Missouri Medicine
The Journal of the Missouri State Medical Association www.msma.org September/October 2013

Getting Comfortable With Death



& Near-Death Experiences

also

Knight ADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

Give them focus.

Give to the Missouri State Medical Foundation.



Helping students focus on their medical education for over 50 years, the Missouri State Medical Foundation has benefitted hundreds of medical students statewide. We thank the many donors who have committed their energy and resources to fulfilling the Foundation's mission, and we are grateful for their generosity.

The Foundation has loaned more than $11 million to Missouri medical school students since its inception in 1960.

Partnerships with the MSMA, the Alliance, component medical societies, and schools of medicine help the Foundation strengthen the patient-physician relationship through its scholarships and health initiatives.

The Missouri State Medical Foundation is a 501(c)3 non profit.

For over ten years, the MSMA Scholarship Program has been funded by the Foundation for students at each of Missouri's four allopathic schools.

Scholarship programs receiving matching funds from the Foundation include Boone County Medical Society, Cole County Medical Society, Metropolitan Medical Society of Greater Kansas City, Northeast Missouri Medical Society, Northwest Missouri Medical Society, Quad Counties Medical Society, Saint Charles-Lincoln County Medical Society, and the MSMA Alliance.

Funds also are awarded to local Alliances to support health programs for the betterment of Missouri communities.

Donations may be sent to
Missouri State Medical Foundation
P.O. Box 1028 - Jefferson City, MO 65102
Contact Pat Mills at 800-869-6762.

Missouri Medicine

The Journal of the Missouri State Medical Association - Since 1904

Volume 110 | Number 5 | September/October 2013 www.msma.org/MissouriMedicine



Knight ADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

Editor's Desk

Medical Metaphysics: What is a Good Death?
What Happens When We Almost Die
by **John C. Hagan, III, MD** 364

Feature Perspectives

Near-Death Experiences:
An Essay in Medicine & Philosophy
by Raymond A. Moody, MD, PhD 368

How Doctors Die: A Model for Everyone?
by Ken Murray, MD 372

PERSPECTIVE

Non-Assigned Medicare Payment Increases Practice Revenue
& Lowers Medicare Costs
by **Patrick K. Price, MD** 376

PRESIDENT'S FORUM

Accountable Care Organizations: Are We Even at the Table?
by **James B. Wolfe, MD** 382



AS I SEE IT

Are We Too Fat? Or Are We Not Fat Enough?
by **Charles W. Van Way, III, MD** 384

DEANS REPORT

Washington University in St. Louis
School of Medicine

Washington University: Transforming ‘
the Future of Medicine
by **Larry Shapiro, MD** 389

SCIENCE OF MEDICINE

Neurodegenerative Disorders of Aging:
The Down Side of Rising Longevity
by **John C. Morris, MD** 393

Alzheimer Disease:
Current Concepts & Future Directions
by Erik S. Musiek, MD, PhD & Suzanne E. Schindler, MD, PhD 395

Advances in Diagnostic Testing for Alzheimer Disease
by Suzanne E. Schindler, MD, PhD, Jonathan
McConathy, MD, PhD, Beau M. Ances, MD, PhD
& Marc I. Diamond, MD 401

Parkinson Disease in the Elderly Adult
by Allison W. Willis, MD, MSCI 406

Unravelling the Mysteries of Frontotemporal Dementia
by Nupur Ghoshal, MD, PhD & Nigel J. Cairns, PhD 411

Management of Amyotrophic Lateral Sclerosis
by Taha Bali, MD & Timothy M. Miller, MD, PhD 417

Diagnosis and Evaluation of a Patient with Rapidly Progressive Dementia
by Robert C. Bucelli MD, PhD & Beau M. Ances MD, PhD 423

A Case for Neuroprotection in Ophthalmology:
Developments in Translational Research
by Andrew J. Payne, PhD, Simon Kaja, PhD,
Nelson R. Sabates, MD & Peter Koulen, MD 429

