

JOURNAL OF

Geriatric Psychiatry and Neurology

ISSN 0891-9887

An Interdisciplinary Forum for Clinicians and Scientists

VOLUME 6, NUMBER 2

APRIL-JUNE 1993

Michael A. Jenike, M.D., Editor

Harvard Medical School
Massachusetts General Hospital

Univ. of Minn.
Bio-Medical
Library
5 24 93

Acute Care of the African American Elder

F.M. Baker, Risa Lavizzo-Mourey, and
Billy E. Jones

**Delayed Late Component of Visual Global
Field Power in Probable Alzheimer's Disease**

Kerry L. Coburn, J. Wesson Ashford, and
Marco A. Moreno

**The Nature and Time Course of Cognitive
Side Effects During Electroconvulsive
Therapy in the Elderly**

Eugene H. Rubin, Dorothy A. Kinscherf,
Figiel, and Charles F. Zorumski

**Year Longitudinal Study of Cognitive
Change in Normal Aging and Alzheimer's**

Flicker, Steven H. Ferris, and
Leisberg

**Analysis of Senile Plaques Using
Electron Microscopy**

Landberg, Brendan McDonald,
Lime, and Frank Watt

**Memory Complaint, Memory Performance,
and Psychiatric Diagnosis: A Community
Study**

Susan Spear Bassett and Marshal F. Folstein

**Successful Treatment With Captopril of an
Elderly Man With Polydipsia and
Hyponatremia**

Michael J. Tueth and John Broderick-Cantwell

**Evaluation of Multiple Doses of Milacemide
in the Treatment of Senile Dementia of the
Alzheimer's Type**

Neal R. Cutler, T. Daniel Fakouhi,
Ward T. Smith, Hugh C. Hendrie,
Fumisuke Matsuo, John J. Sramek,
and Robert L. Herting

**The Prevalence of Late-Onset Schizophrenia
in a Psychogeriatric Population**

R. Yassa, D. Dastoor, C. Nastase, Y. Camille,
and L. Belzile

15P31409 OCT93
Univ of Minnesota
Biomedical Lib
505 Essex St Se
MINNEAPOLIS MN 55455
325a Diehl Hal

Geriatric Psychiatry and Neurology

Editor

Michael A. Jenike, MD
Massachusetts General Hospital
Boston, Massachusetts

Editorial Assistant

Mary T. Dickie

Editorial Board

Marilyn S. Albert, PhD
Massachusetts General Hospital
Boston, Massachusetts

William H. Anderson, MD
St. Elizabeth's Hospital
Brighton, Massachusetts

Lee Baer, PhD
Massachusetts General Hospital
Boston, Massachusetts

D. Frank Benson, MD
UCLA School of Medicine
Los Angeles, California

John P. Blass, MD, PhD
Burke Rehabilitation Center
White Plains, New York

Dan G. Blazer, MD, PhD
Duke University, Medical Center
Durham, North Carolina

Andrew W. Brotman, MD
Freedom Trail Clinic
Boston, Massachusetts

Roger A. Brumback, MD
University of Oklahoma
College of Medicine
Oklahoma City, Oklahoma

Ewald W. Busse, MD
Duke University Medical Center
Durham, North Carolina

Robert N. Butler, MD
Mt. Sinai School of Medicine
New York, New York

Ned H. Cassem, MD
Massachusetts General Hospital
Boston, Massachusetts

Bruce M. Cohen, MD, PhD
McLean Hospital
Belmont, Massachusetts

Gene D. Cohen, MD, PhD
National Institute of Mental Health
Rockville, Maryland

M. Cornelia Cremens, MD
Abstract Editor
Massachusetts General Hospital
Boston, Massachusetts

Jeffrey L. Cummings, MD
Associate Editor for Behavioral Neurology
West Los Angeles VA Medical Center
Los Angeles, California

Kenneth L. Davis, MD
Huntington, New York

David A. Drachman, MD
University of Massachusetts Medical
Center
Worcester, Massachusetts

