Pharmacotherapy Can Be Useful in Child Obesity

BY ROBERT FINN
San Francisco Bureau

SAN FRANCISCO — The epidemic of childhood obesity shows no signs of abating, and studies have demonstrated only modest results from diet and exercise, unless an intensive boot-camp approach is used, Robert H. Lustig, M.D., said at a meeting on clinical pediatrics, sponsored by the University of California, San Francisco.

Intensive treatment—that is, pharmacotherapy or surgery—is indicated in an adolescent whose BMI is greater than two standard deviations from the norm for his or her age, and who has at least one significant comorbidity, said Dr. Lustig of UCSF.

Such comorbidities include metabolic, orthopedic, and cardiopulmonary complications as well as psychological distress, he said, and the majority of obese adolescents have at least one of these.

Unfortunately, pharmacotherapy for obesity has a dubious history. Drugs used in the past, such as thyroid hormone, dinitrophenol, amphetamine, fenfluramine, phenylpropanolamine, and ephedra are well known for significant complications, including death. In addition, many clinicians are hesitant to prescribe drugs to children or adolescents when their long-term effects remain unknown.

Given that obesity can result from a number of underlying conditions and the variable results of many pharmacotherapies, the trick is to pick a drug that matches the patient's characteristics, said Dr. Lustig. He discussed four available drugs, two of which are approved by the Food and Drug Administration for use in children:

► **Sibutramine (Meridia) is an anorectic agent.** Sibutramine should complement a program of diet and exercise. Studies of adolescents who were given sibutramine have shown that they had significant weight loss, especially in the first 6 months. The FDA has approved the drug for use in patients over age 16 years.

Responses to sibutramine are highly variable, however, and few predictors of response have been identified. Moreover, side effects can be significant. In one study, 19 of 43 adolescents had mild hypertension and tachycardia in response to sibutramine, and 5 required discontinuation of the drug.

Other side effects include insomnia, anxiety, headache, depression, and the risk of serotonin syndrome when used in combination with certain other drugs. Sibutramine should not be routinely used in adolescents, said Dr. Lustig.

► **Orlistat (Xenical) is a pancreatic lipase inhibitor.** This drug decreases intestinal fat absorption, and is approved for use in children above age 12 years. Orlistat, in combination with behavioral intervention, results in significant weight loss over 4 months, according to a study of 534 subjects. However, children taking orlistat regained lost weight within a year, although they still remained significantly lighter than the children taking placebo, who gained weight.

Unless fat restrictions can be maintained, side effects include flatulence, diarrhea, and anal leakage.

► **Metformin (Glucophage) is another drug approved for use in children.** It reduces hepatic gluconeogenesis, increases hepatic insulin sensitivity, and lowers fasting insulin levels.

This drug is approved for use in type 2 diabetes mellitus, but not specifically for obesity. Nevertheless, studies have shown that metformin decreases food intake, reduces fat stores, improves lipid profiles, inhibits progression from impaired glucose tolerance to type 2 diabetes, and reduces cardiovascular morbidity and mortality in adults with diabetes.

In obese adolescents with impaired insulin sensitivity, studies have demonstrated significant decreases in BMI even when metformin is administered without dietary restrictions. The drug may be especially useful in adolescents taking psychotropic medications such as olanzapine, risperidone, quetiapine, or valproate.

The drug is most useful in adolescents who have severe insulin resistance, but not those who are insulin sensitive, Dr. Lustig said. Another group that may benefit may be obese girls with polycystic ovarian syndrome.

Metformin's side effects include abdominal discomfort that lasts for about 1 month, rare lactic acidosis, and urinary losses of B vitamins. Dr. Lustig said that all patients taking metformin should also take a daily multivitamin.

► **Octreotide (Sandostatin) inhibits the opening of calcium channels in beta cells and reduces glucose-dependent insulin secretion.**

Not approved for use in obese adolescents, octreotide seems especially effective in children with "hypothalamic obesity" arising from insults to the central nervous system.

Side effects include transient GI distress and gallstones, which can be prevented by ursodiol. Other limitations include its high cost and the requirement for parenteral administration. ■

CLINICAL GUIDELINES FOR FAMILY PHYSICIANS

Treating Obesity

BY NEIL S. SKOLNIK, M.D., AND MICHAEL P. GAGNON, M.D.

Defined as a body mass index of greater than 30 kg/m^2, obesity is one of the fastest-growing health problems in the United States. It is currently estimated that more than 60% of American adults are overweight or obese. This trend translates annually into billions of dollars in expenses for the treatment of health-related consequences, and approximately 300,000 deaths due to related illnesses.