FROM YOUR ASSOCIATION

1 Picture = 1,000 Words 386
In the News 386
Statement of Ownership 387

MSMA member names in bold

MSMA
Missouri State Medical Association

113 Madison Street ◆ P.O. Box 1028 ◆ Jefferson City, MO 65102
800-869-6762 ◆ Fax: 573-636-8552 ◆ www.msma.org/MissouriMedicine
Editor: John C. Hagan, III, MD ◆ jhagan@bizkc.rr.com
Managing Editor: Lizabeth R. S. Fleenor ◆ lfleenor@msma.org

About Missouri Medicine

About Missouri Medicine

In publication since 1904, Missouri Medicine, a peer-reviewed, award-winning* medical journal printed on acid-free paper, is indexed by MEDLINE, the National Library of Medicine, and is linked to PubMed Central, which is the U.S. National Institutes of Health digital archive of biomedical and life sciences journal literature. Missouri Medicine can be found on EBSCOhost databases, which provides researchers with the ability to search full-text articles, and are the most-used, premium online information resources for tens of thousands of institutions worldwide, representing millions of end-users. Missouri Medicine also provides featured content for www.medhelp.org, a top world health care website and the MedHelp.org e-newsletter, which has a quarter million subscribers.

** Ranly Award for Journalism Excellence, established in 2007 by the Missouri Association of Publications: 2007, 2008, 2009, 2011.*

Scan code with your mobile device to read more on how to submit an article for *Missouri Medicine.*

How to Contribute to Missouri Medicine

The Editors want to hear from you. For "Instructions for Authors/Style Sheet," download from www.msma.org/MissouriMedicine.

Letters to the Editor or General Comments

Send an email to jhagan@bizkc.rr.com and copy lfleenor@msma.org. Letters to the editor for publication should be 300 words in length or shorter and should include your full name, specialty and association. Letters are edited for length and clarity.

In the News

To submit yourself or a colleague for a mention, send an email to lfleenor@msma.org. Include information on the significant event, promotion or award. Note that we only include Association members in this column.

Perspectives & As I See It

Missouri Medicine publishes *Perspectives* on a variety of medical trends, topics and policy matters including legal, legislation, advocacy, insurance, practice management, and public health issues. *As I See It* is a forum for opinion pieces, whimsy, humor, irony, and reflection on the practice of medicine. All pieces should be referenced and not exceed 1,500 words.

Scientific Submissions

Scientific articles are peer-reviewed and original articles are accepted for publication on the condition that they have not been published or submitted to other medical journals. MSMA members are given publishing preference and priority. Material appearing in *Missouri Medicine* is protected by copyright. Authors should e-mail copies of the complete article, contact information, references, tables, illustrations, photos to both jhagan@bizkc.rr.com and lfleenor@msma.org. Notification of receipt of your manuscript is within 10 days. Peer review is completed within 30-45 days of receipt. Refer to the American Medical Association Manual of Style, 9th Ed., AMA, Chicago, 1998, to answer questions regarding style or visit www.msma.org/MissouriMedicine for the "Instructions for Authors/Style Sheet."

Reprints

Reprints of the article may be purchased. Single, entire issues may be purchased, if available. Email lfleenor@msma.org or visit www.msma.org/MissouriMedicine for the Reprint Order Form.

Advertising

For reader and demographic profiles, statistics, and advertising rate sheet and contract, download from www.msma.org/MissouriMedicine or email lfleenor@msma.org.

Disclaimer

All articles, editorials, and letters published represent the opinions of the authors and do not reflect the official policy of the MSMA or the institution with which the author is affiliated unless clearly specified.

