CAPSULES CLINICAL

Four Genes Linked to Diabetes Onset Scientists have identified four genetic codes associated with the onset of type 2 diabetes mellitus, according to data from a case-control study.

Researchers from Imperial College London, McGill University in Montreal, and other institutions wrote that the genetic loci they identified, along with another previously discovered locus, help explain about 70% of diabetes cases (Nature 2007 Feb. 11 [Epub doi: 10.1038/nature05616]).

The association between each of the loci and the onset of diabetes was fairly weak,

but establishing the loci provides new pathways to study in diabetes development.

The researchers compared the genetic makeup of about 700 nonobese French patients with diabetes who have at least one first-degree relative with diabetes with that of 700 controls. They examined genotypes for 393,000 single-nucleotide polymorphisms, looking for mutations that might be statistically linked to diabetes. They then tested the genetic makeup of a further 2,600 diabetes patients, no longer restricted on obesity or familial diabetes criteria, and 2,900 controls to confirm the initial findings.

One of the loci identified is known as TCF7L2, a genetic factor in insulin secretion previously linked to diabetes onset. One newly discovered mutation was in SLC30A8, a zinc transporter involved in insulin biosynthesis. Overexpression of the gene in insulinoma cells increases glucose-stimulated insulin secretion, the authors wrote. Patients with the mutation on a single allele are at 15%-65% higher risk of diabetes depending on the mutation.

Repeat BMD Tests Don't Aid Prediction

Repeat bone mineral density testing 8 vears after initial measurement does not improve the ability to predict fractures

Takeda

AMITIZA¹⁷ BRIEF SUMMARY OF PRESCRIBING INFORMATION Please see package insert for complete prescr 720-03565 AMITIZA™ (lubiprostono, Soft Gelatin Car INDICATIONS AND USAGE for the treatment of chronic in the adult population. idiopathic constipation in the auth population. **CONTRAINDEATIONS** AMITIZATM is contraindicated in those patients with a known hypersensitivity to the drug or any of its excipients, and in patients with a history of mechanical gastrointestinal obstruction. WARNINGS Patients with symptoms suggestive of mechanical gastrointestinal obstruction should be evaluated prior to initiating AMITIZA™ treatment. prior to initiating AMITIZA[™] treatment. 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 Teratogenic Effects: Pregnancy Category C).

PRECAUTIONS Patient Information:

Patient Information: AMITIZA^W may cause nausea. If this occurs, concomitant administration of food with AMITIZA^W may reduce symp-toms of nausea. AMITIZA^W should not be administered to patients that have severe diarrhea. Patients should be avare of the possible occurrence of diarrhea during treatment. If the directed become new more than the interview. the diarrhea becomes severe consult your physician.

the diamhea becomes severe curisuit your physician. **Drug Interactions:** Based upon the results of *in vitro* human microsome studies, there is low likelihood of drug-drug interac-tions. *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 reductases to the studies indicate microsomal carbonyl reductases for the studies indicate microsomal carbonyl reductases to the studies indicate microsomal to the studies by the studies to the studies by in vitro studies indicate microsomal carbony reductable may be involved in the extensive biotransformation of lubiprostone to M3. Additionally, in vitro studies in human liver microsomes demonstrate that lubiproshuman liver microsomes demonstrate that lubipros-tone does not inhibit cytochrome P450 isoforms 3A4, 2D6, 1A2, 2A6, 2B6, 2C9, 2C19, or 2E1, and *in vitrc* studies in primary cultures of human hepatocytes show no induction of the cytochrome P450 isoforms 1A2, 2B6, 2C9, and 3A4. 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two 2-year oral (gavage) carcinogenicity studies (one in Crt:B6C3F1 mice and one in Sprague-Davley rats) were conducted with lubiprostone. In the 2-year carcinogenicity Crt.86C3F1 mice and one in Sprague-Dawley rats) were conducted with lubiprostone. In the 2-year carcinogenicity study in mice, lubiprostone doess of 25, 75, 200, and 500 mcg/kg/day (approximately 2, 6, 17, and 42 times the recommended human dose, respectively, based on doot mcg/kg/day (approximately 3, 17, and 68 times the recommended human dose, respectively, based on body surface area) were used. In the 2-year rat car-cinogenicity study, lubiprostone doses of 20, 100, and 400 mcg/kg/day (approximately 3, 17, and 68 times the recommended human dose, respectively, based on body surface area) were used. In the mouse carcinogenicity study, there was no significant increase in any tumor incidence of interstitial cell adenoma of the testes in male rats at the 400 mcg/kg/day dose. In female rats, treatment with lubiprostone produced hepatocellular adenoma at the 400 mcg/kg/day dose. Lubiprostone was not genotoxic in the *in vitro* Ames

auenomia at time 400 mcg/kg/d3y 0059. Lubiprostone was not genotoxic in the *in vitro* Ames reverse mutation assay, the *in vitro* mouse lymphoma (L5178Y TK+/–) forward mutation assay, the *in vitro* Chinese hamster lung (CHL/IU) chromosomal aberra-tion assay, and the *in vivo* mouse bone marrow micronucleus assay.

