

CNS SPECTRUMS[®]

THE INTERNATIONAL JOURNAL OF NEUROPSYCHIATRIC MEDICINE

EXPERT PANEL SUPPLEMENT

MITOCHONDRIA: AN EMERGING THERAPEUTIC FOCUS IN ALZHEIMER'S DISEASE THERAPY

AUTHORS

Stephen Salloway, MD, MS
P. Hemachandra Reddy, PhD
Rachelle S. Doody, MD, PhD

CME COURSE DIRECTOR

James C.-Y. Chou, MD

ABSTRACT

Currently, >5 million people in the United States have been diagnosed with Alzheimer's disease, with projected disease growth shown to be significant throughout the world. There is much interest in adding to the current symptomatic therapies with medications that slow the progression of the underlying disease process, including focusing on mitochondrial abnormalities are involved in aging and in age-related neurodegenerative disease. Mitochondria are cytoplasmic organelles responsible for life and death. Extensive evidence from animal and clinical studies suggests that mitochondria play a critical role in aging, cancer, diabetes, and neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and Huntington's disease. Investigators have begun focusing research efforts on developing therapies targeted to the mitochondria, such as molecules that protect mitochondria and neurons from the toxicity aging and mutant proteins.

In this Expert Panel Supplement, Stephen Salloway, MD, MS, reviews the history of Alzheimer's disease as well as current treatments, including medication mechanisms of action; P. Hemachandra Reddy, PhD, discusses research that has elucidated features of mitochondria which are associated with cellular dysfunction in aging and neurodegenerative diseases, mitochondrial abnormalities, and potential mitochondrial therapeutics in Alzheimer's disease; and Rachelle S. Doody, MD, PhD, reviews data regarding the effects of prospective treatment, dimebon, on patients with mild-to-moderate Alzheimer's disease and its unique mechanism of action.



This activity is jointly sponsored by the Mount Sinai School of Medicine and MBL Communications, Inc.

Copyright ©2009 MBL Communications, Inc. 333 Hudson Street, 7th floor, New York, NY 10013. Printed in the USA.

All rights reserved, including the right of reproduction, in whole or in part, in any form.

MBL
communications

Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Mount Sinai School of Medicine and MBL Communications, Inc. The Mount Sinai School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.



MOUNT SINAI
SCHOOL OF
MEDICINE

Credit Designation

The Mount Sinai School of Medicine designates this educational activity for a maximum of 2 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Faculty Disclosure Policy Statement

It is the policy of the Mount Sinai School of Medicine to ensure objectivity, balance, independence, transparency, and scientific rigor in all CME-sponsored educational activities. All faculty participating in the planning or implementation of a sponsored activity are expected to disclose to the audience any relevant financial relationships and to assist in resolving any conflict of interest that may arise from the relationship. Presenters must also make a meaningful disclosure to the audience of their discussions of unlabeled or unapproved drugs or devices. This information will be available as part of the course material.

Statement of Need and Purpose

Alzheimer's disease is a progressive brain disorder that affects cognitive, behavioral, and functional abilities. Patients progress from mild cognitive impairment to death in a span of 10 years. No currently available treatment has proven effective in stopping the deterioration of brain cells in Alzheimer's disease. While much research continues to focus on the amyloid hypothesis of disease generation, as investigators gain insight into the underlying biology of Alzheimer's disease, new theories and therapeutic targets have emerged. Although the currently-approved treatments for Alzheimer's disease have demonstrated modest effects on cognition, activities of daily living, and global measures of functioning versus placebo, they only temporarily stabilize or slow the progression of deterioration. None of these agents result in sustained improvement in a patient's condition.

Mitochondria represent an emerging therapeutic focus. Mounting evidence suggests that these key cell components—responsible for generating cellular energy, regulating intracellular calcium levels and oxidative changes, and regulating cell death—play an important role in aging and neurodegenerative diseases. Neurons appear to be particularly sensitive to mitochondrial dysfunction, which researchers believe to be an early event in the course of neurodegenerative diseases such as Alzheimer's. Medicines which target the mitochondria are currently being investigated for their possible clinical utility in Alzheimer's disease treatment.

Learning Objectives

At the completion of this activity, participants should be better able to:

- Review current treatments for Alzheimer's disease and their mechanisms of action
- Outline the suggested role of mitochondria in aging and neurodegenerative diseases, particularly Alzheimer's disease

- Discuss recent evidence regarding the efficacy of an agent targeting the mitochondria in the treatment of Alzheimer's disease

Target Audience

This activity is designed to meet the educational needs of neurologists.

