In the interval between the two NHANES studies, the prevalence of functional impairment did not change among normal-weight subjects, but it increased among obese subjects, from 37% to 42%. In a closer analysis that controlled for demographic characteristics, the odds of being functionally impaired rose 43% among the obese but showed no change among normal-weight subjects.

When the subjects were separated into categories of mild, moderate, and extreme obesity, they found that functional impairment had increased in all three. The overall increase in disability, therefore, was not solely because there are more people in the "extremely obese" category in later years, Dr. Alley and Dr. Chang said (JAMA 2007;298:2020-7).

Several obesity-related conditions were strongly associated with disability, including arthritis, diabetes, heart failure, MI, and stroke.

In an accompanying editorial, Dr. Edward W. Gregg of the Centers for Disease Control and Prevention, Atlanta, and Dr. Jack M. Guralnik of the National Institute on Aging, Bethesda, Md., said the most important finding in this study was that obese patients today are more likely to be disabled than obese patients were a decade earlier.

"This finding contrasts with the general reduction in disability reported for older adults" in the general population, they noted. "The authors speculate that this increased disability may be due to the average obese person of the current cohort having spent more years obese than in previous cohorts" and thus having more cumulative exposure to disability-inducing obesit (JAMA 2007;298:2066-7).

"It is also possible that because of declining mortality rates, the obese segment of the population is now composed of more people with multiple chronic conditions who in previous decades would have died at a younger age," they wrote. ■

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Amitiza. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Voluntary reports of adverse reactions occurring with the use of Amitiza include the following: syncope, malaise, increased heart rate, muscle cramps or muscle spasms, rash, and asthenia.

7 DRUG INTERACTIONS

Based upon the results of *in vitro* human microsome studies, there is low likelihood of drug–drug interactions. *In vitro* studies using human liver microsomes indicate that cytochrome P450 isoenzymes are not involved in the metabolism of lubiprostone. Further *in vitro* studies indicate microsomal carbonyl reductase may be involved in the extensive biotransformation of lubiprostone to the metabolite M3 (See *Pharmacokinetics, Metabolism* [12.3].). Additionally, *in vitro* studies in human liver microsomes demonstrate that lubiprostone does not inhibit cytochrome P450 isoforms 3A4, 2D6, 1A2, 2A6, 2B6, 2C9, 2C19, or 2E1, and *in vitro* studies of primary cultures of human hepatocytes show no induction of cytochrome P450 isoforms 1A2, 2B6, 2C9, and 3A4 by lubiprostone. No additional drug–drug interaction studies have been performed. Based on the available information, no protein binding–mediated drug interactions of clinical significance are anticipated.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Pregnancy Category C. [See *Warnings and Precautions* (5.1).]

Teratology studies with lubiprostone have been conducted in rats at oral doses up to 2000 mcg/kg/day (approximately 332 times the recommended human dose, based on body surface area), and in rabbits at oral doses of up to 100 mcg/kg/day (approximately 33 times the recommended human dose, based on body surface area). Lubiprostone was not teratogenic in rats or rabbits. In guinea pigs, lubiprostone caused fetal loss at repeated doses of 10 and 25 mcg/kg/day (approximately 2 and 6 times the recommended human dose, respectively, based on body surface area) administered on days 40 to 53 of gestation.

There are no adequate and well-controlled studies in pregnant women. However, during clinical testing of Amitiza at 24 mcg twice daily, four women became pregnant. Per protocol, Amitiza was discontinued upon pregnancy detection. Three of the four women delivered healthy babies. The fourth woman was monitored for 1 month following discontinuation of study drug, at which time the pregnancy was progressing as expected; the patient was subsequently lost to follow-up.

Amitiza should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If a woman is or becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus.

8.3 Nursing Mothers

It is not known whether lubiprostone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from lubiprostone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been studied.

8.5 Geriatric Use

The efficacy of Amitiza in the elderly (≥ 65 years of age) subpopulation was consistent with the efficacy in the overall study population. Of the total number of constipated patients treated in the dose-finding, efficacy, and long-term studies of Amitiza, 15.5% were ≥ 65 years of age, and 4.2% were ≥ 75 years of age. Elderly patients taking Amitiza (any dosage) experienced a lower incidence rate of associated nausea compared to the overall study population taking Amitiza (18% vs. 29%, respectively).

8.6 Renal Impairment

Amitiza has not been studied in patients who have renal impairment.

8.7 Hepatic Impairment

Amitiza has not been studied in patients who have hepatic impairment.

