drugs by people with lower BMIs is likely to pose more risks than benefits.

How should they be taken?

The NIH guidelines make clear that weight-loss drugs should be used only in combination with lifestyle modifications. There are several reasons for this. To lose weight requires recognizing and changing the behaviors that led to the weight gain. For example, many people gain weight because they’re in situations such as business travel that can trigger overeating and disrupt the body’s normal cues for hunger and satiety. Balancing the demands of job and family can lead to a reliance on prepared foods, take-out, and restaurant meals, which are usually higher in calories than homemade meals. Others eat in response to stressful or emotionally challenging situations. And many people don’t expend enough calories because they don’t incorporate enough physical activity into their daily lives.

Even more disconcerting: Weight loss can result in reduced calorie burning, whether the body is at rest or active. That’s why exercise is so important to weight-loss efforts: Increased muscle mass burns calories more efficiently.

Another response to weight loss is ravenous hunger. A clinician may prescribe an appetite-suppressing drug so that an overweight or obese patient can cut down on portions and not feel like she’s starving. But unless she also understands how to eat less—by such strategies as learning to

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**Prescription medications for weight loss**

<table>
<thead>
<tr>
<th>Medication type/Name(s)</th>
<th>Activity/Side effects/Comments</th>
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<tbody>
<tr>
<td><strong>Noradrenergic drugs</strong></td>
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<tr>
<td>phentermine (Adipex-P)</td>
<td>Increases levels of norepinephrine; suppress appetite. Side effects include rapid heartbeat (phentermine), nervousness, restlessness, and diarrhea. Should not be prescribed for more than three months at a time. Blood pressure should be checked every four weeks.</td>
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<tr>
<td>lorcipramine (Phentermine)</td>
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<tr>
<td>sibutramine (Meridia)</td>
<td>Increases levels of norepinephrine and serotonin; reduces food intake. Side effects include elevated blood pressure. Should not be taken by people with a history of heart disease, cardiac arrhythmia, stroke, or uncontrolled high blood pressure.</td>
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<tr>
<td><strong>Serotonin/norepinephrine reuptake inhibitor</strong></td>
<td></td>
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<tr>
<td>sibutramine (Meridia)</td>
<td></td>
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<tr>
<td><strong>Lipase inhibitor</strong></td>
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<tr>
<td>orlistat ( Xenical)</td>
<td>Cuts fat absorption in the intestine by 30%. Side effects include oily stool leakage, gas, bloating, and malabsorption of fat-soluble vitamins, especially A, D, E, and K. People taking orlistat should take supplements of these vitamins and be closely monitored for vitamin B12 and iron deficiencies.</td>
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<tr>
<td><strong>Antidepressants</strong></td>
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<tr>
<td>buproprion (Wellbutrin),</td>
<td>Wellbutrin increases levels of norepinephrine and dopamine and helps control appetite. Side effects include dry mouth, agitation, constipation or diarrhea, headache, and insomnia. Prozac increases serotonin levels and may help suppress appetite. Side effects include insomnia, agitation, nausea, sleepiness, diarrhea or constipation, and problems with libido. Some people gain weight on Prozac.</td>
</tr>
<tr>
<td>fluoxetine (Prozac)</td>
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*Not all drugs are FDA-approved for weight loss; some are prescribed off-label.
ignore environmental triggers to eat—she won’t benefit from taking an appetite suppressant.

Drug therapy works better when it’s paired with an overall program of lifestyle change. A study published in the Nov. 17, 2005, New England Journal of Medicine found that after one year, Meridia-takers who participated in a comprehensive counseling program that promoted a low-calorie diet and 30-minute daily walks lost twice as much weight as subjects who received counseling alone or Meridia alone. The counseling component of the study involved 10 months of regular meetings led by mental health professionals who utilized the LEARN (Lifestyle, Exercise, Attitudes, Relationships, and Nutrition) program for weight management (see “Selected resources”).

Among its most important benefits, counseling can help establish realistic goals. The idea behind using weight-loss medications is to improve health and reduce disease risk, not to achieve an “ideal body weight.” A 5%–10% reduction in weight over time is one common goal. But even more modest weight loss helps. One study of obese women found that those who intentionally lost any amount of weight experienced a 40%–50% decrease in death from obesity-related cancers and a 30%–40% decline in death from type 2 diabetes.

How do they work?
The prescription weight-loss medications now on the market generally fall into one of three categories:

- **Noradrenergic agents.** These medications increase levels of norepinephrine (also known as noradrenaline), a brain chemical that helps regulate appetite. Phentermine is the safest. On average, people taking phentermine lose 2–13 pounds over a six-month period. After that, weight loss tends to level off—as it does with other diet drugs—for reasons that aren’t entirely clear. These drugs have several side effects; patients should be re-evaluated after three months before continuing on them.

- **Serotonin-norepinephrine reuptake inhibitors.** The only weight-loss drug in this category is sibutramine (Meridia). It works by increasing the availability of serotonin and norepinephrine. Both brain chemicals make people feel full. Initial weight loss with sibutramine predicts long-term response to the drug: One study showed that people who lost more than four pounds in the first month were more likely to lose 10% of their body weight after one year than those who lost less weight initially.

- **Lipase inhibitor.** The only lipase inhibitor in the United States is orlistat (Xenical), which works by blocking the action of lipase, an enzyme released by the pancreas to help digest dietary fat. In a two-year trial, those who used orlistat had average weight losses over 20% better than participants who received a placebo—and more than 50% greater success in keeping weight off.

Certain antidepressant drugs are prescribed on a short-term basis because they’ve been found to help some people lose weight. But their effects are unpredictable, and in some cases they may produce weight gain rather than loss.

Weight-loss drugs don’t work for everyone

Clinical guidelines suggest that if an individual hasn’t lost at least a pound a week in the first month on a weight-loss medication, she’s unlikely to benefit from the drug. Also, people who overeat because of stress, bad habits, or emotional problems tend to get less out of appetite suppressants than those who overeat because of hunger. For them, psychotherapy or behavioral therapy may be a more appropriate first step.

“We don’t know who’s going to respond to these medications,” says Sue Cummings, a registered dietitian and coordinator of clinical programs at the Massachusetts General Hospital Weight Center in Boston. “We may try them, and if there’s no weight loss in one month, or the person reports no difference in appetite, we discontinue them. My preference would be to take a person as far as we can with healthy, sustainable eating habits and exercise, and then, if maintenance is a real problem, offer a medication.”

What now?

If approved, over-the-counter orlistat will be the first test of broader use of a powerful weight-loss agent. More side effects may crop up, especially without the oversight of clinicians or the guidance offered by comprehensive weight-loss programs. Yet there’s an urgent need to make more tools available to the increasing number of people who are overweight or obese, many of them unwilling or unable to seek help from the medical system for this problem. New understanding of the complexities of weight regulation may eventually lead to more targeted therapies. In the meantime, weight-loss drugs can help, but they’re not the ultimate solution. The key to long-term weight loss is effort on many fronts. The National Weight Control Registry (www.nwcr.ws), which tracks people who have maintained a weight loss of at least 30 pounds for one year or more, has found that successful “losers” join support groups, exercise intensively, restrict the amounts and kinds of food they eat, and weigh themselves often.

Selected resources

American Obesity Association
202-776-7711
www.obesity.org

Centers for Disease Control and Prevention
www.cdc.gov/nccdphp/dnspa/obesity/index.htm


Weight Control Information Network
877-946-4627 (toll free)
win.niddk.nih.gov
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