

Disability in Obese Elderly Is Rising, Not Declining

BY MARY ANN MOON
Contributing Writer

Some types of disability are increasing in older obese Americans, even though recent improvements in cardiovascular health care have reduced the risk of disability in older normal-weight people, according to researchers at the University of Pennsylvania, Philadelphia.

Data from recent studies have suggested that the obese elderly population in the

United States may have grown healthier since the 1960s, especially with the widespread use of lipid-lowering and antihypertensive drugs. "If the physiological manifestations of obesity are increasingly treatable, then some of the negative health effects of obesity may be in decline," and obesity may be becoming less disabling, wrote researchers Dawn E. Alley, Ph.D., and Dr. Virginia W. Chang of the University of Pennsylvania, Philadelphia. On the other hand, they wrote, if improvements

in health care are allowing obese people with chronic disease to live longer, then disability may be increasing in this population.

To examine whether the association between obesity and disability has changed over time, they assessed body mass index and disability in subjects aged 60 years and older, comparing data from the National Health and Nutrition Examination Surveys done in 1988-1994 (NHANES III) with data from the NHANES surveys of 1999-2004.

A total of 5,724 subjects from the earli-

er survey and 4,984 subjects from the later survey indicated whether they had no difficulty, some difficulty, much difficulty, or an inability to perform six tasks: walking one-quarter of a mile; walking up 10 steps without resting; stooping, crouching, or kneeling; lifting or carrying 10 pounds; walking between rooms on the same floor; and standing up from an armless chair. The subjects also reported on their ability to perform three activities of daily living: getting in and out of bed, eating, and dressing.

Amitiza®
(lubiprostone) Capsules

Initial U.S. Approval: 2006

BRIEF SUMMARY OF PRESCRIBING INFORMATION- Please see package insert for complete prescribing information.

1 INDICATIONS AND USAGE

Amitiza® is indicated for the treatment of chronic idiopathic constipation in adults.

2 DOSAGE AND ADMINISTRATION

The recommended dosage for Amitiza is 24 mcg taken twice daily orally with food. Physicians and patients should periodically assess the need for continued therapy.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

Amitiza is contraindicated in patients with known mechanical gastrointestinal obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Pregnancy

The safety of Amitiza in pregnancy has not been evaluated in humans. In guinea pigs, lubiprostone has been shown to have the potential to cause fetal loss. Amitiza should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women who could become pregnant should have a negative pregnancy test prior to beginning therapy with Amitiza and should be capable of complying with effective contraceptive measures. See *Use in Specific Populations* (8.1).

5.2 Nausea

Patients taking Amitiza may experience nausea. If this occurs, concomitant administration of food with Amitiza may reduce symptoms of nausea. See *Adverse Reactions* (6.1).

5.3 Diarrhea

Amitiza should not be prescribed to patients that have severe diarrhea. Patients should be aware of the possible occurrence of diarrhea during treatment. Patients should be instructed to inform their physician if severe diarrhea occurs. See *Adverse Reactions* (6.1).

5.4 Bowel Obstruction

In patients with symptoms suggestive of mechanical gastrointestinal obstruction, the treating physician should perform a thorough evaluation to confirm the absence of such an obstruction prior to initiating therapy with Amitiza.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Adverse reactions in dose-finding, efficacy, and long-term clinical studies: The data described below reflect exposure to Amitiza in 1175 patients (29 at 24 mcg once daily, 1113 at 24 mcg twice daily, and 33 at 24 mcg three times daily) over 3- or 4-week, 6-month, and 12-month treatment periods; and from 316 patients receiving placebo over short-term exposure (≤ 4 weeks). The total population (N = 1491) had a mean age of 49.7 (range 19-86) years; was 87.1% female; 84.8% Caucasian, 8.5% African American, 5.0% Hispanic, 0.9% Asian; and 15.5% elderly (≥ 65 years of age). Table 1 presents data for the adverse reactions that occurred in at least 1% of patients who received Amitiza (any dosage) and that occurred more frequently with study drug than placebo. In addition, corresponding adverse reaction incidence rates in patients receiving Amitiza 24 mcg once daily and in patients receiving Amitiza 24 mcg twice daily are shown.