Lubiprostone, at oral doses of up to 1000 mcg/kg/day, had no effect on the fertility and reproductive function of male and female rats. The 1000 mcg/kg/day dose in rats is approximately 166 times the recommended human dose of 48 mcg/day, based on the body surface area. Teratogenic Effects: Pregnancy Category C: 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 and rabbits. In guinea pigs, lubiprostone caused fetal loss at repeated doses of 10 and 25 mcg/kg/day (approximately 2 and 6 times the human dose, respec-tively, based on body surface area) administered on days 40 to 53 of gestation. days 40 to 53 of gestation

uays 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 BID, four women became pregnant Per protocol, AMITIZA[™] was discontinued upon preg-nancy 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

AMITIZA^{III} 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.

nazaro to the retus. 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 seriou adverse reactions in nursing infants from lubiproston 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.

Pediatric Use: AMITIZA™ has not been studied in pediatric patients.

ADVERSE REACTIONS In clinical trials, 14/29 patients received AMITIZA[™] 24 mcg BID or placebo. Table 1 presents data for the adverse experiences that were reported in at least 1% of patients who received AMITIZA[™] and that occurred more fre-quently on study drug than placebo. It should be noted that the placebo data presented are from short-term exposure (s4 weeks) whereas the AMITIZA[™] data are cumulative data that were collected over 3- or 4-week, 6-month, and 12-month observational periods and that some conditions are common among ntherwise healthur ADVERSE REACTIONS onth, and 12-month observational periods and that e conditions are common among otherwise health ints over a 6- and 12-month observational period. some co

 Table 1: Adverse Events Reported for Patients Treated with AMITIZA¹¹²

 System/Adverse Experience
 a - 316
 24 mcg 100
 24 mcg 100
 AMITIZA¹¹²

 System/Adverse Experience
 a - 316
 24 mcg 100
 a - 317
 24 mcg 100
 a - 317

	78	n = 29 %	n = 1113 %	n=11/5 %
Gastrointestinal disorders		10	70	10
lausea	5.1	17.2	31.1	30.9
Diarrhea	0.9	10.3	13.2	13.2
Abdominal distension	2.2	0.0	7.1	6.8
Abdominal pain	2.8	3.4	6.7	6.8
latulence	1.9	3.4	6.1	5.9
omiting	0.9	0.0	4.6	4.4
oose stools	0.0	0.0	3.4	3.2
Vspepsia	1.3	0.0	2.9	2.7
bdominal pain upper	1.9	0.0	2.2	2.1
bdominal pain lower	0.6	0.0	1.9	1.8
astroesophageal reflux disease	0.6	0.0	1.8	1.7
bdominal discomfort	0.0	3.4	1.5	1.5
Iry mouth	0.3	0.0	1.5	1.4
Constipation	0.9	0.0	1.1	1.0
tomach discomfort	0.9	0.0	1.1	1.0
nfections and infestations	0.3	0.0	L.I	1.0
inusitis	1.6	0.0	4.9	4.8
Irinary tract infections	1.9	3.4	4.9	4.3
innary tract infections	0.9	0.0	4.4	4.3
Ipper respiratory tract intection lasopharyngitis	2.2	0.0	2.9	2.7
asopharyngitis ifluenza	0.6	0.0	2.9	1.9
Ironchitis	0.6	3.4	2.0	1.9
astroenteritis viral	0.3	3.4	1.0	1.0
iral infection	0.0	3.4	0.5	0.6
lervous system disorders	0.3	0.4	0.5	0.0
eadache	6.6	3.4	13.2	13.0
izziness	1.3	3.4	4.1	4.0
ypoesthesia	0.0	3.4	4.1	4.0
eneral disorders and site a	0.0	0.4	0.5	0.0
dema peripheral	0.3	0.0	3.8	3.6
atique	1.9	6.9	2.3	2.5
hest discomfort	0.0	3.4	1.6	1.6
hest pain	0.0	0.0	1.1	1.0
yrexia	0.3	0.0	1.1	1.0
lusculoskeletal and connect		e disorders		
rthralgia	0.3	0.0	3.1	3.0
Back pain	0.9	3.4	2.3	2.3
ain in extremity	0.0	3.4	1.9	1.9
luscle cramp	0.0	0.0	1.0	0.9
lespiratory, thoracic, and m				
yspnea	0.0	3.4	2.4	2.5
haryngolaryngeal pain	2.2	0.0	1.7	1.6
ough	0.6	0.0	1.6	1.5
ivestigations				
/eight increased	0.0	0.0	1.0	0.9
sychiatric disorders	0.0	0.0		
epression	0.0	0.0	1.4 1.4	1.4 1.4
nxiety				
nsomnia lascular disorders	0.6	0.0	1.4	1.4
	0.0	0.0	1.0	0.9
lypertension			1.0), and 24 mc	

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AMITIZA[™]-induced Diarthea: AMITIZA[™]-induced Diarthea: Among constipated patients, 13.2% of those receiving AMITIZA[™] 24 mog BID reported diarthea. of those patients, 3.4% reported severe diarthea and 2.2% discontinued treat-ment due to diarthea. The incidence of diarthea did not appear to be dose-dependent. No serious adverse events were reported for electrolyte imbalance in the six clinical trials and no clinically significant changes were seen in serum electrolyte levels while patients were receiving AMITIZA[™].

