# MDs Call for More Funding for Disaster Planning

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New York Bureau

ublic health systems need more federal funding in order to respond to both day-to-day emergencies and also mass-casualty events, according to disaster preparedness recommendations that were released by a coalition of 18 major health organizations.

The coalition, which was led by the American Medical Association (AMA) and the American Public Health Association, issued a report with 53 recommendations that were aimed at leaders in medicine and government.

Some of the other coalition members

No one can predict the time, place, or magnitude of terrorist attacks. But there is no excuse for failing to plan responses to these mass casualty events.

added.

included the American Academy of Pediatrics, the American College of Emergency Physicians, and also the American College of Surgeons.

The project was funded under a cooperative agreement from the Cen-

ters for Disease Control and Prevention. "The only thing we can probably predict with any certainty about terrorism attacks and other mass casualty events is this—we're not going to know the time, location, and magnitude in advance," Dr. Ronald M. Davis, president of the AMA, said at a press conference to release the report. "But we have no excuse if our responses aren't known in advance," he

The report identifies nine critical areas that require immediate action, including: ► Increased federal funding should be allocated for the purpose of expanding emergency medical, trauma care, and disaster health preparedness systems across the country.

► Governmental entities and health systems must develop and evaluate processes to ensure a return to readiness for routine health care and future mass casualty events following a disaster.

# INDEX OF ADVERTISERS

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- ► Funding for economic recovery after a disaster needs to emphasize the reestablishment of public health and health care
- ► The Institute of Medicine should perform a comprehensive study of health system surge capacity.
- ► Emergency and disaster preparedness must be integrated with public health and health care systems nationwide to provide effective emergency and trauma
- ▶ Public health and health care officials must participate directly in disaster preparedness planning, mitigation, response, and recovery operations.
- ▶ Health disaster communications and health information exchange networks must be fully integrated and interoperable at every level of government and health
- The government, health systems, and all professional organizations should work together to develop and distribute infor-

mation on the management of adult and pediatric patients in both day-to-day emergency situations as well as catastrophic

▶ Public health and health care responders must each be awarded adequate legal protections for providing care during

The full text of the report is available online at www.ama-assn.org/go/ disasterpreparedness.



### Brief Summary of Prescribing Information.

For complete details, please see full Prescribing Information for Namenda. INDICATIONS AND USAGE

Namenda (memantine hydrochloride) is indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

CONTRAINDICATIONS
Namenda (memantine hydrochloride) is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation.

PRECAUTIONS
Information for Patients and Caregivers: Caregivers should be instructed in the recommended administration (twice per day for doses above 5 mg) and dose escalation (minimum interval of one week between dose increases).

dose escalation (minimum interval of one of the control of the con

# of patients related with Marienta and 0.5 % of patients related with placebo. Genitourinary Conditions Conditions that raise urine pH may decrease the urinary elimination of memantine resulting in increased plasma levels of memantine.

## Special Populations Hepatic Impairment

Hepatic Impairment
Mamenda undergoes partial hepatic metabolism, with about 48% of
administered dose excreted in urine as unchanged drug or as the sum of
parent drug and the H-glucuronide conjugate (74%). No dosage adjustment
is needed in patients with mild or moderate hepatic impairment. Namenda
should be administered with caution to patients with severe hepatic
impairment.

Henal impairment
No dosage adjustment is needed in patients with mild or moderate renal
impairment. A dosage reduction is recommended in patients with severe
renal impairment (see CLINICAL PHARMACOLOGY and DOSAGE AND
ADMINISTRATION in Full Prescribing Information).

Drug-Drug Interactions
N-methyl-0-aspartate (NMDA) antagonists: The combined use of Namenda with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) has not been systematically evaluated and such use should be approached with caution

snoun oe approached with caution. Effects of Namenda on substrates of microsomal enzymes: In vitro studies conducted with marker substrates of CYP450 enzymes (CYP1A2, -2A6, -2C9, -2D6, -2E1, -3A4) showed minimal inhibition of these enzymes by memantine. In addition, in vitro studies indicate that at concentrations exceeding those associated with efficacy, memantine does not induce the cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2E1, and CYP3A4/5. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected.

