

# Imaging Sheds Light on Lasting Effects of TBI

BY MICHELE SULLIVAN

BANGKOK, THAILAND — New imaging techniques may help to explain the disabling symptoms that can plague patients with traumatic brain injury long after their acute problems have resolved, and eventually guide the best choice for medical therapy.

Survivors of traumatic brain injury who complain of depression, irritability,

and memory or cognitive problems may be written off as psychiatric cases or malingerers, Dr. Ramon Diaz-Arrastia said at the World Congress of Neurology. “This is the frustrating thing about TBI. The patients might look OK—they don’t have paralysis, they are walking around. But their cognitive and behavioral problems are real.”

Imaging techniques that are now well established in other areas of neurology—

such as diffusion-weighted and susceptibility-weighted MRI—are now being used to show that brain injuries leave permanent, life-altering marks behind after the contusions and hematomas have healed.

These findings may have both immediate and long-range benefits, said Dr. Diaz-Arrastia, a professor of neurology at the University of Texas Southwestern Medical Center, Dallas. “Right now, imaging these patients has the primary value

of providing a prognosis and perhaps helping them obtain the care that they need. In terms of reimbursement, it’s useful to have an objective documentation of the injury when trying to convince insurers to cover rehabilitative service.”

In the future, imaging the post-TBI brain may help guide medical treatment choices and monitor drugs’ effectiveness. So far, nearly 30 drugs have provided effective neuroprotection in animal models of TBI, he said. However, no drug that has undergone testing in well-designed phase III trials has proven beneficial to humans.

Part of the problem may be the heterogeneity of human brain injury, Dr. Diaz-Arrastia said. There are many subtypes of TBI, yet “from the point of view of the clinical trials, all patients who present in a coma [after a brain injury] are treated the same way, even though the injuries can be very different, with very different prognoses.”



**TBI patients ‘might look OK ... but their cognitive and behavioral problems are real.’**

DR. DIAZ-ARRASTIA

Susceptibility-weighted imaging (SWI) is one technique being studied in TBI patients. It measures the paramagnetic shift of intravascular deoxyhemoglobin and methemoglobin, amplifying the appearance of microhemorrhages and making them much easier to identify. “SWI picks up 640% more lesions and 200% more lesion volume than does gradient-recall echo,” Dr. Diaz-Arrastia said, referring to work by Dr. Karen Tong from Loma Linda (Calif.) University.

SWI is very good at identifying diffuse microvascular injury, a marker for diffuse axonal injury that is usually invisible on computed axial tomography. “The only problem is that SWI may be overly sensitive,” he said. “One patient with a lot of microhemorrhages might be complaining only of headache and dizziness, whereas another with a similar volume might have a lot more problems.”

Diffusion-weighted imaging (DWI), which is well established in the stroke world, is understudied in TBI, probably because it’s a challenge to perform MRI on these acutely ill patients. But this technique provides detailed information about the makeup of lesions, showing vasogenic and cytotoxic edema, as well as location in the superficial or deep structures in both gray and white matter.

Dr. Diaz-Arrastia and his colleagues performed DWI on 99 patients with TBI. Of these, the study identified corpus callosum lesions in 84%. It was able to differentiate between patients with primarily cytotoxic lesions (54%) and those with vasogenic lesions (46%). “We also found that the volume of these brain le-

Continued on following page

## 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 lipodosis. 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, Special Populations, 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.

### DOSE 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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Continued from previous page

sions, irrespective of location, explained about 28% of the variance in outcome among these patients," he said. "It's a relatively modest correlation with outcome, but it shows that what we are measuring is something that is functionally important and affects outcome."

Diffusion tensor imaging shows how water tracks along the axons, giving a good view of white matter lesions. Follow-up scans on TBI patients have shown tantalizing clues to the possible causes of their long-term problems.

"When we scan patients within a day or two of injury, we may see subtle changes in the parameters. But if we come back 6 months later and rescan, we see much greater dropout of axons. Initially, the patient may be in a coma, and when they are scanned later they are usually much improved and walking around, albeit with problems with memory or executive function. So this tells us that something is happening weeks or months after the injury that results in white matter dropout," he said.