Carl Eisdorfer, MD, PhD
University of Miami School of Medicine
Miami, Florida

Barry Fogel, MD
Rhode Island Hospital
Providence, Rhode Island

Marshal F. Folstein, MD
Johns Hopkins University School of
Medicine
Baltimore, Maryland

Alan J. Gelenberg, MD
University of Arizona
Tucson, Arizona

Donald C. Goff, MD
Massachusetts General Hospital
Boston, Massachusetts

C. G. Gottfries
University of Göteborg
Hisings Backa, Sweden

John Growdon, MD
Associate Editor for Geriatric Neurology
Massachusetts General Hospital
Boston, Massachusetts

Cyril I. Gryfe, MD, FRCPC
Toronto, Canada

Albert Heyman, MD
Duke University Medical Center
Durham, North Carolina

Steven E. Hyman, MD
Massachusetts General Hospital
Boston, Massachusetts

Lissy F. Jarvik, MD, PhD
UCLA Neuropsychiatric Institute
Los Angeles, California

Hideyo Katsunuma, MD
Tokyo Medical College Hospital
Tokyo, Japan

Jonathan D. Lief, MD
Hahnemann Hospital
Brighton, Massachusetts

Benjamin Liptzin, MD
McLean Hospital
Belmont, Massachusetts

Charles A. Marotta, MD, PhD
Associate Editor for Neuroscience
Massachusetts General Hospital
Boston, Massachusetts

Joseph B. Martin, MD, PhD
University of California
San Francisco, California

Marek-Marsel Mesulam, MD
Beth Israel Hospital
Boston, Massachusetts

Gary D. Miner, PhD
*Associate Editor for Alzheimer's and Other
Dementias*
Alzheimer's Foundation
Tulsa, Oklahoma

George B. Murray, MD
Massachusetts General Hospital
Boston, Massachusetts

Michael Otto, PhD
Massachusetts General Hospital
Boston, Massachusetts

Eric A. Pfeiffer, MD
University of South Florida College
of Medicine
Tampa, Florida

Chester M. Pierce, MD
Nichols House
Cambridge, Massachusetts

Derek M. Prinsley, MD
University of Texas Medical Branch
Galveston, Texas

Peter V. Rabins, MD
Johns Hopkins University School of
Medicine
Baltimore, Maryland

Murray A. Raskind, MD
VA Geriatric Research Education
and Clinic Center
Seattle, Washington

Barry Reisberg, MD
New York University Medical Center
New York, New York

E. P. Richardson, Jr, MD
Associate Editor for Neuropathology
Massachusetts General Hospital
Boston, Massachusetts

Paavo J. Riekinen, MD
University of Kupio
Department of Neurology
Kupio, Finland

Jerrold F. Rosenbaum, MD
Massachusetts General Hospital
Boston, Massachusetts

John Rowe, MD
Mt. Sinai Medical Center
New York, New York

Carl Salzman, MD
Massachusetts Mental Health Center
Boston, Massachusetts

Lon Schneider, MD
University of Southern California
Los Angeles, California

Charles A. Shamoian, MD, PhD
New York Hospital—Cornell Medical
Center
White Plains, New York

James R. Slaughter, MD
VA Medical Center
Salt Lake City, Utah

Gary W. Small, MD
UCLA Neuropsychiatric Institute
Los Angeles, California

Theodore A. Stern, MD
Massachusetts General Hospital
Boston, Massachusetts

Paul Summergrad, MD
Massachusetts General Hospital
Boston, Massachusetts

Owen S. Surman, MD
Massachusetts General Hospital
Boston, Massachusetts

Virginia E. Tay, RN, MSN
Cambridge, Massachusetts

Charles E. Wells, MD
Vanderbilt University School of Medicine
Nashville, Tennessee

Linda Winter-Miner, PhD
Alzheimer's Foundation
Tulsa, Oklahoma

William Yamanashi, PhD
Tulsa, Oklahoma

Jerome A. Yesavage, MD
VA Medical Center
Palo Alto, California

Official publication of
the Alzheimer's Foundation



Copyright © 1993 Decker Periodicals Inc.

