BONING UP

FDA advisers recommend drug for osteoporosis

A new, nonhormonal drug to treat osteoporosis may soon become a reality. The Food & Drug Administration's Endocrinologic & Metabolic Drugs Advisory Committee has unanimously voted to recommend approval of Fosamax (alendronate sodium) by Merck & Co. for treatment of osteoporosis in postmenopausal women. If approved, alendronate sodium will be the first in a new class of drugs called aminobisphosphonates, which decrease the rate of bone resorption.

The July 13 recommendation followed clinical trials that demonstrated the drug's ability to reduce thinning of bones in postmenopausal women. Data from the three-year study revealed that alendronate sodium actually increased bone mineral density at the spine and hip by 8.2% and 7.2%, respectively, while patients treated with placebo lost 0.7% at each site. Alendronate sodium also reduced the number of new vertebral fractures by 48% compared with placebo. The study followed 994 women with osteoporosis in 16 countries.

Though the advisory committee did recommend approval of the drug, it expressed concern that doctors might incorrectly prescribe it to prevent rather than to treat osteoporosis. Committee members suggested that the labeling clearly state that the drug is not to be used as a preventive treatment and explicitly define which patients can benefit from using the drug. The committee also recommended continued study of its long-term use and suggested that, for improved absorption, the drug be taken one hour before eating or drinking (other than water) rather than the half-hour waiting period currently advised by Merck.

Approval of the drug would help Merck tap into a large market. It is estimated that 25 million Americans suffer from osteoporosis, which causes 1.5 million fractures each year. Two other drugs are currently used to treat the disease: estrogen and calcitonin-salmon.

Premarin (conjugated estrogen) by Wyeth-Ayerst, a subsidiary of American Home Products, is currently the leading treatment for osteoporosis. However, American Home Products has agreed to help Merck promote alendronate sodium to gynecologists as a treatment for osteoporosis while promoting its own drug, Premarin, as a treatment for menopausal symptoms.

Merck is prohibited from promoting the drug until it's been approved by the FDA. In the meantime, the company has been trying to build the market by educating health-care professionals and the public about the disease. The FDA's advisory committee suggested that Merck include information on the limitations of the drug in its education programs to help doctors learn to prescribe it selectively.

Karyn Snyder

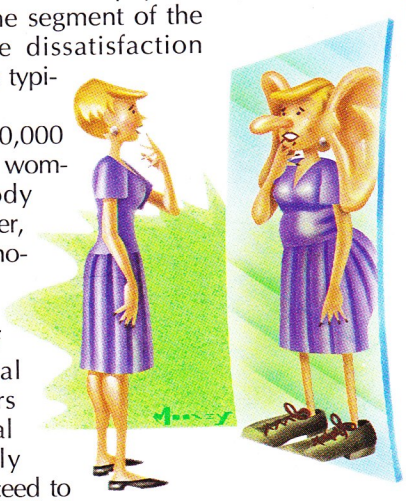
Body disorder shows beauty isn't always in eye of beholder

Snow White's wicked stepmother became enraged with her mirror when it told her Snow White's beauty surpassed her own. While this is the stuff of fairy tales, many people today are just as dissatisfied with the way they see themselves.

Although it isn't difficult to understand the average person's concern about appearance in a world that emphasizes the importance of physical beauty, there is one segment of the population whose dissatisfaction extends beyond the typical complaints.

An estimated 200,000 American men and women suffer from Body Dysmorphic Disorder, a debilitating psychological condition that distorts a person's perception of his or her physical qualities. Sufferers often see a normal feature as grossly abnormal and proceed to become obsessed with it. Many focus so much attention on imagined imperfections that they are unable to hold a job or even leave the house because they are so distraught.

In the past, BDD was thought to be purely psychological, but several studies conducted by Eric Hollander, M.D., associate professor of psychiatry and director of clinical psychopharmacology at Mount Sinai School of Medicine, New York City, suggest a biochemical factor. "It seems to be driven by a type of chemical messenger, or neurotransmitter, in the brain called serotonin."



Serotonin sets off an alarm in the brain, signaling that something is wrong, explained Hollander; in these cases, however, there isn't anything wrong except perception. The brain is misinterpreting what the eyes are see-

ing. As a result, patients fear that "people will reject them, that they may be embarrassed or humiliated in social situations," he said.

The Food & Drug Administration is funding a study to compare the action of two drugs, clomipramine and desipramine, in such patients. This is the first large, double-blind controlled study of the drugs for treatment of BDD, said Hollander, the study's director. Researchers at Mount Sinai have been studying BDD since 1989. According to Hollander, past studies have demonstrated that serotonin reuptake inhibitors are highly effective in treating BDD, while antidepressants are completely ineffective.