Quantitative volumetric assessment of the cortical field measures the thickness

and volume of different regions, Dr. Diaz-Arrastia said. "In our patients, we have found that the brain shrinks overall after a severe traumatic injury, but that not all structures shrink at the same rate. Some cortical regions shrink very little, while others, like the hippocampus, appear particularly sensitive to injury." This makes sense given the cognitive and mood issues that TBI patients can experience.

On average, whole brain volume and both gray and white matter volumes decreased by 3%-10% in the first few months after severe TBI. In comparison, Dr. Diaz-Arrastia said, the rate of atro-

phy for patients with Alzheimer's disease is about 1%-2% a year.

Functional MRIs also provide some clues that the injured brain sustains long-term problems. The blood oxygen level dependent signal typically shows seemingly random fluctuations when the brain is at rest. But recent studies have shown that these fluctuations actually represent the communication between brain regions that work together. "In our patients, we found a very high indication that the functional connectivity between the hippocampi was greatly reduced," compared with controls, he said. ■

## Daily Headache Develops in 20% After Blasts

PHILADELPHIA — About 20% of soldiers returning from Iraq or Afghanistan develop chronic daily headache after blast exposure or concussion, according to a preliminary study.

Dr. Brett Theeler and his colleagues found that newly returned soldiers who were exposed to blast explosions within 60 feet and those who suffered concussion injuries with or without loss of consciousness were likely to develop headache within 1 week of their experience. Chronic daily headache (CDH) was defined as headaches occurring at least 15 days per month.

In the cohort of 5,270 soldiers who completed a 13-question headache survey, 957 screened positive for any of the risk factors: 196 were classified as having CDH and 761 did not. The mean headache frequency was 23 days per month for the CDH group and 5 days per month for the non-CDH group. Headaches were migraine type in 66% of soldiers with CDH and 48% of soldiers without CDH. Most of those with CDH (55%) developed headaches within 1 week of having had a concussion, compared with 33% of those without CDH, Dr. Theeler reported at the International Headache Congress.

Soldiers with CDH were also exposed to more blasts on average than those without CDH (six vs. five, respectively). Although the average difference in blast exposure was small, there was a very wide range of exposures among those with CDH, "leading us to consider that there may be a dose-response relationship between blast exposure and headache," said Dr. Theeler, a neurologist and U.S. Army captain at William Beaumont Army Medical Center, El Paso, Tex.

More than twice as many soldiers with CDH also screened positive for post-traumatic stress disorder (40% vs. 17%).

Dr. Theeler said his data were preliminary. However, he published a recent article suggesting that a history of mild head trauma consistent with blast exposure was present in 50% of soldiers who screened positive for headache (Headache 2009;49:529-34).

The International Headache Society and the American Headache Society sponsored the congress.

—Michele G. Sullivan



**NEW INDICATION**

## MICARDIS 80 mg

**Now for Cardiovascular (CV) Risk Reduction<sup>1</sup>**

MICARDIS<sup>®</sup> (telmisartan) tablets are indicated for reduction of the risk of **myocardial infarction, stroke, or death from CV causes in patients 55 years of age or older** at high risk of developing major CV events who are **unable to take ACE inhibitors.**<sup>1</sup>

### IMPORTANT SAFETY INFORMATION

**WARNING: AVOID USE IN PREGNANCY**  
When used in pregnancy, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, MICARDIS<sup>®</sup> (telmisartan) tablets should be discontinued as soon as possible (See Warnings and Precautions).

Because studies with telmisartan did not exclude that it may not preserve a meaningful fraction of the effect of the ACE inhibitor to which it was compared, consider using the ACE inhibitor first.

Volume depletion and/or salt depletion should be corrected in patients before initiation of therapy or symptomatic hypotension may occur.

In patients with renal artery stenosis or severe renal impairment, care should be exercised with dosing of MICARDIS. In patients with severe heart failure, decline in renal function and, rarely, acute renal failure and/or death has been associated with inhibiting the renin-angiotensin system.

Use of MICARDIS with an ACE inhibitor is not recommended.

Please see Brief Summary of Prescribing Information, including full indication, on adjacent page.

Reference: 1. Micardis PI. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2009.

**MICARDIS**  
(telmisartan) tablets **80 mg**



**For additional information, please ask your local sales representative.**