

New Study: Hypnotic Agents May Prevent Falls

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DENVER — The conventional wisdom holding that prescribing hypnotic agents for nursing home patients increases their risk of falling and hip fracture may not be correct.

A recent study involving more than 34,000 Michigan nursing home residents suggests an alternative explanation: The increased risk of falls may be attributable to

the insomnia for which hypnotic agents are so often prescribed, rather than to the drugs themselves, W. Vaughn McCall, M.D., said at a satellite symposium held in conjunction with the annual meeting of the Associated Professional Sleep Societies.

He cited an analysis of a Michigan Medicare database by Alon Y. Avidan, M.D., and coinvestigators at the University of Michigan and the Veterans Affairs Medical Center in Ann Arbor. They examined the risk of falls and hip fracture

over roughly 6 months of follow-up in 34,163 elderly residents in 437 Michigan nursing homes.

During follow-up, 42.9% of patients fell and 2.5% sustained a hip fracture. After adjusting for numerous potential confounders in a multiple logistic regression analysis, the investigators concluded that insomnia—but not hypnotic use per se—was predictive of future falls, noted Dr. McCall, professor and chairman of the department of psychiatry and behavioral

medicine at Wake Forest University, Winston-Salem, N.C.

Dr. Avidan and colleagues went on to speculate that the use of hypnotics to treat insomnia in the frail elderly might actually protect against falls. That is “a very provocative statement,” Dr. McCall said at the symposium, which was sponsored by Sepracor, but “I’m not ready to state this as the final word on the subject. I’m personally not prepared to go that far, even though this is a large study of debilitated nursing home patients. But I do think the study opens the door to looking at this issue more carefully.”

In the Michigan study, supported by the National Institute on Aging, the 259 insomniac nursing home residents on a hypnotic agent had an adjusted 32% greater risk of falls than did the 31,391 who did not have insomnia and were not on a hypnotic. Particularly noteworthy was the

finding that the 1,890 individuals with insomnia who were not taking a hypnotic agent had a 55% greater risk of falls. Among the nursing home population who did not have insomnia, the 632 on a hypnotic agent did not

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have a significantly greater risk of falling than did those who were not on this class of medication (J. Am. Geriatr. Soc. 2005;53:955-62).

Regardless of whether a randomized trial ever actually demonstrates that hypnotics do not increase and perhaps even do protect against falling in the frail elderly, Dr. McCall said there is no doubt that sleep problems are more common in the elderly than in any other age group, and that those sleep difficulties produce next-day impairments in cognitive ability that can be confused with dementia. This underscores the importance of appropriately assessing and treating elderly patients with sleep problems using the behavioral therapies and/or medications with demonstrated efficacy in this setting, he said.

Of interest in this regard, Dr. McCall continued, is a recent multicenter double-blind randomized trial in which he was a coinvestigator. It involved 231 patients aged 65-85 years with primary insomnia randomized to nightly 1- or 2-mg eszopiclone (Lunesta) or placebo for 2 weeks.

Although the lower dose of eszopiclone effectively induced sleep compared with placebo, the higher dose induced and maintained sleep. The 2-mg dose was accompanied by significantly higher patient-reported ratings of daytime alertness, sense of physical well-being, and quality of life. Moreover, the total nap time was cut in half in patients on the 2-mg dose compared with placebo (Sleep 2005;28:720-7).

The trial also was sponsored by Sepracor. Dr. McCall serves as a consultant to the company. ■

Namenda memantine HCl

Rx Only
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).

Neurological Conditions

Seizures: Namenda has not been systematically evaluated in patients with a seizure disorder. In clinical trials of Namenda, seizures occurred in 0.2% of patients treated with Namenda and 0.5% of patients treated 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

Namenda 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 N-glucuronide conjugate (74%). The pharmacokinetics of memantine in patients with hepatic impairment have not been investigated, but would be expected to be only modestly affected.

Renal 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.

Drug-Drug Interactions

N-methyl-D-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.

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.

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 the metabolism of memantine.

Acetylcholinesterase (AChE) inhibitors: Coadministration of Namenda with the AChE 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 donepezil alone.

Drugs eliminated via renal mechanisms: Because memantine is eliminated in 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 result in altered plasma levels of both agents. However, coadministration of Namenda and HCTZ/TA 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 antihyperglycemic drug Glucovance® (glyburide and metformin HCl) 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 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.

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 in males.

Pregnancy

Pregnancy Category B: Memantine given orally to pregnant rats and pregnant rabbits during the period of organogenesis was not teratogenic up to the highest doses tested (18 mg/kg/day in rats and 30 mg/kg/day in rabbits, which are 9 and 30 times, respectively, the maximum recommended human dose [MRHD] on a mg/m² basis).

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 postpartum period. The no-effect dose for these effects was 6 mg/kg, which is 3 times the MRHD on a mg/m² 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 documenting the safety and efficacy of memantine in any illness occurring in children.

ADVERSE REACTIONS

The experience described in this section derives from studies in patients 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 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-Treated Patients.

Body System Adverse Event	Placebo (N = 922) %	Namenda (N = 940) %
Body as a Whole		
Fatigue	1	2
Pain	1	3
Cardiovascular System		
Hypertension	2	4
Central and Peripheral Nervous System		
Dizziness	5	7
Headache	3	6
Gastrointestinal System		
Constipation	3	5
Vomiting	2	3
Musculoskeletal System		
Back pain	2	3
Psychiatric Disorders		
Confusion	5	6
Somnolence	2	3
Hallucination	2	3
Respiratory System		
Coughing	3	4
Dyspnea	1	2

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.

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.

Laboratory Changes: Namenda and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables 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 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 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, 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, amnesia, apathy, paranoid reaction, thinking abnormal, crying abnormal, appetite increased, paranoia, delirium, depersonalization, neurosis, suicide attempt.

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

Skin 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, hematuria, urinary retention.

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: atrioventricular block, bone fracture, carpal tunnel syndrome, cerebral infarction, chest pain, claudication, colitis, dyskinesia, dysphagia, gastritis, gastroesophageal reflux, grand mal convulsions, intracranial hemorrhage, hepatic failure, hyperlipidemia, hypoglycemia, ileus, impotence, malaise, neuroleptic malignant syndrome, acute pancreatitis, aspiration pneumonia, acute renal failure, prolonged QT interval, restlessness, Stevens-Johnson syndrome, sudden death, supraventricular tachycardia, tachycardia, tardive dyskinesia, and thrombocytopenia.

ANIMAL TOXICOLOGY

Memantine 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 unknown.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Memantine HCl is not a controlled substance.

Physical and Psychological Dependence: Memantine HCl 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

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. In a documented case of an overdose with up to 400 mg of memantine, the patient experienced restlessness, psychosis, visual hallucinations, somnolence, stupor and loss of consciousness. The patient recovered without permanent sequelae.

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