Copyright & Postal Entry

Owned and published since 1904 by the Missouri State Medical Association. Missouri Medicine, the Journal of the Missouri State Medical Association [ISSN 0026-6620], is published bi-monthly at 113 Madison Street, Jefferson City, Missouri 65102. Periodicals postage paid at Jefferson City, Missouri and at additional mailing offices. Postmaster: Send address changes to Missouri State Medical Association, c/o Membership Dept., P.O. Box 1028, Jefferson City, MO 65102. Copyright 2013 by the Missouri State Medical Association. Printed by the Ovid Bell Press, Inc., Fulton, Missouri. The subscription price per year for non-members is $75.00. Annual subscription for members is included in the annual membership dues. Single copies are $12.00 and the per copy cost of the annual August Directory is $50.00.

Missouri Medicine Editorial Board

Owner & Publisher

Missouri State Medical Association

Missouri Medicine Editor*

John C. Hagan, III, MD
9401 North Oak Trafficway, Ste. 200
Kansas City, MO 64155
Tel: 816-478-1230 / Fax: 816-454-8478
jhagan@bizkc.rr.com

Managing Editor

Lizabeth R. S. Fleenor
Missouri State Medical Association
113 Madison Street / P.O. Box 1028
Jefferson City, MO 65102
800-869-6762 / Fax: 573-636-8552
lfleenor@msma.org / www.msma.org

Contributing Editors*

Milamari A. Cunningham, MD
David A. Fleming, MD
Arthur H. Gale, MD
William R. Reynolds, DDS, MD
Charles W. Van Way, III, MD

Editorial Board

Justin M. Albani, MD, Urology
Mitchell D. Botney MD, Pulmonary Medicine
Susan H. Brown, MD, Nephrology
Nancy J. Bunge, MD, Pediatrics
Edmond B. Cabbabe, MD, Plastic Surgery
Octavio R. Chirino, MD, OB/Gyn
Joseph A. Corrado, MD, General Surgery
David H. Cort, MD, Gastroenterology
Juan C. Corvalan, MD, Psychiatry
John S. Daniels, MD, Internal Medicine
Louis P. Dehner, MD, Pathology
Chitra Dinakar, MD, Allergy & Immunology
Jon A. Dyer, MD, Dermatology
John F. Eisenbeis, MD, Otolaryngology
Eden M. Esguerra, MD, Infectious Disease
Lancer Gates, DO, Hospital Medicine
James J. Gibbons, MD, Anesthesiology
Gary S. Gottesman, MD, Medical Genetics
Pamela Honeycutt, MD, Oncology & Hematology
Roger P. Jackson, MD, Orthopedic Surgery
Jerry D. Kennett, MD, Cardiology
Charles M. Lederer, MD, Ophthalmology
Eric D. Lederman, MD, Colon & Rectal Surgery
Brian L. Mahaffey, MD, Sports Medicine
Michael C. Murphy, MD, Cardiac Surgery
W. Kirt Nichols, MD, Vascular Surgery
John H. Niemeyer, MD, Radiology
James H. O'Keefe, MD, Preventive Medicine
John A. Pardalos, MD, Neonatology
Keith M. Rich, MD, Neurosurgery
Ann M. Romaker, MD, Sleep Medicine
Howard M. Rosen, MD, Endocrinology
Marilyn M. Rymer, MD, Neurology
Mark T. Steele, MD, Emergency Medicine
Harold A. Williamson, MD, Family Practice
Anne E. Winkler, MD, Rheumatology
Gregory M. Worsowicz, MD, Physical Med & Rehab

Editors Emeritus

Jordan W. Burkey, MD, 1982-1988
Donald G. Sessions, MD, 1988-1992
J. Regan Thomas, MD, 1992-2000