are expected. Effects of inhibitors and/or substrates of microsomal enzymes on Namenda: Memantine is predominantly renally eliminated, and drugs that are substrates and/or inhibitors of the CYP450 system are not expected to alter

Substrates and imministration in the OTT-Do System as the Composition of Namenda with the McAbe inhibitor donepezil HCl did not affect the pharmacokinetics of either compound. In a 24-week controlled clinical study in patients with moderate to severe Alzheimer's disease, the adverse event profile observed with a combination of memantine and donepezil was similar to that of

inated via renal mechanisms: Because memantine is eliminated in Drugs eminiated with elean mechanisms, because intendintine is entimated in a part by tubular secretion, coadministration of drugs that use the same renal cationic system, including hydrochlorothiazide (HCTZ), triamterene (TA), metformin, cimetidine, ranitidine, quinidine, and nicotine, could potentially retormin, cimetidine, rantidine, quinidine, and nicotine, could potentially result in altered plasma levels of both agents. However, coadministration of Namenda and HCTZTM did not affect the bioavailability of either memantine or TA, and the bioavailability of HCTZ decreased by 20%. In addition, coadministration of memantine with the anthyperglycemic drug Glucovance® (glyburide and metformin HCI) did not affect the pharmacokinetics of memantine, metformin and glyburide. Furthermore, memantine did not modify the serum glucose lowering effect of Glucovance®. Drugs that make the urine alkaline: The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by diet, drugs (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) and clinical state of the patient (e.g. renal tubular acidosis or severe infections of the urinary tract). Hence, memantine should be used with caution under these conditions.

Carcinogenesis, Mutagenesis and Impairment of Fertility
There was no evidence of carcinogenicity in a 113-week oral study in mice at doses up to 40 mg/kg/day (10 times the maximum recommended human dose [MRHD] on a mg/m² basis). There was also no evidence of control of the co

dose [MRHD] on a mg/m² basis). There was also no evidence or carcinogenicity in rats orally dosed at up to 40 mg/kg/day for 71 weeks followed by 20 mg/kg/day (20 and 10 times the MRHD on a mg/m² basis, respectively) through 128 weeks.

Memantine produced no evidence of genotoxic potential when evaluated in the in vitro S. typhimurium or E. coli reverse mutation assay, an in vitro chromosomal aberration test in human lymphocytes, an in vivo cytogenetics assay for chromosome damage in rats, and the in vivo mouse micronucleus assay. The results were equivocal in an in vitro gene mutation assay using Chinese hamster V79 cells. Chinese hamster V79 cells.

No impairment of fertility or reproductive performance was seen in rats administered up to 18 mg/kg/day (9 times the MRHD on a mg/m² basis) orally from 14 days prior to mating through gestation and lactation in females, or for 60 days prior to mating through gestation and lactation in

Slight maternal toxicity, decreased pup weights and an increased incidence of non-ossified cervical vertebrae were seen at an oral dose of 18 mg/kg/day in a study in which rats were given oral memantine beginning pre-mating and continuing through the postpartum period. Slight maternal toxicity and decreased pup weights were also seen at this dose in a study in which rats were treated from day 15 of gestation through the post-partum period. The no-effect dose for these effects was 6 mg/kg, which is 3 times the MRHD on a md/m² hasis

on a myrm basis. There are no adequate and well-controlled studies of memantine in pregnant women. Memantine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether memantine is excreted in human breast milk.

Because many drugs are excreted in human milk, caution should be exercised when memantine is administered to a nursing mother.

Pediatric Use
There are no adequate and well-controlled trials document and efficacy of memantine in any illness occurring in childre ADVERSE REACTIONS

ADVENSE REACTIONS

The experience described in this section derives from studies in patients with Alzheimer's disease and vascular dementia.

with Alzheimer's disease and vascular dementia.

Adverse Events Leading to Discontinuation: In placebo-controlled trials in which dementia patients received doses of Namenda up to 20 mg/day, the likelihood of discontinuation because of an adverse event was the same in the Namenda group as in the placebo group. No individual adverse event was associated with the discontinuation of treatment in 1% or more of Namenda-treated patients and at a rate greater than placebo.

