

the geometry and complexity of the adult brain. Cannabinoids seem to have profound and permanent effects on brain organization, connectivity, and geography when exposure occurs during critical periods in utero, early childhood, or adolescence (Science 2007;316:1212-6).

Pharmacologic interference with endocannabinoid signals during fetal development leads to long-lasting modifications of synaptic structure and function. In fact, endocannabinoids are critical in shaping the development of the central nervous system. Marijuana abuse during pregnancy can impair social behaviors, cognition, and motor functions in the offspring, with

the impact lasting into adulthood. Similar effects can occur when cannabinoid use occurs during puberty and peak periods of brain growth and development.

Nonmedical drug use, including smoking marijuana, can cause long-term, if not permanent, changes in the brain. Marijuana smoking may make mental illness and drug dependence itself more likely.

The take-home message is that marijuana is a potent drug that can cause serious depression and elevated mental health risk profiles. In other words, drug abuse prevention also is mental illness prevention. As such, reducing adolescent use of marijuana and other drugs must

be a priority for mental health treatment.

The common comorbidity of mental illness and substance abuse underscores the importance of universal screening of patients with serious mental disorders for substance use. When drug use is detected in this high-risk population, substance abuse treatment and ongoing monitoring for drug use should be a routine part of mental health care. ■

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## Varenicline May Help Curb Heavy Drinking

BY KERRI WACHTER  
Senior Writer

WASHINGTON — The antismoking drug varenicline also appears to curb alcohol cravings in smokers who are heavy drinkers, results of a small study show.

Nondependent heavy drinkers taking varenicline (Chantix) were nine times more likely to be abstinent during the 2-hour period of free access to alcoholic drinks than were those in the placebo group, based on logistic regression analysis, Sherry A. McKee, Ph.D., reported at a joint meeting sponsored by the Research Society on Alcoholism and the International Society for Biomedical Research on Alcoholism.

Participants were male and female non-treatment seeking, nondependent heavy drinkers who also were daily smokers, said Dr. McKee of Yale University, New Haven, Conn.

Subjects were titrated to steady-state levels of varenicline (2 mg/day) or placebo over the course of a week. On day 8, all participants were given free access to cigarettes and were administered a priming drink, which was designed to raise blood alcohol levels to 0.03 g/dL.

Subjective and psychological responses to alcohol were then assessed. A 2-hour period of self-administration followed, during which time participants could choose to consume up to eight additional drinks (designed to raise blood alcohol levels by 0.015 g/dL) or to receive monetary reinforcement for drinks not consumed.

Participants had to have smoked at least 10 cigarettes/day for the last year. Men had to consume more than 14 drinks/week or 5 or more drinks on one occasion; women had to consume more than 7 drinks/week or 4 or more drinks on one occasion. Urine testing was used to assess varenicline compliance on days 4-8.

A total of 20 participants were enrolled—10 in each arm. The groups were matched in terms of age, gender, number of cigarettes per day, weekly frequency of drinking, and number of drinks per episode.

During the period of unrestricted access to alcohol, varenicline “significantly reduced drinking by about two drinks,” Dr. McKee said. Two subjects in the varenicline group consumed drinks, compared with seven in the placebo group. After the priming drink, no difference was found in blood alcohol levels between the two groups. However, a significant difference was found in alcohol craving. Those on varenicline reported a sharp decrease in alcohol craving; those on placebo reported an increase.

The subjective effects of alcohol remained steady for those in the varenicline group but increased in the placebo group. The difference was statistically significant. There was no effect of varenicline on tobacco craving in this period.

Adverse events were few and included nausea, sleep disturbance, abnormal dreams, constipation, flatulence, and vomiting. Dr. McKee said that she had no conflicts of interest. ■

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

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

<sup>1</sup>Includes 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.

### 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.

### 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.

### Marketed by:

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