Faculty Affiliations and Disclosures

Stephen Salloway, MD, MS, is director of neurology and the Memory and Aging Program at Butler Hospital, and professor of clinical neurosciences and psychiatry at the Warren Alpert Medical School of Brown University, both in Providence. Dr. Salloway is a consultant to Athena, Bristol-Myers Squibb, Eisai, Elan, Medivation, Merck, Myriad, and sanofi-aventis; is on the advisory board's of Bristol-Myers Squibb, Eisai, and Pfizer; has received research support from Bristol-Myers Squibb, Eisai, Elan, GlaxoSmithKline, Forest, Myriad, Pfizer, and Wyeth; and has received honoraria from Athena, Eisai, Elan, Forest, Novartis, and Pfizer. Dr. Salloway discusses unapproved/investigational treatments for Alzheimer's disease.

P. Hemachandra Reddy, PhD, is a scientist in the Division of Neuroscience at the Oregon National Primate Research Center in Beaverton. Dr. Reddy reports no affiliation with or financial interest in any organization that may pose a conflict of interest. Dr. Reddy discusses unapproved/experimental uses of dimebon in the treatment of Alzheimer's disease.

Rachelle S. Doody, MD, PhD, is Effie Marie Cain Chair in Alzheimer's Disease Research and director of the Alzheimer's Disease and Memory Disorders Center at the Baylor College of Medicine in Houston, Texas. Dr. Doody is a consultant to, is on the advisory board of, and owns stock options in Medivation. Dr. Doody discusses unapproved/experimental uses of dimebon in the treatment of Alzheimer's disease.

CME Course Director **James C.-Y. Chou, MD**, is associate professor of psychiatry at Mount Sinai School of Medicine. Dr. Chou has received honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, and Pfizer.

Samuel Gandy, MD, PhD, is professor of psychiatry at Mount Sinai School of Medicine. Dr. Gandy is a consultant to Amicus and Diagenic, is on the Data and Safety Monitoring Board of Wyeth, and receives research support from Forest.

Activity Review Information

The activity content has been peer-reviewed and approved by Samuel Gandy, MD, PhD.

Review Date: August 1, 2009.

Acknowledgment of Commercial Support

Funding for this activity has been provided by an educational grant from Medivation and Pfizer Inc.

To Receive Credit for this Activity

Read this Expert Panel Supplement, reflect on the information presented, and complete the CME posttest and evaluation on pages 19 and 20. To obtain credit, you should score 70% or better. Early submission of this posttest is encouraged. Please submit this posttest by August 1, 2011 to be eligible for credit.

Release date: August 31, 2009

Termination date: August 31, 2011

The estimated time to complete this activity is 2 hours.

EDITORS

EDITOR IN CHIEF

Andrew A. Nierenberg, MD
Harvard Medical School
Boston, MA

FOUNDING EDITOR

Eric Hollander, MD
Institute of Clinical Neuroscience
New York, NY

INTERNATIONAL EDITOR

Joseph Zohar, MD
Chaim Sheba Medical Center
Tel-Hashomer, Israel

ASSOCIATE INTERNATIONAL EDITORS

EUROPE

Donatella Marazziti, MD
University of Pisa
Pisa, Italy

MID-ATLANTIC

Dan J. Stein, MD, PhD
University of Cape Town
Cape Town, South Africa

ASIA

Shigeto Yamawaki, MD, PhD
Hiroshima University School
of Medicine
Hiroshima, Japan

FIELD EDITOR

Michael Trimble, MD, FRCP, FRPsych

COLUMNISTS

Uriel Halbrich, MD
Sarah H. Lisanby, MD
Stefano Pailanti, MD, PhD
Thomas E. Schlaepfer, MD
Stephen M. Stahl, MD, PhD
Dan J. Stein, MD, PhD