*Publications Committee

Medical & Service Bureau Contact Information

MSMA Insurance Agency, Inc.
www.msma.biz
866-676-2467

American Medical Association
www.ama-assn.org
312-464-5000

MO Association of Osteopathic Physicians & Surgeons
www.maops.org
573-634-3415

Board of Registration
www.pr.mo.gov/healingarts.asp
573-751-0098

Bureau of Narcotics & Dangerous Drugs
www.dhss.mo.gov/BNDD
573-751-6321

CCPA Purchasing Partners, L.P.
773-868-8008
www.childrensmemorial.org/ccpa

Dept of Health & Senior Services
www.dhss.mo.gov
573-751-6400

Missouri Drug Card
www.msma.org/missouridrugcard
800-869-6762

MO HealthNet
www.dss.mo.gov/mhd
573-751-3425

MO Hospital Association
web.mhanet.com
573-893-3700

Dept of Insurance
www.insurance.mo.gov
573-751-4126

Centers for Medicare & Medicaid
www.cms.hhs.gov
816-426-5033

National Medicare Helpline
800-633-4227

Medicare Part B/MO Medicare
www.momedicare.com
866-736-0799

CLAIM Helpline
800-390-3330

Provider Hotline
800-735-6776

Physicians Health Program
800-274-0933

Primaris
www.primaris.org
800-735-6776

MO Center for Patient Safety
www.mocps.org
573-636-1014

Dept of Social Services
www.dss.mo.gov
573-751-2086

Oakstone Online CME
800-952-0690
www.oakstonepublishing.com

DocbookMD
www.docbookmd.com

Epocrates - Mobile Software
www.epocrates.com

GoNext - Travel
www.gonext.com

Resolve Physician Agency
www.resolvephysicianagency.com
877-758-3318

I.C. System, Inc. Collection Service
800-279-3511

Moneta Financial & Retirement Planning
800-833-1301

Part B News Group Publication Subscriptions
877-397-1496

TaxResource Tax Audit Service
800-922-8348

Go to www.msma.org for details and descriptions of Membership Services or call 800-869-6762.

MSMA Office & Staff Contact Information

113 Madison Street / P.O. Box 1028
Jefferson City, MO 65102
573-636-5151 / 800-869-6762 / Fax 573-636-**8552**
www.msma.org

Executive Vice President: Tom Holloway	Tel Ext - 123	tholloway@msma.org
Field Services: Fred Brown	Tel Ext - 130	fbrown@msma.org
Communications: Lizabeth Fleenor	Tel Ext - 134	lfleenor@msma.org
Govt Relations/Legal: Jeff Howell	Tel Ext - 128	jhowell@msma.org
Legislative Affairs: Kenny Jackson	Tel Ext - 122	kjackson@msma.org
Health Care Finance: Patrick Mills	Tel Ext - 126	pmills@msma.org
Scientific Affairs: Benita Stennis	Tel Ext - 138	bstennis@msma.org
Membership: Haley Wansing	Tel Ext - 135	hwansing@msma.org
Office: Linda Bremer	Tel Ext - 121	lbremer@msma.org
Membership Database: Lois Chronister	Tel Ext - 127	lois@msma.org
Reception: Fran Draper	Tel Ext - 120	fran@msma.org
Finance: Brenda Kinney	Tel Ext - 133	bkinney@msma.org
Administrative: Carol Meyer	Tel Ext - 132	cmeyer@msma.org



by John C. Hagan, III, MD

The Near-Death Experience part of this *Missouri Medicine* series will be the most encyclopedic and up-to-date in the world's literature.



John C. Hagan, III, MD, FACS, is a Kansas City ophthalmologist and *Missouri Medicine* Editor since 2000. *Contact: jhagan@bizkc.rr.com*

July 2, 1954, about 2:30 p.m. near Rush Hill, Missouri, on a brutally hot afternoon, an aircraft flies over a corn field infested with grasshoppers. The pilot of the Piper PA-18A has been aloft most of the day, his alternate pilot is ill. The spray chemical is the highly toxic Aldrin. Shorthanded, the pilot has filled his plane with the noxious poison four times this day without the recommended gloves and mask. Guided by a ground spotter with a flag on a long pole, the bright yellow plane finishes a pass spraying less than three feet about the corn tops. The plane laboriously rises and banks to turn. About 125 feet from the ground, the heavily loaded aircraft stalls and plunges nose first into the earth with a ferocious and fiery explosion. The pilot - my father - John C. Hagan II, age 42, dies instantly. (See photo, next page.)

