

# Findings 'Certainly Tilt the Scale'

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betes in four communities across the United States. During the first 6 years, 7,697 enrollees who were nondrinkers at baseline began moderate consumption of alcohol, defined in accord with the AHA and American Diabetes Association as not more than two drinks per day for men and one for women. An additional 0.4% of former nondrinkers began heavier drinking, said Dr. King.

During the next 4 years of follow-up, the combined rate of fatal and nonfatal car-

diovascular events was 6.9% among new moderate drinkers and 10.7% in the continued teetotalers. After adjustment for age, race, sex, diabetes, hypertension, hyperlipidemia, and physical activity, adoption of moderate alcohol intake remained an independent protective factor against cardiovascular events, with an associated 38% relative risk reduction.

All-cause mortality didn't differ significantly between the two groups, perhaps because of the limited number of fatali-

ties, but it trended in favor of the new moderate drinkers, who showed a 29% relative risk reduction.

The new heavy drinkers displayed a nonsignificant trend for more cardiovascular events than did continued nondrinkers over the 4-year period.

The reasons why former nondrinkers in ARIC began consuming alcohol in middle age weren't assessed as part of the study. "We would presume that it was for the health benefits, but we don't know," Dr. King said in an interview.

He added that he wouldn't anticipate a formal change in AHA policy on the basis of a single study. Yet these ARIC findings

"certainly tilt the scale" in favor of physician counselling on a case-by-case basis that patients consider making alcohol part of a heart-healthy diet, provided they don't use certain medications or have a strong family or personal history of problem drinking, liver disease, or selected other health problems.

"It's a small minority of the population that gets in trouble with drinking, and perhaps we should not restrict the benefit of this healthy lifestyle choice in people who don't have a problem with alcohol," he said.

Follow-up in ARIC will continue. That's important because some possible adverse consequences of new drinking—for example, a potential increase in certain types of cancer—might take longer than 4 years to become apparent.

The ARIC alcohol adoption findings were published simultaneously with Dr. King's presentation at the annual conference (Am. J. Med. 2008;121:201-6). ■

## Mortality Benefit Seen in Moderate Drinking Post MI

COLORADO SPRINGS — Moderate alcohol consumption following a first nonfatal acute MI appeared to protect against cardiovascular and all-cause mortality in the Physicians' Health Study.

This protective effect of moderate drinking was most robust in male physicians who had a nonanterior MI, Jennifer K. Pai, Sc.D., of the Harvard School of Public Health, Boston, reported at a conference sponsored by the American Heart Association. Previous studies have shown a link between moderate alcohol intake and lower risk of coronary heart disease in healthy individuals. But there have been few data on the impact of drinking after a first MI.

Dr. Pai and colleagues used data from the Physicians' Health Study, a National Institutes of Health-sponsored prospective cohort study involving more than 20,000 male physicians begun 26 years ago. Alcohol consumption data were available on 1,879 physicians immediately before they experienced a first nonfatal acute MI sometime after 1986. The drinking data were updated every 4 years afterward through 2004, at which point there were 317 deaths.

Physicians were classified into four groups on the basis of their pattern of alcohol use: an average of 0.1-9.9 g of alcohol a day, 10.0-29.9 g/day, 30 g or more/day, and nondrinkers. An alcoholic beverage typically contains 7-12 g of alcohol.

After multivariate adjustment for demographic and cardiovascular risk factors, and information on MI severity and treatment, the relative risk of all-cause mortality in physicians who drank up to 9.9 g of alcohol/day after their MI was reduced by 34%, compared with nondrinkers. In those who averaged 10.0-29.9 g/day, the relative risk reduction was 40%. For heavier drinkers, the all-cause-mortality risk reduction was 30%. For cardiovascular mortality, the adjusted relative risk reductions were 34%, 48%, and 31%, respectively, for the lightest to heaviest drinkers versus nondrinkers.

—Bruce Jancin

### AMRIX™

(Cyclobenzaprine Hydrochloride Extended-Release Capsules)

Rx Only

**BRIEF SUMMARY** of Prescribing Information. The following is a brief summary only. Please see full Prescribing Information for complete product information.

#### DESCRIPTION

AMRIX™ (Cyclobenzaprine Hydrochloride Extended-Release Capsules) is a skeletal muscle relaxant which relieves muscle spasm of local origin without interfering with muscle function. The active ingredient in AMRIX™ extended-release capsules is cyclobenzaprine hydrochloride, USP.

