High Anxiety Rate Warrants Screening in MS

BY DAMIAN MCNAMARA Miami Bureau

BAL HARBOUR, FLA. — All people with multiple sclerosis should be screened for anxiety, according to a study presented at the annual meeting of the American Neuropsychiatric Association.

Researchers randomly selected 100 people with multiple sclerosis and screened them for anxiety using DSM-IV criteria. "We found the rates of anxiety were high.

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They would not have been diagnosed without neuropsychiatry screening for anxiety and depression," Juan Carlos Urizar, M.D., told this newspaper.

"Data are very preliminary, but this is a good start to see how one can intervene clinically and not forget anxiety and depression in multiple sclerosis. This has implications for quality of life," said Dr. Urizar of the department of psychiatry at Brigham and Women's Hospital, Boston, who was the second author of the study.

Early in multiple sclerosis, patients can also experience decreased memory and concentration. Some anxiety also may be related to demyelinization and brain function. "Although we know this is true for depression as many studies have correlated depression to white matter changes and undermining of cortical fibers by subcortical lesions," lead author Zeina Chemali, M.D., said in a follow-up interview. "Not much is published in regard to anxiety."

ARICEPT® (Donepezil Hydrochloride Tablets)	
ARICEPT® ODT (Donepezil Hydrochloride) Orally Disintegrating Tablets	
Brief Summary—see package insert for full prescribing information. INDICATIONS AND USAGE ARICEPT® is indicated for the treatment	
of mild to moderate dementia of the Alzheimer's type. CONTRAINDICATIONS ARICEPT® is contraindicated in patients with known	
hypersensitivity to donepezil hydrochloride or to piperidine derivatives. WARNINGS Anesthesia: ARICEPT®, as a cholinesterase	
inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia. Cardiovascular Conditions: Because of their	
pharmacological action, cholinesterase inhibitors may have vagotonic effects on the sinoatrial and atrioventricular nodes. This effect may	
manifest as bradycardia or heart block in patients both with and without known underlying cardiac conduction abnormalities. Syncopal	
episodes have been reported in association with the use of ARICEPT®. Gastrointestinal Conditions: Through their primary action,	
cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should	
be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers,	
e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies	
of ARICEPT® have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. ARICEPT®,	
as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea and vomiting. These effects,	
when they occur, appear more frequently with the 10 mg/day dose than with the 5 mg/day dose. In most cases, these effects have been	
mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of ARICEPT®. <i>Genitourinary:</i> Although	
not observed in clinical trials of ARICEPT®, cholinomimetics may cause bladder outflow obstruction. Neurological Conditions: Seizures:	
Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a	
manifestation of Alzheimer's Disease. Pulmonary Conditions: Because of their cholinomimetic actions, cholinesterase inhibitors	
should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. PRECAUTIONS Drug-Drug Interactions (see Clinical Pharmacology: Clinical Pharmacokinetics: Drug-drug Interactions) Effect of ARICEPT® on the Metabolism	
of Other Drugs: No in vivo clinical trials have investigated the effect of ARICEPT® on the clearance of drugs metabolized by CYP 3A4	
(e.g. cisapride, terfenadine) or by CYP 2D6 (e.g. imipramine). However, <i>in vitro</i> studies show a low rate of binding to these enzymes (mean	
K_{i} about 50–130 μ M), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference.	
Whether ARICEPT® has any potential for enzyme induction is not known. Formal pharmacokinetic studies evaluated the potential of ARICEPT®	
for interaction with theophylline, cimetidine, warfarin, digoxin and ketoconazole. No effects of ARICEPT® on the pharmacokinetics of these	
drugs were observed. Effect of Other Drugs on the Metabolism of ARICEPT®: Ketoconazole and quinidine, inhibitors of CYP450,	
3A4 and 2D6, respectively, inhibit donepezil metabolism in vitro. Whether there is a clinical effect of quinidine is not known. In a 7-day crossover	
study in 18 healthy volunteers, ketoconazole (200 mg q.d.) increased mean donepezil (5 mg q.d.) concentrations (AUC _{n-24} and C_{max}) by	
36%. The clinical relevance of this increase in concentration is unknown. Inducers of CYP 2D6 and CYP 3A4 (e.g., phenytoin,	
carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of ARICEPT®. Formal pharmacokinetic	
studies demonstrated that the metabolism of ARICEPT® is not significantly affected by concurrent administration of digoxin or cimetidine.	
Use with Anticholinergics: Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity	
of anticholinergic medications. Use with Cholinomimetics and Other Cholinesterase Inhibitors: A synergistic effect may be expected	