Thus was death suddenly, brutally, irrevocably visited upon our unsuspecting and unprepared family. The consequences of that sudden death, almost 60 years ago, resonate to this day. My mother, then age 37, my brother 5, my sister 8, and me, age 10, were left widowed and fatherless. Physicians and the general public knew little then about the pathophysiology of grief and grief recovery. There were no effective anti-anxiety or anti-depression medications. Psychiatric care was stigmatized and for "crazies and the near crazy"; there were no grief support groups. That generation's answer was to "tough it out."

Already an anxious child, I was told by everyone that came to express their regrets that "you're the man of the family now and you have to be strong and brave." A pretty formidable task for an insecure ten-year old boy that believed only very old people died and his parents would live forever. Another bromide repeatedly thrown at our family was "in time your grief will fade." For my brother and me that was the case; ultimately we decided it would make our father sad to spend our lives raging at the vicissitudes of malevolent fate and the injustice of it all. My mother and sister never got over their grief, depression, and anger. Perhaps with better medical and psychiatric care they would have.

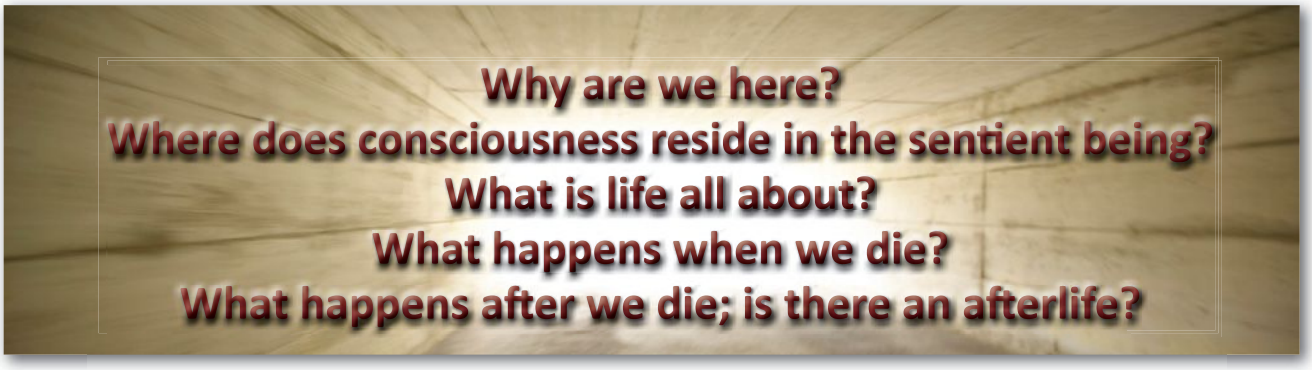
December 24, 2004. Audrain Medical Center, Mexico, Missouri. The patient is an 87-year old retired registered nurse who has long worked in ICU and surgical recovery. She has on many occasions fervently told her family that she does not wish to die hooked to a bevy of life support systems, especially a respirator. She has current advanced directives and limited power of attorney papers. Her quality of life has been good until about two years before this admission when she sustained a stroke. Debility and dependence progressed relentlessly. Now in a nursing home, she has not had a happy day since the stroke. She sustains an acute abdomen. Her surgeon doubts she can make it through abdominal surgery. The physicians and family explain to the patient they think this is a terminal event. If she lives through surgery it's unlikely she'll be able to get off the respirator or survive sepsis from the perforated viscus. The alternative is to give Schedule IV narcotics and keep her pain-free and gently sedated until she dies. She indicates she wishes the surgery. Her family is incredulous. They ask again, "Do you understand you will likely die hooked up to all those machines? You told us you never wanted to do that!" She nods and reaffirms she wants the surgery. She dies several days later, unable to speak and physically uncomfortable due to the respirator. The constant spectators embracing her in death are the medical instruments that she has always called "those damn machines."

