

Pilot Program Cuts Cardiovascular Risk in Type 2

BY BRUCE JANCIN
Denver Bureau

COLORADO SPRINGS — A novel pharmacist-led, multidisciplinary program of group medical visits for patients with type 2 diabetes can reduce multiple cardiovascular risk factors, randomized trial data show.

More than 21 million Americans have type 2 diabetes. Two-thirds will die of cardiovascular disease. One-on-one interac-

tions between patient and nurse or physician are not a practical way to address the multiple cardiovascular risk factors in the diabetic population, Tracey H. Taveira, Pharm.D., said at a conference sponsored by the American Heart Association.

A collaborative, multidisciplinary intervention involving groups of patients provides economy of scale and the opportunity to harness group dynamics constructively. Plus, a program led by a pharmacist offers significant cost advantages because of

the substantially lower cost of a pharmacist's time, said Dr. Taveira, a pharmacist at the Providence (R.I.) VA Medical Center.

She presented a randomized controlled prospective trial that evaluated the effectiveness of a program—the Multidisciplinary Education and Diabetes Intervention for Cardiac risk reduction, or MEDIC—that she and her colleagues developed at the VA center. The study involved 110 men with type 2 diabetes who had a hemoglobin A_{1c} (HbA_{1c}) value of 7%-9% within the previ-

ous 6 months. Half of the patients were obese. They were randomized to MEDIC or to usual care, which included an invitation to participate in the hospital's American Diabetes Association-certified diabetes program, as well as an obesity program.

Participation in MEDIC involved a 2-hour meeting weekly for 4 weeks. There were six to eight patients per class. The first hour of each session involved patient education provided by a registered dietician, a physical therapist, and a nurse with expertise in the behavioral aspects of cardiovascular risk and diabetes. The educational content, adapted from national guidelines for diabetes self-management, was delivered using principles of social learning theory. Patients learned to carry a personal health care

report card; set goals; and self-monitor blood pressure, blood glucose, and physical activity. They received weekly individualized dietary and physical exercise homework.

In the second hour of each class, a clinical pharmacist cre-

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dentialed as a certified diabetes educator aggressively titrated medications for the treatment of diabetes, hypertension, hyperlipidemia, and tobacco cessation using algorithms adapted from national guidelines.

The study end points involved changes in cardiovascular risk factors 4 months from baseline. Systolic blood pressure in the MEDIC group fell by 7.3 mm Hg from a mean of 134 mm Hg at baseline, compared with a 1.7-mm Hg decrease in the usual-care group. From a baseline diastolic blood pressure of 74 mm Hg, there was a 6.5-mm Hg drop in MEDIC patients and a 1.0-mm Hg increase in controls.

HbA_{1c} decreased by 0.9% in MEDIC patients from a baseline of 8.1%, and by 0.1% with usual care. The total cholesterol/HDL ratio dropped from 4.6 to 4.2 in the MEDIC group and increased from 4.3 to 4.4 in controls. From a mean baseline LDL level of 93 mg/dL, there was a 12.2-mg/dL decrease in the MEDIC patients and a 7.8-mg/dL drop in the usual-care group. Body mass index declined from 33.9 kg/m² at baseline to 33.7 kg/m² in the MEDIC group, and was unchanged over time in controls.

Half of the MEDIC patients achieved an HbA_{1c} below 7%, as did 28% of controls. Two-thirds of MEDIC patients got their systolic blood pressure below 130 mm Hg, compared with 39% of controls. A diastolic blood pressure less than 80 mm Hg was achieved in 88% of MEDIC patients and in 69% of controls. The overall cardiovascular risk burden as reflected in the United Kingdom Prospective Diabetes risk score dipped by 15% at 4 months in the MEDIC group and rose by 3% in controls, said Dr. Taveira.

A larger multicenter randomized controlled trial is underway, as is a separate study of the program's utility in diabetic patients with comorbid mental illness. ■

Table 2: Percent of Patients with Adverse Reactions (IBS-C Studies)

System/Adverse Reaction ¹	Placebo N = 435 %	Amitiza 8 mcg Twice Daily N = 1011 %
Gastrointestinal disorders		
Nausea	4	8
Diarrhea	4	7
Abdominal pain	5	5
Abdominal distension	2	3

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

Less common adverse reactions: The following adverse reactions (assessed by investigator as probably related to treatment) occurred in less than 1% of patients receiving Amitiza 8 mcg twice daily in clinical studies, occurred in at least two patients, and occurred more frequently in patients receiving study drug than those receiving placebo: dyspepsia, loose stools, vomiting, fatigue, dry mouth, edema, increased alanine aminotransferase, increased aspartate aminotransferase, constipation, eructation, gastroesophageal reflux disease, dyspnea, erythema, gastritis, increased weight, palpitations, urinary tract infection, anorexia, anxiety, depression, fecal incontinence, fibromyalgia, hard feces, lethargy, rectal hemorrhage, pollakiuria.

One open-labeled, long-term clinical study was conducted in patients with IBS-C receiving Amitiza 8 mcg twice daily. This study comprised 476 intent-to-treat patients (mean age 47.5 [range 21–82] years; 93.5% female; 79.2% Caucasian, 11.6% African American, 8.6% Hispanic, 0.2% Asian; 7.8% ≥ 65 years of age) who were treated for an additional 36 weeks following an initial 12–16-week, double-blinded treatment period. The adverse reactions that were reported during this study were similar to those observed in the two double-blinded, controlled studies.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Amitiza 24 mcg for the treatment of chronic idiopathic constipation. 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, allergic-type reactions (including rash, swelling, and throat tightness), 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* [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 highest 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, six women became pregnant. Per protocol, Amitiza was discontinued upon pregnancy detection. Four of the six women delivered healthy babies. The fifth 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. The sixth pregnancy was electively terminated.

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

Chronic Idiopathic Constipation

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).

Irritable Bowel Syndrome with Constipation

The safety profile of Amitiza in the elderly (≥ 65 years of age) subpopulation (8.0% were ≥ 65 years of age and 1.8% were ≥ 75 years of age) was consistent with the safety profile in the overall study population. Clinical studies of Amitiza did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients.

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 overdose 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 highest 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%).

17 PATIENT COUNSELING INFORMATION

17.1 Dosing Instructions

Amitiza should be taken twice daily with food and water to reduce potential symptoms of nausea. The capsule should be taken once in the morning and once in the evening daily as prescribed. The capsule should be swallowed whole and should not be broken apart or chewed. Physicians and patients should periodically assess the need for continued therapy.

Patients on treatment who experience severe nausea, diarrhea, or dyspnea should inform their physician. Patients taking Amitiza may experience dyspnea within an hour of the first dose. This symptom generally resolves within 3 hours, but may recur with repeat dosing.

Chronic Idiopathic Constipation

Patients should take a single 24 mcg capsule of Amitiza twice daily with food and water.

Irritable Bowel Syndrome with Constipation

Patients should take a single 8 mcg capsule of Amitiza twice daily with food and water.

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