when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists	
such as bethanechol. Carcinogenesis, Mutagenesis, Impairment of Fertility No evidence of a carcinogenic potential was	
obtained in an 88-week carcinogenicity study of donepezil hydrochloride conducted in CD-1 mice at doses up to 180 mg/kg/day	
(approximately 90 times the maximum recommended human dose on a mg/m ² basis), or in a 104-week carcinogenicity study in Sprague-Dawley rats at doses up to 30 mg/kg/day (approximately 30 times the maximum recommended human dose on a mg/m ² basis).	
Donepezil was not mutagenic in the Ames reverse mutation assay in bacteria, or in a mouse lymphoma forward mutation assay in vitro.	
In the chromosome aberration test in cultures of Chinese harnster lung (CHL) cells, some clastogenic effects were observed. Donepezil	
was not clastogenic in the <i>in vivo</i> mouse micronucleus test and was not genotoxic in an <i>in vivo</i> unscheduled DNA synthesis assay in rats.	
Donepezil had no effect on fertility in rats at doses up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose	
on a mq/m ² basis). Pregnancy <i>Pregnancy Category C:</i> Teratology studies conducted in pregnant rats at doses up to 16 mq/kq/day	
(approximately 13 times the maximum recommended human dose on a mg/m ² basis) and in pregnant rabbits at doses up to 10 mg/kg/day	
(approximately 16 times the maximum recommended human dose on a mg/m² basis) did not disclose any evidence for a teratogenic potential	
of donepezil. However, in a study in which pregnant rats were given up to 10 mg/kg/day (approximately 8 times the maximum recommended	
human dose on a mg/m ² basis) from day 17 of gestation through day 20 postpartum, there was a slight increase in still births and a slight	
decrease in pup survival through day 4 postpartum at this dose; the next lower dose tested was 3 mg/kg/day. There are no adequate or	
well-controlled studies in pregnant women. ARICEPT® should be used during pregnancy only if the potential benefit justifies the potential	
risk to the fetus. Nursing Mothers It is not known whether donepezil is excreted in human breast milk. ARICEPT® has no indication for	
use in nursing mothers. Pediatric Use There are no adequate and well-controlled trials to document the safety and efficacy of ARICEPT®	
in any illness occurring in children. Geriatric Use Alzheimer's disease is a disorder occurring primarily in individuals over 55 years of	
age. The mean age of the patients enrolled in the clinical studies with ARICEPT® was 73 years; 80% of these patients were between 65	
and 84 years old and 49% of the patients were at or above the age of 75. The efficacy and safety data presented in the clinical trials section	
were obtained from these patients. There were no clinically significant differences in most adverse events reported by patient groups B65	
years old and <65 years old. ADVERSE REACTIONS Adverse Events Leading to Discontinuation The rates of discontinuation	
from controlled clinical trials of ARICEPT® due to adverse events for the ARICEPT® 5 mg/day treatment groups were comparable to those of placebox treatment groups at approximately 5%. The rate of discontinuation of rationate who received 7 day associations from 5 mg/day	
of placebo-treatment groups at approximately 5%. The rate of discontinuation of patients who received 7-day escalations from 5 mg/day to 10 mg/day, was higher at 13%. The most common adverse events leading to discontinuation, defined as those occurring in at least	
2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1.	
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Table 1. Most Frequent Adverse Events Leading to Withdrawal	

Table 1. Most Frequent Adverse Events Leading to Withdrawal from Controlled Clinical Trials by Dose Group							
Dose Group	Placebo	5 mg/day ARICEPT®	10 mg/day ARICEPT®				
Patients Randomized Event/% Discontinuing	355	350	315				
Nausea	1%	1%	3%				
Diarrhea	0%	<1%	3%				
Vomiting	<1%	<1%	2%				

Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT® The most common adverse even Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT® The most common adverse events, defined as those occurring at a frequency of at lass 15% in patients readving 10 mg/day and wice the placebo rate, are largely predicted by ARICEPT®'s cholinomimetic effects. These include nausea, diarrhea, insomnia, vomiting, muscle cramp, fatigue and anorexia. These adverse events were often of mild intensity and transient, resolving during continued ARICEPT® traitment without the need for dose modification. There is evidence to suggest that the frequency of these common adverse events may be affected by the rate of traitation. An open-label study was conducted with 269 patients who received placebo in the 15 and 30-week studies. These patients were titrated to a dose of 10 mg/day over a 6-week period. The rates of common adverse events were tower than those seen in patients titrated to 10 mg/day over one week in the controlled clinical triats and were comparable to those seen in patients on 5 mg/day. See Table 2 for a comparison of the most common adverse events following one and six week titration regimens.