Thus did my mother pass, and leave my sister and physician brother orphans.

Did she die a good death? Which course of action should her surgeons and family have followed?



John C. Hagan, II, commercial pilot and charter member of the Missouri Pilots' Association, left a young family of three after a dying suddenly 1953 in a fiery crash while crop spraying in a light plane.



The oft stated wish to withhold extraordinary treatment at end of life? Or the decision of a very elderly woman with her a brain damaged by stroke and likely impaired judgment? Questions like these and the difficult decisions they engender are everyday occurrences for many physicians. *Missouri Medicine* will study them in this series.

Missouri Medicine began to feature theme publications with "End-of-Life Issues" (November/December 2002) and "Care of the Dying Patient" (January/February 2003). The manuscripts came from the University of Missouri School of Medicine and were coordinated by Contributing Editor David Fleming, MD. A widely used medical textbook (see sidebar, next page) was developed from those articles.

Over the coming two years, starting with this issue, we will revisit death and dying and consider what advances have transpired; what challenges and problems remain. My parents' deaths illustrate many of these: how to handle the inevitable physical and psychiatric problems of family and friends after a loved one's sudden death? How do physicians deal with the grief, anxiety, depression, rage, and uncertainties of the patient and family faced with a terminal illness? Thankfully, we have moved past two former problems: whether to tell the patient they are dying and abandoning dying patients' mental, physical, and spiritual needs by sticking them in an out-of-the way hospital room. There to be neglected by their physicians and nursing staff because "They're dying and we can't do anything for them and the other patients need us more." Regrettable actions that must never occur in contemporary medicine.

What constitutes "extraordinary measures" at end-of-life in a patient that wishes to decline futile medical heroics? When is "Do Not Resuscitate" the best possible medical care? What can we do to make the dying patient comfortable, pain-free and not feel isolated? What are our skills and attitudes towards providing care to the dying and dealing with their family and friends? Do we feel death is a failure and repudiation of our physician skills? What are our beliefs and comfort levels with contemplating our own deaths? Kenneth Murray, MD, on page 372 presents the case that physicians may face death with more equanimity and tread a different path than most of our patients at end-of-life. *Missouri Medicine* will update best practices for end-of-life problems and care of the dying patient (and their grieving family) using a distinguished group of internationally acclaimed authors.

And what happens during the act of dying? Our best answer comes from people that almost die but return to life and recall events that occurred while emergency resuscitation, critical care or surgery was performed to snatch life back from the jaws of death. Their recounting often factually refutes our physiological concept of consciousness residing in the functioning brain. As our medical and surgical skills increase, we can bring back sojourner patients who have traveled farther on the path to death than at any other time in history. What is a "near-death experience"? The term was coined by Raymond Moody, MD, in 1975 in his seminal book *Life After Life,* which is a perennial best-seller; over 13 million copies sold to date. Doctor Moody's summation of his peerless life's work appears on page 368.

The Near-Death Experience (NDE) part of this *Missouri Medicine* series will be the most encyclopedic and up-to-date in the world's literature. We used two criteria when recruiting authors: 1) physicians or evidence-based medicine researchers in the field of near death experiences (which includes several prospective studies); 2) physicians who have themselves had a near-death experience. The response to our invitations has been 100% and includes two physicians that now have best-selling books on their NDE, Harvard neurosurgeon Eben

Alexander II, MD, and Jackson, Wyoming, orthopedic surgeon Mary Neal, MD.

We scrupulously avoided recounting of NDEs by non-physicians. Too often these people follow this suspect sequence: report a NDE, write a book on their NDE that purports knowing the meaning of life, the answer to what happens after we die, and confirms that there is a heavenly life after death. Then they start giving seminars, lectures, paid consultations, writing more books, sell DVDs, blogging, and shilling on their website. NDE-related money soon constitutes the bulk of their income. Like the long ago purveyors of ectoplasm, there is a fringe commercial NDE industry whose testimony lacks credibility. We eschew this element. Lastly, we physicians must learn how to appropriately deal with our patients that report a NDE. They are much more common than you think.