SUPPLEMENT EDITOR

Joseph Zohar, MD

CME COURSE DIRECTOR

James C.-Y. Chou, MD
Mount Sinai School of Medicine
New York, NY

PUBLICATION STAFF

CEO & PUBLISHER

Darren L. Brodeur

VP, MANAGING EDITOR

Christopher Naccari

VP, HUMAN RESOURCES

Kimberly A. Brodeur

GLOBAL ACCOUNT MANAGER

Kelly Notine

SENIOR PROJECT EDITOR

Deborah Hughes Levy

SENIOR EDITOR-PRIMARY PSYCHIATRY

Dena Croog

EDITOR-CNS SPECTRUMS

Virginia Jackson

EDITORIAL ADVISORY BOARD

Lenard Adler, MD
New York University Medical School
New York, NY

Dennis S. Charney, MD
Mount Sinai School of Medicine
New York, NY

Jeffrey L. Cummings, MD
University of California, Los Angeles
Los Angeles, CA

Thilo Deckersbach, PhD
Harvard Medical School
Boston, MA

John Geddes, MD, FRCPsych
University of Oxford
Oxford, United Kingdom

Mark S. George, MD
Medical University of South Carolina
Charleston, SC

Daphne Holt, MD
Massachusetts General Hospital
Charlestown, MA

Andres M. Kanner, MD
Rush University
Chicago, IL

Siegfried Kasper, MD
University of Vienna
Vienna, Austria

Yves Lecrubier, MD
Hôpital de la Salpêtrière
Paris, France

Sarah H. Lisanby, MD
Columbia University
New York, NY

Herbert Y. Meltzer, MD
Vanderbilt University Medical Center
Nashville, TN

Mario F. Mendez, MD
University of California, Los Angeles
Los Angeles, CA

Philip Mitchell, MB BS, MD, FRANZCP, FRCPsych
University of New South Wales
Sydney, Australia

Stuart A. Montgomery, MD
St. Mary's Hospital Medical School
London, United Kingdom

Humberto Nicolini, MD, PhD
National Mexican Institute of Psychiatry
Mexico City, Mexico

Stefano Pallanti, MD, PhD
University of Florence
Florence, Italy

Katharine Phillips, MD
Brown Medical School
Providence, RI

Diego A. Pizzagalli, PhD
Harvard University
Boston, MA

Mark H. Pollack, MD
Massachusetts General Hospital
Charlestown, MA

Mark Rapaport, MD
University of California, Los Angeles
Los Angeles, CA

Scott L. Rauch, MD
Massachusetts General Hospital
Charlestown, MA

Peter P. Roy-Byrne, MD
University of Washington School of Medicine
Seattle, WA

Gerard Sanacora, MD
Yale University
New Haven, CT

Alan F. Schatzberg, MD
Stanford University School of Medicine
Stanford, CA

Thomas E. Schlaepfer, MD
University of Bonn
Bonn, Germany

Jordan W. Smoller, MD, ScD
Massachusetts General Hospital
Charlestown, MA

Stephen M. Stahl, MD, PhD
University of California, San Diego
La Jolla, CA

Stephen Strakowski, MD
University of Cincinnati
Cincinnati, OH

Scott Stroup, MD, MPH
University of North Carolina, Chapel Hill
Chapel Hill, NC

Norman Sussman, MD
New York University Medical School
New York, NY

Pierre N. Tariot, MD
University of Arizona
Phoenix, AZ

Michael E. Thase, MD
University of Pennsylvania School of Medicine
Philadelphia, PA

Michael Trimble, MD, FRCP, FRPsych
National Hospital for Neurology and Neurosurgery
London, United Kingdom

Madhukar H. Trivedi, MD
University of Texas Southwestern Medical Center
Dallas, TX

Karen Dineen Wagner, MD, PhD
The University of Texas Medical Branch
Galveston, TX

Herman G.M. Westenberg, MD
University Hospital Utrecht
Utrecht, The Netherlands

Carlos A. Zarate, Jr., MD
National Institute of Mental Health
Bethesda, MD

GRAPHIC DESIGNER

Michael J. Vodilko

CHIEF FINANCIAL OFFICER

John Spano

ACCOUNTING INTERN

Stephanie Spano

SALES & EVENT COORDINATOR

Kimberly Schneider

INFORMATION TECHNOLOGY

Clint Bagwell Consulting

CORPORATION COUNSEL

Lawrence Ross, Esq.
Bressler, Amery, and Ross

CNS Spectrums (ISSN 1092-8529) is published monthly by MBL Communications, Inc., 333 Hudson Street, 7th Floor, New York, NY 10013.

SUBSCRIBERS: Send address changes to *CNS Spectrums*, 333 Hudson Street, 7th Floor, New York, NY 10013.

Opinions and views expressed by authors are their own and do not necessarily reflect the views of the publisher, MBL Communications, Inc., *CNS Spectrums*, LLC, or the editorial advisory board.

Copyright © 2009 by MBL Communications, Inc. All rights reserved. Printed in the United States.