Table 2. Comparison of Rates of Adverse Events in Patients Titrated to 10 mg/day Over 1 and 6 Weeks						
Adverse Event	No tit Placebo (n=315)	ration 5 mg/day (n=311)	One week titration 10 mg/day (n=315)	Six week titration 10 mg/day (n=269)		
Nausea	6%	5%	19%	6%		
Diarrhea	5%	8%	15%	9%		
Insomnia	6%	6%	14%	6%		
Fatigue	3%	4%	8%	3%		
Vomiting	3%	3%	8%	5%		
Muscle cramps	2%	6%	8%	3%		
Anorexia	2%	3%	7%	3%		

Adverse Events Reported in Controlled Trials The events cited reflect experience gained under closely monitored conditions of clinica Anotase technological methods and the most back and the control of the source of the s

Body System/Adverse Event	Placebo (n=355)	ARICEPT® (n=747)
Percent of Patients with any Adverse Event Body as a Whole	72	74
Headache	9	10
Pain, various locations	8	9
Accident	6	7
Fatigue	3	5
Cardiovascular System	0	0
Syncope	1	2
Digestive System		-
Nausea	6	11
Diarrhea	5	10
Vomiting	3	5
Anorexia	2	4
Hemic and Lymphatic System		
Ecchymosis	3	4
Metabolic and Nutritional Systems		
Weight Decrease	1	3
Musculoskeletal System		
Muscle Cramps	2	6
Arthritis	1	2
Nervous System		
Insomnia	6	9
Dizziness	6	8
Depression	<1	8 3 3
Abnormal Dreams	0	
Somnolence	<1	2
Urogenital System		
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The researchers did not assess patient anxiety according to lesions visible on magnetic resonance imaging (MRI) or disease burden, but they plan to do so in the future. Dr. Chemali is the director of neuropsychiatry at the Brigham Behavioral Neurology Group at Brigham and Women's Hospital.

Researchers grouped the 70 women and 30 men according to the types of multiple sclerosis episodes. Participants included 49% with relapse-remitting disease, 32% with secondary progressive multiple sclerosis, 16% who experienced their first multiple sclerosis attack, and 3% with primary progressive disease.

Results indicate that anxiety is not related to severity or chronicity of multiple

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sclerosis, suggesting that screening is appropriate for all patients with the disease.

Researchers assessed prevalence of affective disorders, anxiety disorders, and comorbidity between the two. "An interesting finding is the

higher level of anxiety than depression," Dr. Urizar said.

A total of 37% of participants had an anxiety disorder, 20% had depression, and 20% had comorbid anxiety and depression. In addition, 21% presented with cognitive decline. Manic-depressive disorder was included with depression in the study, Dr. Chemali said.

The neuropsychological battery of tests included:

► The Boston Naming Test for language. ▶ The Drilled Word Span Test or the Buschke Selective Reminding Test for memory.

► The Trail Making Test (Parts A and B), a digit span test, and letter cancellation tested for attention.

 Beck Depression Inventory for mood assessment.

▶ Beck Anxiety Inventory for anxiety.

Participants also were asked to copy a cube and place the numbers and hands in a clock, and were given the Rey-Osterrieth Complex Figure Test.

The prevalence of anxiety was higher among women than men. "The gender difference ... reflects the fact that MS is more common in women than in men," Dr. Chemali said. The disparity could also reflect the reportedly higher prevalence of anxiety in women compared with men in the general population—a highly debated subject, because women present at or use more medical/psychiatric services than do men, which may result in prevalence being recorded as higher among women.

The study findings demonstrate that patients with multiple sclerosis can suffer debilitating anxiety with or without an affective disorder. However, the authors wrote in their poster, "Further study is needed to confirm these findings."



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