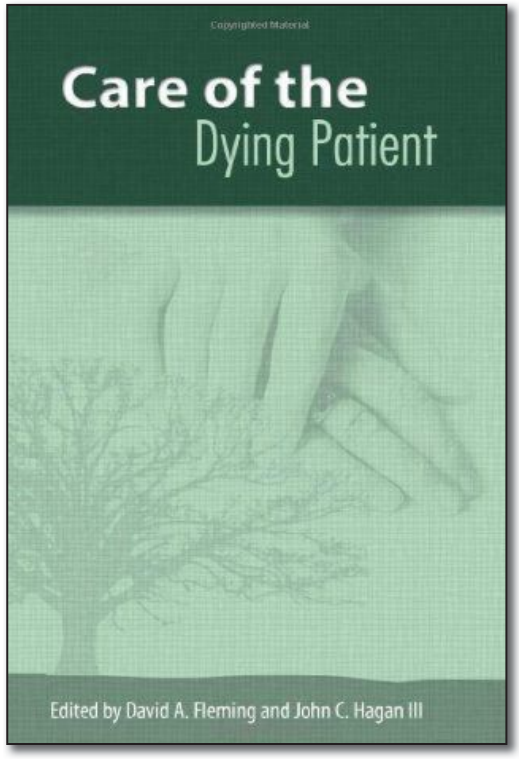
Metaphysics includes the study of cosmology, epistemology, and ontology. There are many metaphysical questions that are encountered in NDE study. NDE reports challenge many of our deep-seated medical beliefs about what happens to the mind and consciousness at the threshold of death. They make us reflect, perhaps with some discomfort, on mankind's oldest and most profound questions: Why are we here? Where does consciousness reside in the sentient being? What is life all about? What happens when we die? And lastly, mortal man's transcendent question that science will never answer but forms the bedrock of religion and spirituality: What happens after we die; is there an afterlife?

It is summer of 1952 in my home town of Mexico, Missouri. The day is as perfect as God has ever made. I am 9 years old and my cousin Jim is almost 11. We are inseparable friends and live only two blocks apart. The halcyon summers of our youth seem to last forever. I assume that Jim, being 18 months older and more experienced, has all the answers. Jim does nothing to disabuse me of this belief.

Playing in a ditch outside my home, on an impulse I ask, "Jimmy, do you think we will ever get old and die?" He thought for a few seconds then said, "Yes, but that day is so far away it will never get here."

Jim died last year at age 69. What was death like Jim? Where are you now? I guess we all just have to wait and find out ourselves. I miss you Jim, part of me died with you. **MM**