10 OVERDOSAGE

There have been two confirmed reports of overdosage with Amitiza. The first report involved a 3-year-old child who accidentally ingested 7 or 8 capsules of 24 mcg of Amitiza and fully recovered. The second report was a study patient who self-administered a total of 96 mcg of Amitiza per day for 8 days. The patient experienced no adverse reactions during this time. Additionally, in a Phase 1 cardiac repolarization study, 38 of 51 patients given a single oral dose of 144 mcg of Amitiza (6 times the recommended dose) experienced an adverse event that was at least possibly related to the study drug. Adverse reactions that occurred in at least 1% of these patients included the following: nausea (45%), diarrhea (35%), vomiting (27%), dizziness (14%), headache (12%), abdominal pain (8%), flushing/hot flash (8%), retching (8%), dyspnea (4%), pallor (4%), stomach discomfort (4%), anorexia (2%), asthenia (2%), chest discomfort (2%), dry mouth (2%), hyperhidrosis (2%), and syncope (2%).

16 HOW SUPPLIED/STORAGE AND HANDLING

Amitiza is available as an oval, orange, soft gelatin capsule with "SPI" printed on one side. Each capsule contains 24 mcg of lubiprostone. Amitiza is available as follows:

- Bottles of 100 (NDC 64764-240-10)
- Bottles of 60 (NDC 64764-240-60)

Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F).
PROTECT FROM EXTREME TEMPERATURES.

17 PATIENT COUNSELING INFORMATION

17.1 Dosing Instructions

Patients should take a single 24 mcg capsule of Amitiza twice daily with food or a meal. The capsule should be taken once in the morning and once in the evening daily as prescribed. Physicians and patients should periodically assess the need for continued treatment with Amitiza.

17.2 Nausea and Diarrhea

Patients should take Amitiza with food or a meal to reduce symptoms of nausea. Patients on treatment who experience severe nausea or diarrhea should inform their physician.

Marketed by:
Sucampo Pharmaceuticals, Inc., Bethesda, MD 20814
and
Takeda Pharmaceuticals America, Inc., Deerfield, IL 60015

750-03568-1 06/07
L-LUB-0607-5

Low-Carb Diet May Be Best in Type 2

BY FRAN LOWRY
Orlando Bureau

NEW ORLEANS —A low-carbohydrate diet, which used to be the only treatment for diabetes before the advent of insulin, may turn out to be the preferred diet for overweight individuals with type 2 diabetes, researchers said at the annual meeting of NAASO, the Obesity Society.

In a poster, preliminary results from a randomized trial of two dietary regimens for weight loss—a low-carbohydrate, ketogenic diet alone, or a low-fat, energy-restricted diet plus drug therapy with orlistat (Xenical)—showed that the low-carb regimen produced more favorable changes in hemoglobin A_{1c} (HbA_{1c}) in a subset of diabetic patients. The diet also reduced or eliminated their need for insulin or other diabetes medications, more so than the orlistat diet, said Jennifer R. McDuffie, Ph.D., of Duke University, Durham, N.C.

'We think that the low-carbohydrate ketogenic diet may be exerting its good effects on HbA_{1c} because of its low carbohydrate content.'

In the 6 months that the trial has been ongoing, weight loss with both regimens has been similar (10-12 kg) and so has the reduction in waist circumference. "Because the weight loss has been the same in both groups, we think that the low-carbohydrate ketogenic diet may be exerting its good effects on HbA_{1c} because of its low carbohydrate content," Dr. McDuffie said in an interview.

The study, which is planned to last 48 weeks, includes 146 outpatients from the Durham Veterans Affairs Medical Center. All have a body mass index 27 kg/m^2 or greater, and 46 of the patients also have type 2 diabetes. Their mean age is 56 years (range, 48-64 years); the majority are male, and roughly half are black.

After 24 weeks, the mean HbA_{1c} among the 22 type 2 diabetes patients in the low-carb arm dropped from 7.5% to 6.8%, a significant reduction. The HbA_{1c} in the 24 type 2 diabetes patients in the orlistat arm went from 7.6 to 7.4, and did not fall significantly from baseline, Dr. McDuffie said.

The need for metformin was decreased or eliminated in 15 (68%) of the 22 patients on the low-carbohydrate ketogenic diet, compared with 7 (29%) of the 24 patients on the orlistat low-fat diet. The low-carbohydrate ketogenic diet also had a favorable effect on HDL-cholesterol levels in all patients, regardless of their type 2 diabetes status. The mean increase in HDL cholesterol was 4 mg/dL in the low-carb group, compared with 0.4 mg/dL in the orlistat group.

Dr. McDuffie stressed that these results are preliminary, and that further analysis of factors such as adherence, physical activity, and adverse events is needed. ■