Other Adverse Events: The following list of adverse events include those that The following list of adverse events include those that were considered by the investigator to be possibly relater. to AMITIZA[™] than placebo and those that lead to dis-continuation more frequently (20.2%) on AMITIZA[™] than placebo. Although the events reported occurred during treatment with AMITIZA[™], they were not necessarily attributed to dosing of AMITIZA[™]. Gastrointestinal disorders: watery stools, fecal incontinence, abnormal bowel sounds, frequent bowel movements, reclain and sources of the source to bowel movements. reclain a source of the source the source of the source to bowel movements. reclain the source the sour

Nervous system disorders: syncope, tremor

- dysgeusia, paraesthesia

 General disorders and administration site
- General disorders and administration site conditions: rigors, pain, asthenia, malaise, edema Respiratory, thoracic, and mediastinal disorders asthma, painful respiration, throat tiphtness Skin and subcutaneous tissue disorders: hyperhidrosis, urticaria, rash Psychiatric disorders: nervousness
- Vascular disorders: flushing, palpitations
 Metabolism and nutrition disorders: decreased

• Ear and labyrinth disorders: vertigo

INPERCENTION OF A DEPARTMENT OF A DEPARTMEN hase 1 cardiac repolarization study, 51 patients adminis-red a single oral dose of 144 mcg of AMITIZA[™], which is times the normal single administration dose. Thirty-nine

OSAGE AND ADMINISTRATION The recommended dosage for AMITLATM is 24 mcg taken vice daily (BID) orally with food. Physicians and patients hould periodically assess the need for continued therapy. ARKETED BY

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in healthy elderly women, according to Dr. Teresa A. Hillier and her associates.

The Study of Osteoporotic Fractures included 9,704 white women aged 65 years and older who were living in four regions of the United States. Of the women, 4,124 underwent initial BMD measurement in 1989-1990 and then had a repeat BMD measurement a mean of 8 years later, forming the sample for the current study, said Dr. Hillier of Kaiser Permanente Center for Health Research Northwest. Portland, Ore., and her associates (Arch. Intern. Med. 2007;167:155-60).

They were followed for an additional 5 years to track the incidence of fractures. The BMD measurements were taken at the proximal femur, femoral neck, trochanter, intertrochanter, and Ward's triangle.

Both measurements of BMD were significant predictors of hip fracture and nonspinal fracture risks. However, the repeat BMD did not add to the overall predictive value for any type of fracture risk. These results persisted in subgroup analyses of women who used estrogen or bisphosphonate, compared with those who did not.

The findings do not imply that repeat BMD measurement may not be useful for certain individual patients, "particularly if intervening clinical factors are present that would likely accelerate BMD loss greater than average," they asserted. They also noted that the results may not be generalizable to men, nonwhite women, or women younger than 65 years.

Glycemic Control in Young Diabetics

Poorer glycemic control was independently associated with higher serum lipid levels in children with both type 1 and type 2 diabetes in a large, cross-sectional study.

Higher hemoglobin A_{1c} levels (HbA_{1c}) were associated with significantly higher total cholesterol, LDL cholesterol, and triglycerides in a study of 1,963 children aged 10 years and older. The findings were significant even after adjustment for age, gender, diabetes duration, body mass index, and race / ethnicity. Glycemic control did not correlate with HDL cholesterol levels (Arch. Pediatr. Adolesc. Med. 2007;161:159-65).

The data were extracted from the SEARCH for Diabetes in Youth Study, a comprehensive, ethnically diverse study of children with diabetes managed in a variety of settings (J. Pediatr. 2006;149:314-9).

Mean HbA_{1c} concentration was 8.6% in the 1,680 children with type 1 diabetes and 8.3% in the 283 with type 2 diabetes. In those with type 1 diabetes and poor glycemic control, 35% had high concentrations of total cholesterol (200 mg/dL or greater), 27% had high LDL cholesterol (130 mg/dL or greater), and 12% had high triglycerides (200 mg/dL or greater). In type 2 diabetes patients with poor glycemic control, 65% had high total cholesterol levels, 43% had high LDL cholesterol, and 40% had high triglycerides.

For each unit increase in HbA_{1c}, the slope of the increase in total cholesterol was 7.8 mg/dL in the type 1 group and 8.1 mg/dL in the type 2 group.

The authors were not able to establish a cause-and-effect relationship between poor glycemic control and elevated serum lipids because of the cross-sectional design of the study.