AMRIX extended-release capsules for oral administration are supplied in 15 and 30 mg strengths.

#### INDICATIONS AND USAGE

AMRIX is indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions. Improvement is manifested by relief of muscle spasm and its associated signs and symptoms, namely, pain, tenderness, and limitation of motion.

AMRIX should be used only for short periods (up to two or three weeks) because adequate evidence of effectiveness for more prolonged use is not available and because muscle spasm associated with acute, painful musculoskeletal conditions is generally of short duration and specific therapy for longer periods is seldom warranted.

AMRIX has not been found effective in the treatment of spasticity associated with cerebral or spinal cord disease or in children with cerebral palsy.

#### CONTRAINDICATIONS

- Hypersensitivity to any component of this product.
- Concomitant use of monoamine oxidase (MAO) inhibitors or within 14 days after their discontinuation.
- Hyperpyretic crisis seizures and deaths have occurred in patients receiving cyclobenzaprine (or structurally similar tricyclic antidepressants) concomitantly with MAO inhibitor drugs.
- During the acute recovery phase of myocardial infarction, and in patients with arrhythmias, heart block conduction disturbances, or congestive heart failure.
- Hyperthyroidism.

#### WARNINGS

AMRIX is closely related to the tricyclic antidepressants, e.g., amitriptyline and imipramine. In short term studies for indications other than muscle spasm associated with acute musculoskeletal conditions, and usually at doses somewhat greater than those recommended for skeletal muscle spasm, some of the more serious central nervous system reactions noted with the tricyclic antidepressants have occurred (see **WARNINGS**, below, and **ADVERSE REACTIONS** section of full Prescribing Information).

Tricyclic antidepressants have been reported to produce arrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke. AMRIX may enhance the effects of alcohol, barbiturates, and other CNS depressants.

As a result of a two-fold higher cyclobenzaprine plasma levels in subjects with mild hepatic impairment, as compared to healthy subjects, following administration of immediate-release cyclobenzaprine and because there is limited dosing flexibility with AMRIX, use of AMRIX is not recommended in subjects with mild, moderate or severe hepatic impairment.

As a result of a 40% increase in cyclobenzaprine plasma levels and a 56% increase in plasma half-life following administration of AMRIX in elderly subjects as compared to young adults, use of AMRIX is not recommended in elderly.

#### PRECAUTIONS

##### General

Because of its atropine-like action, AMRIX should be used with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure, and in patients taking anticholinergic medication.

##### Information for Patients

AMRIX, especially when used with alcohol or other CNS depressants, may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

##### Drug Interactions

AMRIX may have life-threatening interactions with MAO inhibitors. (See **CONTRAINDICATIONS**.) AMRIX may enhance the effects of alcohol, barbiturates, and other CNS depressants. Tricyclic antidepressants may block the antihypertensive action of guanethidine and similarly acting compounds. Tricyclic antidepressants may enhance the seizure risk in patients taking tramadol (ULTRAM® [tramadol HCl tablets, Ortho-McNeil Pharmaceutical] or ULTRACET® [tramadol HCl and acetaminophen tablets, Ortho-McNeil Pharmaceutical]).

##### Carcinogenesis, Mutagenesis, Impairment of Fertility

In rats treated with cyclobenzaprine for up to 67 weeks at doses of approximately 5 to 40 times the maximum recommended human dose, pale, sometimes enlarged, livers were noted and there was a dose-related hepatocyte vacuolation with lipidosis. Cyclobenzaprine did not affect the onset, incidence, or distribution of neoplasia in an 81-week study in the mouse or in a 105-week study in the rat. At oral doses of up to 10 times the human dose, cyclobenzaprine did not adversely affect the reproductive performance or fertility of male or female rats.

A battery of mutagenicity tests using bacterial and mammalian systems for point mutations and cytogenic effects have provided no evidence for a mutagenic potential for cyclobenzaprine.

##### Pregnancy

**Pregnancy Category B:** Reproduction studies have been performed in rats, mice, and rabbits at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cyclobenzaprine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

##### Nursing Mothers

It is not known whether this drug is excreted in human milk. Because cyclobenzaprine is closely related to the tricyclic antidepressants, some of which are known to be excreted in human milk, caution should be exercised when AMRIX is administered to a nursing woman.

##### Pediatric Use

Safety and effectiveness of AMRIX has not been studied in pediatric patients.