Table 1: Percent of Patients with Adverse Reactions in Clinical Studies of Amitiza

System/Adverse Reaction ¹	Placebo	Amitiza 24 mcg Once Daily	Amitiza 24 mcg Twice Daily	Amitiza Any Dosage ²
	N = 316 %	N = 29 %	N = 1113 %	N = 1175 %
Gastrointestinal disorders				
Nausea	3	17	29	29
Diarrhea	<1	7	12	12
Abdominal pain	3	3	8	8
Abdominal distension	2	—	6	6
Flatulence	2	3	6	5
Vomiting	—	—	3	3
Loose stools	—	—	3	3
Abdominal discomfort ³	—	3	2	2
Dyspepsia	<1	—	2	2
Dry mouth	<1	—	1	1
Stomach discomfort	<1	—	1	1
Nervous system disorders				
Headache	5	3	11	11
Dizziness	<1	3	3	3
General disorders and site administration conditions				
Edema	<1	—	3	3
Fatigue	<1	—	2	2
Chest discomfort/pain	—	3	2	2
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	—	3	2	2

¹ Includes only those events associated with treatment (possibly, probably, or definitely related, as assessed by the investigator).

² Includes patients dosed at 24 mcg once daily, 24 mcg twice daily, and 24 mcg three times daily.

³ This term combines "abdominal tenderness," "abdominal rigidity," "gastrointestinal discomfort," and "abdominal discomfort."

Nausea: Approximately 29% of patients who received Amitiza (any dosage) experienced an adverse reaction of nausea; 3% of patients had severe nausea while 8% of patients discontinued treatment due to nausea. The rate of nausea associated with Amitiza (any dosage) was substantially lower among male (7%) and elderly patients (18%). Further analysis of the safety data revealed that long-term exposure to Amitiza does not appear to place patients at an elevated risk for experiencing nausea. The incidence of nausea increased in a dose-dependent manner with the lowest overall incidence for nausea reported at the 24 mcg once daily dosage (17%). In open-labeled, long-term studies, patients were allowed to adjust the dosage of Amitiza down to 24 mcg once daily from 24 mcg twice daily if experiencing nausea. Nausea decreased when Amitiza was administered with food. No patients in the clinical studies were hospitalized due to nausea.

Diarrhea: Approximately 12% of patients who received Amitiza (any dosage) experienced an adverse reaction of diarrhea; 3% of patients had severe diarrhea while 2% of patients discontinued treatment due to diarrhea.

Electrolytes: No serious adverse reactions of electrolyte imbalance were reported in clinical studies, and no clinically significant changes were seen in serum electrolyte levels in patients receiving Amitiza.

Less common adverse reactions: The following list of adverse reactions includes those that occurred in less than 1% of patients receiving Amitiza (any dosage) in dose-finding, efficacy, and long-term clinical studies and that were considered by the investigator to be probably or definitely related to treatment with study drug. Moreover, the list includes only those events that occurred in at least two patients and more frequently in patients receiving Amitiza than those receiving placebo.

Gastrointestinal disorders: fecal incontinence, defecation urgency, frequent bowel movements, intestinal functional disorder, constipation, eructation
Musculoskeletal and connective tissue disorders: muscle cramp, joint swelling, myalgia

Nervous system disorders: dysgeusia, syncope, tremor

Respiratory, thoracic, and mediastinal disorders: pharyngolaryngeal pain, cough

Skin and subcutaneous tissue disorders: hyperhidrosis, cold sweat
General disorders and administration site conditions: influenza, pain

Metabolism and nutrition disorders: decreased appetite

Psychiatric disorders: anxiety

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 peo-

ple 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 obesity (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. ■

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.

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 circum-

ference. “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/m² 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. ■

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval 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.

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and

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