Adverse Events Reported in Controlled Trials: The reported adverse events in Namenda (memantine hydrochloride) trials reflect experience gained under closely monitored conditions in a highly selected patient population. In actual practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use reporting behavior and the types of natients.

apply, as the conditions of use, reporting behavior and the types of patie apply, as the conditions of use, reporting behavior and the types of patients treated may differ. Table 1 lists treatment-emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled dementia trials and for which the rate of occurrence was greater for patients treated with Namenda than for those treated with placebo. No adverse event occurred at a frequency of at least 5% and twice the placebo rate.

Table 1: Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving Namenda and at a Higher Frequency than Placebo

	ivamenda
(N = 922)	(N = 940)
` %	%
1	2
1	3
2	4
	7
3	6
	5
2	3
2	3
5	6
	3
2	3
3	4
1	2
	1 1 1 2 5 3 3 2 2 2 5 5 2

Other adverse events occurring with an incidence of at least 2% in Other adverse events occurring with an incidence of at least 2% in Namenda-treated patients but at a greater or equal rate on placebo were agitation, fall, inflicted injury, urinary incontinence, diarrhea, bronchitis, insomnia, urinary tract infection, influenza-like symptoms, abnormal gait, depression, upper respiratory tract infection, anxiety, peripheral edema, nausea, anorexia, and arthralgia.

The overall profile of adverse events and the incidence rates for individual adverse events in the subpopulation of patients with moderate to severe Alzheimer's disease were not different from the profile and incidence rates described above for the overall dementia population.

described above for the overall dementia population.

Vital Sign Changes: Namenda and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, diastolic blood pressure, and weight) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. There were no clinically important changes in vital signs in patients treated with Namenda. A comparison of supine and standing vital sign measures for Namenda and placebo in elderly normal subjects indicated that Namenda treatment is not associated with orthostatic changes.

with orthostatic changes. L<mark>aboratory Changes:</mark> Namenda and placebo groups were compared with respect to (1) mean change from baseline in various serum hematology, and urinalysis variables and (2) the incidence or meeting criteria for potentially clinically significant changes from in these variables. These analyses revealed no clinically importar in laboratory test parameters associated with Namenda treatment.

ECG Changes: Namenda and placebo groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in ECG parameters associated with Namenda

treatment.

Other Adverse Events Observed During Clinical Trials

Namenda has been administered to approximately 1350 patients with dementia, of whom more than 1200 received the maximum recommended dose of 20 mg/day, Patients received Namenda treatment for periods of up to 884 days, with 862 patients receiving at least 24 weeks of treatment and 387 patients receiving 48 weeks or more of treatment. Treatment emergent signs and symptoms that occurred during 8 controlled clinical trials and 4 open-label trials were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized

categories using WHO terminology, and event frequencies were calculated across all studies.

All adverse events occurring in at least two patients are included, except for those already listed in Table 1, WHO terms too general to be informative, minor symptoms or events unlikely to be drug-caused, e.g., because they are common in the study population. Events are classified by body system and listed using the following definitions frequent definitions. are common in the study population. Events are classified by 000y System and listed using the following definitions: frequent adverse events - those occurring in at least 1/100 patients; infrequent adverse events - those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to Namenda treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies. Body as a Whole: Frequent: syncope. Infrequent: hypothermia, allergic

reaction.

Cardiovascular System: Frequent: cardiac failure. Infrequent: angina pectoris, bradycardia, myocardial infarction, thrombophlebitis, atrial fibrillation, hypotension, cardiac arrest, postural hypotension, pulmonary embolism, pulmonary edema.

Central and Peripheral Nervous System: Frequent: transient ischemic attack, cerebrovascular accident, vertigo, ataxia, hypokinesia. Infrequent: paresthesia, convulsions, extrapyramidal disorder, hypertonia, tremor, aphasia, hypoesthesia, abnormal coordination, hemiplegia, hyperkinesia, involuntary muscle contractions, stupor, cerebral hemorrhage, neuralgia, ptosis, neuropathal.

ptosis, neuropathy.

Gastrointestinal System: Infrequent: gastroenteritis, diverticulitis, gastrointestinal hemorrhage, melena, esophageal ulceration.

Hemic and Lymphatic Disorders: Frequent: anemia. Infrequent: leukopenia.