Journal of Geriatric Psychiatry and Neurology (ISSN 0891-9887) is published quarterly, January, April, July, and October, by Decker Periodicals Inc., One James Street South, P.O. Box 620, L.C.D. 1, Hamilton, Ontario, Canada L8N 3K7. The known office of publication is The Sheridan Press, Fame Avenue, Hanover, PA 17331. Second Class postage paid at Hanover, PA, and additional offices.

Subscription information, orders, or changes of address: Decker Periodicals Inc., One James Street South, P.O. Box 620, L.C.D. 1, Hamilton, Ontario, Canada L8N 3K7 or P.O. Box 785, Lewiston, NY, 14092-0785. Tel: (416) 522-7017; Fax: (416) 522-7839. In Canada and the United States: (800) 568-7281. In Japan, contact Igaku-Shoin Ltd., Tokyo International, P.O. Box 5063, 1-28-36 Hongo, Bunkyo-Ku, Tokyo 113, Japan. Tel: 81-3-817-5685; Fax: 81-3-815-7805; Telex: 27222738 ISTKFDJ.

Annual subscription rates: U.S. and Canada \$69.00 individual, \$94.00 institutional, \$40.00 student/resident, \$30.00 single issue; International \$89.00 individual, \$114.00 institutional, \$60.00 student/resident, \$35.00 single issue. All prices are in U.S. currency and are subject to change without notice. All orders from overseas subscribers or from subscription agencies are payable in U.S. funds. All rates include surface mail delivery costs. Rates for airmail delivery available upon request. Copies will be replaced without charge if the publisher receives a request within 90 days of the mailing date in the U.S. or within 6 months in all other countries. Duplicate copies will not be sent to replace those undelivered through failure to notify the publisher of change of address.

Advertising: Inquiries should be addressed to John Birkby, Decker Periodicals Inc., One James Street South, P.O. Box 620, L.C.D. 1, Hamilton, Ontario, Canada L8N 3K7. Tel: (416) 522-7017; Fax: (416) 522-7839; in Canada and U.S.: (800) 568-7281.

The *Journal of Geriatric Psychiatry and Neurology* is indexed in *Index Medicus*, *EMBASE the Excerpta Medica Database*, *Psychological Abstracts*, and *Neuroscience Citation Index and Research Alert*. The *Journal* is available in microform from University Microfilms International, 300 North Zeeb Road, Ann Arbor, MI 48106.

Contents

Editorial

- 65 Alzheimer's Disease: Headlines, Confusion, and the Unknown
Linda E. Nee, MSW

Commentary

- 66 Acute Care of the African American Elder
F.M. Baker, Risa Lavizzo-Mourey, and Billy E. Jones

Original Articles

- 72 Delayed Late Component of Visual Global Field Power in Probable Alzheimer's Disease
Kerry L. Coburn, J. Wesson Ashford, and Marco A. Moreno
- 78 The Nature and Time Course of Cognitive Side Effects During Electroconvulsive Therapy in the Elderly
Eugene H. Rubin, Dorothy A. Kinscherf, Gary S. Figiel, and Charles F. Zorumski
- 84 A Two-Year Longitudinal Study of Cognitive Function in Normal Aging and Alzheimer's Disease
Charles Flicker, Steven H. Ferris, and Barry Reisberg
- 97 Microanalysis of Senile Plaques Using Nuclear Microscopy
Judith Landsberg, Brendan McDonald, Geoff Grime, and Frank Watt
- 105 Memory Complaint, Memory Performance, and Psychiatric Diagnosis: A Community Study
Susan Spear Bassett and Marshal F. Folstein

Case Studies

- 112 Successful Treatment With Captopril of an Elderly Man With Polydipsia and Hyponatremia
Michael J. Tueth and John Broderick-Cantwell
- 115 Evaluation of Multiple Doses of Milacemide in the Treatment of Senile Dementia of the Alzheimer's Type
Neal R. Cutler, T. Daniel Fakouhi, Ward T. Smith, Hugh C. Hendrie, Fumisuke Matsuo, John J. Sramek, and Robert L. Herting
- 120 The Prevalence of Late-Onset Schizophrenia in a Psychogeriatric Population
R. Yassa, D. Dastoor, C. Nastase, Y. Camille, and L. Belzile