Hollander is seeking up to 80 patients to participate in his latest study, which is expected to last a year and a half. Patients will be treated for 10 weeks with desipramine and for another 10 weeks with clomipramine. They will then participate in a maintenance period lasting up to six months, during which they will take the drug that worked for them. Patients will then receive behavioral therapy.

"One thing that's amazing is the excellent response once these people get on the medicine. Even without psychotherapy, they can do extremely well, which makes it so convincing that this is a biochemical type of problem," said Hollander.

Mark (name changed to protect privacy), a patient who was treated in Hollander's last study, is an advocate of the drug therapy. Before he began taking the medication, Mark was isolated and even suicidal. He had dropped out of school and had withdrawn from social situations, believing that his feet gave off a highly offensive odor. Though his family, friends, and therapist weren't able to help him overcome this obsession, treatment with clomipramine was. "It's been great. I can't emphasize enough how different I feel today from a year ago," said Mark, who cited only nausea during the first few weeks as a negative aspect of the drug. Mark now has a job requiring much interaction with people and is taking night classes to obtain his college degree.

For more information about the study, contact Mount Sinai at (212) 241-2994.

Karyn Snyder

New alternative oral agent approvable for Type II diabetes

Type II (noninsulin-dependent) diabetics, who account for 90%-95% of those with diabetes, can soon be treated by three types of oral agents, each of which has a different mechanism of action. The old standbys, sulfonylureas, work by increasing insulin secretion; the recently approved metformin hydrochloride (Glucophage, Bristol-Myers Squibb) makes the insulin secreted more effective at the level of the liver and probably the muscles.

The newest approvable agent is acarbose (Precose, Bayer), which could be available in the spring. Acarbose "decreases the rise in blood sugar after a person eats a meal," said Harold Lebovitz, M.D., professor of medicine and chief of the section of endocrinology and diabetes at the SUNY Health Sciences Center in Brooklyn, N.Y. "Acarbose keeps the glucose from going too high. It acts in the entire intestine. It delays the absorption of carbohydrate, which is digested primarily in the upper intestine, so the glucose is absorbed throughout the length of the intestine."

He sees the new drug as valuable, because not all Type II patients have the same problem. "Those who are obese and who are under a lot of stress will have a lot of insulin resistance. Those who are thinner may have more in the way of a decrease in insulin secretion.... And most people have some component of each," he told *Drug Topics*.

Harold Braunstein, M.D., who chaired the Food & Drug Administration advisory committee that gave acarbose approvable status, said he believes the product will be marketed as monotherapy as well as for use with the sulfonylureas or with metformin. The dose will probably be no more than 200 mg three times a day, he said. Braunstein is also chief of the department of medicine at the Cedar Sinai Medical Center in Los Angeles and professor of medicine at the University of California at Los Angeles. "Several of us on the committee thought that 100 mg t.i.d. was very safe and almost as effective" as the 200 mg three times a day in the studies.

Braunstein expects that if exercise and diet don't get serum glucose to a desirable range, M.D.s will still start patients on the sulfonylureas, which control HbA1-C hemoglobin over time better than acarbose. So does metformin, he added, which he believes would be the second-line agent in many cases.

Acarbose has some unpleasant side effects, he said. The abdominal pain usually disappears with time; the gas formation in the intestine, and its resulting flatulence, does not. The committee was also concerned with the rise in transaminases in some patients. But Lebovitz, a speaker at the advisory committee, said this side effect was more prevalent in patients receiving 300 mg of acarbose three times a day, early in the studies. "At 200 mg, very few developed it, and I believe there were none at 100 mg."

What made acarbose's approval more likely this time around—under the trade name Glucobay (Miles), it was turned down in 1991—were the results of several trials demonstrating not only safety and efficacy but the importance of good glucose control. Thus the committee extrapolated to Type IIs the results reported last year in the Diabetes Control and Complications Trial (DCCT) for Type I diabetics. The DCCT had shown conclusively that tight glucose control greatly reduces the serious microvascular complications of diabetes, including neuropathy, retinopathy, and nephropathy. There is no evidence, however, that good glucose control will prevent the macrovascular complications, such as stroke and heart attack, that occur in those with diabetes, cautioned Braunstein.

He and Lebovitz were also unclear on whether the availability of three oral agents will reduce the number of Type II patients, estimated at 35%, who ultimately need insulin as well as an oral agent. "We need to get a larger experience with patients in real life, not just in controlled trials," Braunstein emphasized.

Jean McCann

THE AUTHOR writes frequently on clinical subjects.