Obesity screening in the primary care setting has been recommended by the U.S. Preventative Services Task Force (Ann. Intern. Med. 2003;139:930-2). First-line obesity treatment is diet, exercise, and lifestyle changes.

Guidelines are most useful when they are available at the point of care. A concise yet complete handheld computer version of this guideline is available for download, compliments of FAMILY PRACTICE NEWS, *at www.redi-reference.com.*

New guidelines from the American College of Physicians both suggest the use of pharmacologic agents to help augment weight loss and encourage discussion of surgical options with morbidly obese patients who have significant obesity-related health problems and who fail first-line treatment (Ann. Intern. Med. 2005;142:525-31).

Medical Treatment

Diet and exercise remain the first-line treatment of choice for obesity, with an emphasis on high-intensity counseling (more than once per month for 3 months) with regard to lifestyle modifications. There is no evidence that lifestyle modification reduces morbidity and mortality; however, the benefits gained from even modest weight loss may include reduction in hypertension, improved glucose tolerance, and decreased lipid levels. These benefits provide indirect measures of improved health. Weight loss and exercise regimens should be tailored to each patient. No specific diet is recommended.

For patients who fail to achieve weight loss through diet and exercise alone, pharmacologic therapy may be instituted. Prior to initiation of therapy, a candid discussion between doctor and patient with regard to side effects, efficacy, and lack of long-term safety data for these drugs needs to occur. The weight loss associated with these drugs is modest (less than 5 kg a year), and there are no long-term trial data following patients for more than 1 year. In addition, there is no evidence of increased efficacy of combination therapy and no data on weight gain after treatment is discontinued.

Recommended drug therapies include appetite suppressants and lipase inhibitors. The drug options include sibutramine, orlistat, phentermine, diethylpropion, fluoxetine, and bupropion. Treatment should be chosen based on a side-effects profile and on patient tolerance.

Fluoxetine and bupropion are not currently approved for weight loss by the Food and Drug Administration; however, these drugs have been shown in studies to be effective in helping patients achieve weight loss. Studies on fluoxetine for the treatment of obesity utilized higher dosages than those normally used for depression, up to 60 mg/day.

Sibutramine is among the more commonly used medications, and its prominent side effects include increased blood pressure and heart rate. Orlistat is another commonly used agent; its most frequent side effects are fecal urgency, oily spotting, and flatulence.

Surgical Treatment

For patients with a BMI greater than 40 who fail first-line therapy of diet and exercise with or without pharmacologic treatment, and who have significant obesity-related comorbidities, surgical treatments can be considered. Patients need to be counseled about possible side effects and complications of surgery.

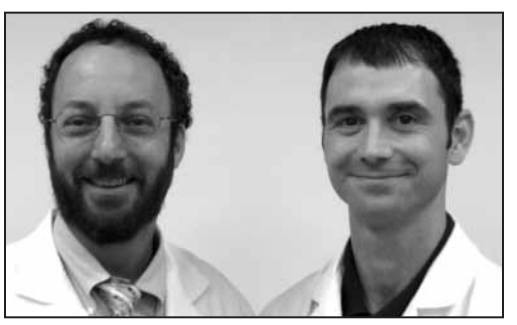
There are several options, including the Roux-en-Y gastric bypass, biliopancreatic bypass, laparoscopic adjustable gastric banding, and vertical banded gastroplasty.

Bariatric surgery should be done at a high-volume center, given that the morbidity and mortality data are significantly improved at these institutions. Randomized, controlled trials comparing surgical procedures with gastroplasty revealed gastric bypass procedures to be superior. Currently, there is no proven benefit to cardiovascular morbidity and mortality with bariatric surgery. The weight-loss outcomes of these procedures are much greater (20 kg at 8 years) than are those with pharmacolgic therapy, but this finding is based largely on one Swedish observational study.

There have been no randomized, controlled trials with current surgical procedures comparing bariatric surgery with a nonsurgically treated group. In the 8-year follow-up of the Swedish study, the surgical patients had a significant reduction in diabetes risk (odds ratio 0.16); however, the initial improvement in hypertension seen in the first 2 years of the study was lost over time. Small benefits in overall quality of life and in reducing sleep apnea persisted through to 10 years for the surgical group.

The Bottom Line

Pharmacologic treatment of obesity (BMI greater than 30) in patients who fail to lose weight with diet and exercise should be considered carefully and discussed with the patient. Surgical treatment for patients with a BMI greater than 40 and comorbid obesity-related conditions can be considered after diet and exercise have failed. Diet and exercise must be a mainstay of treatment even after surgery.



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