Topics in Geriatrics

- 126 Dementia in a Population-Based Study
- 127 Mechanisms of Memory

Departments

- 111 Notices
- 128 Abstracts
- 130 Instructions for Authors

Evaluation of Multiple Doses of Milacemide in the Treatment of Senile Dementia of the Alzheimer's Type

Neal R. Cutler, MD; T. Daniel Fakouhi, PhD, MBA; Ward T. Smith, MD; Hugh C. Hendrie, MD; Fumisuke Matsuo, MD; John J. Sramek, PharmD; Robert L. Herting, MD, PhD

Abstract

A multicenter, double-blind, placebo-controlled, parallel group study was conducted to assess the safety and efficacy of three doses of milacemide in the treatment of patients with senile dementia of the Alzheimer type of mild to moderate severity. Patients were randomly assigned to receive one of three dosages of milacemide (400, 800, or 1200 mg/day) or placebo for 4 weeks followed by a single-blind 4-week placebo period. One hundred forty-eight men and women older than 50 years of age were enrolled, and 129 patients completed the study. The differences among treatment groups were not statistically different with respect to total scores on the Alzheimer's Disease Assessment Scale or any items and subscales that were examined, nor were significant differences on the Clinical Global Impression Scale found. Clinically significant increases in liver function tests, specifically aspartate aminotransferase and alanine aminotransferase (AST and ALT), were reported for five of the patients receiving milacemide, requiring their withdrawal from the study. (*J Geriatr Psychiatry Neurol* 1993;6:115-119).

Senile dementia of the Alzheimer type (SDAT) is a progressive condition that is principally manifested by memory deficits and loss of other intellectual abilities of sufficient severity to interfere with social or occupational functioning.¹⁻⁵

Neurochemical studies have identified several neurotransmitter systems that are known to have an impact on memory processes, primarily the cholinergic system, as evidenced by loss of cholinergic neurons in the nucleus basalis in Alzheimer's patients, as well as the adrenergic-dopaminergic, γ -aminobutyric acid (GABA)-ergic, and glutamater-

gic systems.⁶⁻¹¹ In several studies glutamate binding to *N*-methyl-D-aspartate (NMDA) receptor sites was significantly reduced in Alzheimer's disease patients,¹²⁻¹⁴ although negative studies also demonstrated no reduction in NMDA receptor sites despite apparent reduction of glutamate uptake.¹⁵⁻¹⁷ Marked decreases in glutamate levels were also found in a dissection of the perforant pathway zone.¹⁸ Coupling in the glycine recognition site in the NMDA-receptor may also be impaired.¹⁹

It has been reported that activation of the NMDA subtype of glutamate receptors leads to long-term potentiation in the postsynaptic neurons when stimulated by either NMDA or the natural agonist, the excitatory amino acid glutamate.^{20,21} Because long-term potentiation has been suggested as a mechanism for memory formation, positive modulation of NMDA-receptors should lead to memory and learning enhancement.

Milacemide (2-*n*-pentylaminoacetamide hydrochloride), a monoamine oxidase-B inhibitor and a prodrug for glycine, has been shown to have a

Received Jan 12, 1992. Received revised Feb 25, 1992. Accepted for publication March 20, 1992.

From California Clinical Trials (Drs Cutler and Sramek), Beverly Hills, CA, Searle Research and Development (Drs Fakouhi and Herting), Skokie, IL, the Pacific Northwest Clinical Research Center (Dr Smith), Portland, OR, the Indiana University Medical Center (Dr Hendrie), Indianapolis, IN, and the University of Utah School of Medicine (Dr Matsuo), Salt Lake City, UT.