##### Use in the Elderly

The plasma concentration and half-life of cyclobenzaprine are substantially increased in the elderly when compared to the general patient population (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, Elderly** in full Prescribing Information). Accordingly, AMRIX should not be used in the elderly.

#### ADVERSE REACTIONS

The most common adverse reactions in the two 14-day clinical efficacy trials are presented in Table 1.

Table 1: Incidence of the most common adverse reactions occurring in ≥3% of subjects in any treatment group in the two Phase 3, double-blind AMRIX trials			
	AMRIX 15 mg N = 127	AMRIX 30 mg N = 126	Placebo N = 128
Dry mouth	6%	14%	2%
Dizziness	3%	6%	2%
Fatigue	3%	3%	2%
Constipation	1%	3%	0%
Somnolence	1%	2%	0%
Nausea	3%	3%	1%
Dyspepsia	0%	4%	1%

In a postmarketing surveillance program (7607 patients treated with cyclobenzaprine 10 mg TID), the adverse reactions reported most frequently were drowsiness, dry mouth, and dizziness.

Among the less frequent adverse reactions, there was no appreciable difference in incidence in controlled clinical studies or in the surveillance program. Adverse reactions which were reported in 1% to 3% of the patients were: fatigue/tiredness, asthenia, nausea, constipation, dyspepsia, unpleasant taste, blurred vision, headache, nervousness, and confusion. The following adverse reactions have been reported in post-marketing experience or with an incidence of less than 1% of patients in clinical trials with the 10 mg TID tablet:

**Body as a Whole:** Syncope; malaise.

**Cardiovascular:** Tachycardia; arrhythmia; vasodilatation; palpitation; hypotension.

**Digestive:** Vomiting; anorexia; diarrhea; gastrointestinal pain; gastritis; thirst; flatulence; edema of the tongue; abnormal liver function and rare reports of hepatitis, jaundice, and cholestasis.

**Hypersensitivity:** Anaphylaxis; angioedema; pruritus; facial edema; urticaria; rash.

**Musculoskeletal:** Local weakness.

**Nervous System and Psychiatric:** Seizures; ataxia; vertigo; dysarthria; tremors; hypertonia; convulsions; muscle twitching; disorientation; insomnia; depressed mood; abnormal sensations; anxiety; agitation; psychosis, abnormal thinking and dreaming; hallucinations; excitement; paresthesia; diplopia.

**Skin:** Sweating.

**Special Senses:** Ageusia; tinnitus.

**Urogenital:** Urinary frequency and/or retention.

#### DRUG ABUSE AND DEPENDENCE

Pharmacologic similarities among the tricyclic drugs require that certain withdrawal symptoms be considered when AMRIX (Cyclobenzaprine Hydrochloride Extended-Release Capsules) is administered, even though they have not been reported to occur with this drug. Abrupt cessation of treatment after prolonged administration rarely may produce nausea, headache, and malaise. These are not indicative of addiction.

#### OVERDOSAGE

Although rare, deaths may occur from overdosage with AMRIX. Multiple drug ingestion (including alcohol) is common in deliberate cyclobenzaprine overdose. **As management of overdose is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment.** Signs and symptoms of toxicity may develop rapidly after cyclobenzaprine overdose; therefore, hospital monitoring is required as soon as possible.

All patients suspected of an overdose with AMRIX should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage and emesis is contraindicated.

The principles of management of child and adult overdosage are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

#### DOSAGE AND ADMINISTRATION

The recommended adult dose for most patients is one (1) AMRIX 15 mg capsule taken once daily. Some patients may require up to 30 mg/day, given as one (1) AMRIX 30 mg capsule taken once daily or as two (2) AMRIX 15 mg capsules taken once daily.

It is recommended that doses be taken at approximately the same time each day.

Use of AMRIX for periods longer than two or three weeks is not recommended (see **INDICATIONS AND USAGE**).

**Dosage Considerations for Special Patient Populations:** AMRIX should not be used in the elderly or in patients with impaired hepatic function (see **WARNINGS**).

#### HOW SUPPLIED

AMRIX extended-release capsules are available in 15 and 30 mg strengths, packaged in bottles of 60 capsules.

**KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN. IN CASE OF ACCIDENTAL OVERDOSE, SEEK PROFESSIONAL ASSISTANCE OR CONTACT A POISON CONTROL CENTER IMMEDIATELY.**

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