Metabolic and Nutritional Disorders: Frequent: increased alkaline
phosphatase, decreased weight. Infrequent: dehydration, hyponatremia,
aggravated diabetes mellitus.

Psychiatric Disorders: Frequent: aggressive reaction. Infrequent: delusion,
personality disorder, emotional lability, nervousness, sleep disorder, libido
increased, psychosis, amensia, apathy, paranoid reaction, thinking abnormal,
crying abnormal, appetite increased, paroniria, delirium, depersonalization,
neurosis, suicide attempt.

Resoiratory System: Frequent: pneumonia. Infrequent: annea. asthma.

Respiratory System: Frequent: pneumonia. Infrequent: apnea, asthma

ONIN and Appendages: Frequent: rash. Infrequent: skin ulceration, pruritus, cellulitis, eczema, dermatitis, erythematous rash, alopecia, urticaria.

Special Senses: Frequent: cataract, conjunctivitis. Infrequent: macula lutea degeneration, decreased visual acuity, decreased hearing, tinnitus, blepharitis, blurred vision, corneal opacity, glaucoma, conjunctival hemorrhage, eye pain, retinal hemorrhage, xerophthalmia, diplopia, abnormal lacrimation, myopia, retinal detachment.

Urinary System: Frequent: frequent micturition. Infrequent: dysuria Events Reported Subsequent to the Marketing of Namenda, both US and

Events Reported subsequent to the Marketing of Namenda, both Us and Ex-US

Although no causal relationship to memantine treatment has been found, the following adverse events have been reported to be temporally associated with memantine treatment and are not described elsewhere in labeling: aspiration pneumonia, asthenia, atrioventricular block, bone fracture, carpal tunnel syndrome, cerebral infarction, chest pain, cholelithiasis, claudication, colitis, deep venous thrombosis, depressed level of consciousness (including loss of consciousness and rare reports of coma), dyskinesia, dysphagia, encephalopathy, gastritis, gastroesophageal reflux, grand mal convulsions, intracranial hemorrhage, hepatitis (including increased ALT and AST and hepatic failure), hyperglycemia, hyperlipidemia, hypoglycemia, ileus, increased INR, impotence, lethargy, malaise, myoclonus, neuroleptic malignant syndrome, acute pancreatitis, Parkinsonism, acute renal failure (including increased creatinine and renal insufficiency), prolonged OT interval, restlessness, sepsis, Stevens-Johnson syndrome, suicidal ideation, sudden death, supraventricular tachycardia, tachycardia, tardive dyskinesia, thrombocytopenia, and hallucinations (both visual and auditory).

ANIMAL TOXICOLOGY

ANNIMAL IOALOULOUT Memantia induced neuronal lesions (vacuolation and necrosis) in the multipolar and pyramidal cells in cortical layers III and IV of the posterior cingulate and retrosplenial neocortices in rats, similar to those which are known to occur in rodents administered other NMDA receptor antagonists. Lesions were seen after a single dose of memantine. In a study in which rats were given daily oral doses of memantine for 14 days, the no-effect dose for neuronal necrosis was 6 times the maximum recommended human dose on a mg/m² basis. The potential for induction of central neuronal vacuolation and necrosis by NMDA receptor antagonists in humans is

### DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Memantine HCl is not a controlled substance. Physical and Psychological Dependence: Memantine HCI is a low to moderate affinity uncompetitive NMDA antagonist that did not produce any evidence of drug-seeking behavior or withdrawal symptoms upon discontinuation in 2,504 patients who participated in clinical trials at therapeutic doses. Post marketing data, outside the U.S., retrospectively collected, has provided no evidence of drug abuse or dependence.

OVERDOSAGE
Signs and symptoms associated with memantine overdosage in clinical trials and from worldwide marketing experience include agitation, confusion, ECG changes, loss of consciousness, psychosis, restlessness, slowed movement, somnolence, stupor, unsteady gait, visual hallucinations, vertigo, vomiting, and weakness. The largest known ingestion of memantine worldwide was 2.0 grams in a patient who took memantine in conjunction with unspecified antidiabetic medications. The patient experienced coma, diplopia, and agitation, but subsequently recovered.

Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug. As in any cases of overdose, general supportive measures should be utilized, and treatment should be symptomatic. Elimination of memantine can be enhanced by acidification of urine.



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