Address correspondence to Dr N.R. Cutler, California Clinical Trials, 8500 Wilshire Boulevard, 7th Floor, Beverly Hills, CA 90211.

unique action in several tests that evaluate short-term memory. Milacemide was able to reverse memory impairment induced by electroshock in the passive avoidance task in rats, as well as memory loss by scopolamine and diazepam in the spontaneous alternation test in mice.²² It also facilitated memory consolidation in the passive avoidance model in rats.²³ These results in animal studies indicate that milacemide may have beneficial effects on cognition. They are consistent with the hypothesis that milacemide exerts stimulatory effects through the newly discovered supraspinal glycine receptors associated allosterically with NMDA-receptors.²⁴⁻²⁶ Glycine does not readily cross the blood-brain barrier, but milacemide does and is then metabolized to glycina-mide and glycine.²⁷ Because this biotransformation results in a marked increase in glycine concentration in the central nervous system, milacemide may be considered a prodrug for glycine. Thus, milacemide was identified as one of the first drugs modulating these supraspinal glycine receptors positively, with the consequence of offering benefit in the treatment of memory impairment and, possibly, learning deficiencies. Because of these properties, it seemed justified to objectively evaluate the efficacy and safety of milacemide in the treatment of the cognitive and memory disorders that occur in patients suffering from SDAT.

Methods

Men and women, aged 50 years or older, with Alzheimer's disease were enrolled into the study at 10 sites. The presence of SDAT was determined by clinical evaluation supported by NINCDS criteria, a Mini-Mental State Examination score between 10 and 27, a Dementia Rating Scale score less than 20, a Global Deterioration Scale score of 3 to 5, a Hachinski Cerebral Ischemia Scale score of 4 or less, and a history of progressive worsening of memory and other cognitive functions documented for at least 1 year before enrollment. A computed tomographic or magnetic resonance imaging scan within 1 year of enrollment must have been compatible with a diagnosis of SDAT. Patients were excluded if they had evidence of cerebral ischemia or other brain disorders; neurologic, substance abuse, or psychiatric disorders (other than SDAT); or significant cardiovascular, thyroid, hepatic, renal, pulmonary, gastrointestinal, or other clinically significant medical conditions as determined by physical examination, electrocardiogram, and laboratory tests (including triiodothyronine, thyroxine, folic acid, and vitamin B₁₂ determinations). Patients who had

participated in an investigational drug trial within the last 30 days before entering this study were also excluded. Concomitant psychoactive medication was prohibited unless prescribed by the physician or investigator on a prn basis. Calcium channel blockers, angiotensin-converting enzyme inhibitors, β -blockers, and anticholinergic drugs were also prohibited.

Study Design

This was a multicenter, randomized, double-blind, parallel group, dose-response study of milacemide in patients with SDAT. After screening determination of eligibility, patients received milacemide in single oral doses of 400, 800, or 1200 mg/day or matching placebo for 4 weeks during the double-blind treatment period, which was followed by a 4-week placebo washout period. All patients (or their family member or legal guardian) provided oral and written signed consent.

Efficacy was assessed by the subject's performance using the Alzheimer's Disease Assessment Scale (ADAS),²⁸ the Clinical Global Impression Scale (CGI), the Patient Global Improvement Rating,²⁹ the Physical Self-Maintenance Scale, and the Instrumental Activities of Daily Living Scale (IADL).³⁰ Efficacy measures were evaluated at the screening visit (visit 1) and biweekly during the double-blind period (at visits 3 and 5) and during the placebo washout period (at visits 7 and 9). A 17-item Hamilton Depression Scale was administered at baseline and at the end of the double-blind drug administration period to rule out any major depressive state. Safety measures, including electrocardiogram, hematology and biochemistry screens, and urinalysis were performed weekly.

Statistical Methods

Treatment groups were compared with respect to age by a two-way analysis of variance (ANOVA) using study site and treatment group as factors in the model. A power calculation yielded sample groups of 30 patients (total 120) based on a standard deviation of 15 and a 5-point drop in the ADAS from baseline with an α of .05 and power slightly greater than .90. Treatment groups were compared with respect to sex and race using the Cochran-Mantel-Haenszel test. At the screening visit, eligibility for enrollment in the study was assessed with the Mini-Mental State Examination, the Dementia Rating Scale, the Global Deterioration Scale, and the Hachinski Cerebral Ischemia Scale. Treatment groups were compared with respect to total scores on these scales by

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.