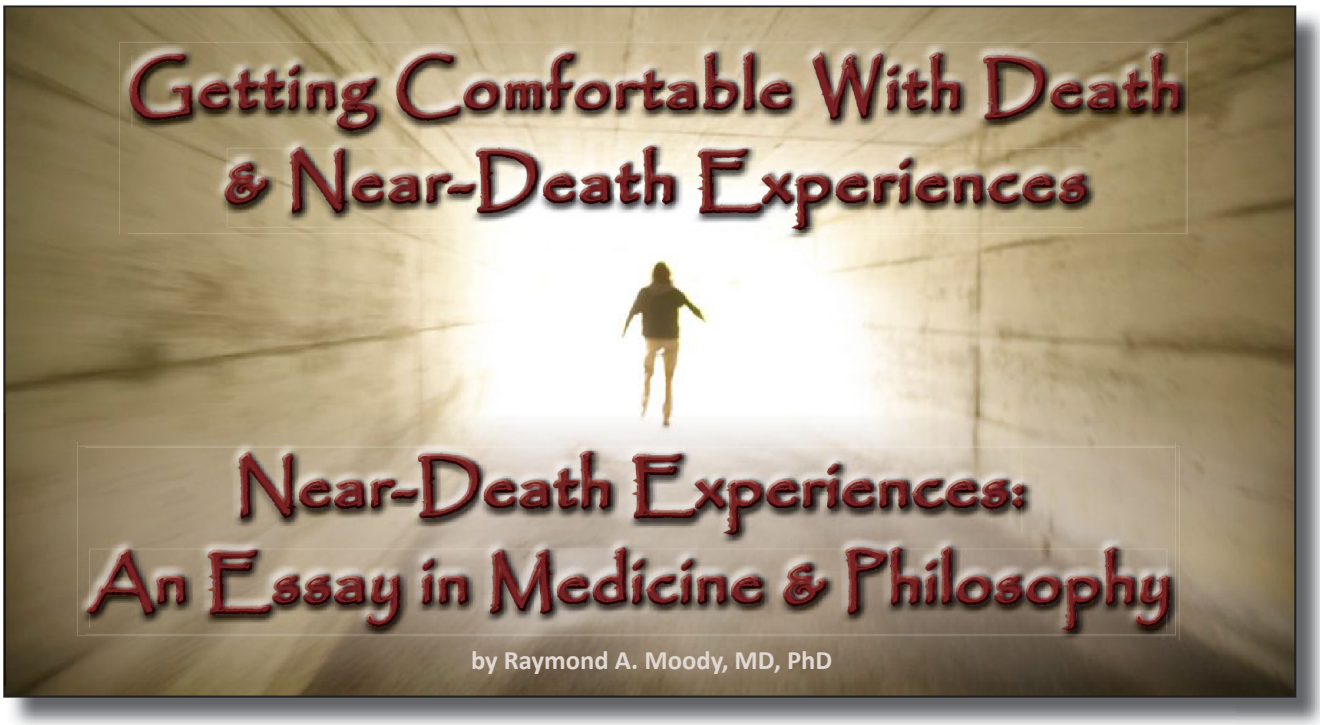
Book Review



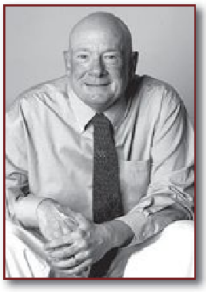
"A fine book that will function as a guide to excellent care of the dying patient. It offers a wealth of accurate medical information, carefully developed rationales for care, and explanations of clinical usefulness."
—Daniel H. Winship, M.D., secretary, Council on Medical Education, American Medical Association

"Care of the Dying Patient will fill an important niche in any physician's library. Well written and extensively referenced."
—Allen B. Weisse, M.D., author of Lessons in Mortality: Doctors and Patients Struggling Together

Paperback: 170 pages
Publisher: University of Missouri; 1 edition (April 15, 2010)
Language: English
ISBN-10: 0826218903
ISBN-13: 978-0826218902



Near-death experiences are an ancient and very common phenomenon that spans from ancient philosophy, religion and healing to the most modern clinical practice of medicine.



Raymond Moody, MD, PhD, is a world-renowned author, lecturer, and psychiatrist whose seminal book, *Life After Life*, completely changed the way death and dying are viewed. He is widely acknowledged as the world's leading expert in the field of near death experience. His books are perennial best sellers and over 20 million have been sold.
Contact: Raymond@LifeAfterLife.com

Modern advances in medical knowledge make it possible to revive patients from increasingly severe, life-threatening injuries and illnesses, including cardiac arrest. Upon being revived, such patients often report experiencing life-changing alternate states of consciousness, which they tend to interpret in spiritual terms. Beginning in 1965, I interviewed several thousand individuals who had near-death experiences when they narrowly survived grave medical crises. I conducted the interviews first as a professor of philosophy and logic, then later as a medical doctor and psychiatrist. This paper is an overview of my research on near-death experiences their historical significance, their characteristics, their sociological dimension and their clinical implications.

History of Near-Death Experiences

Near-death experiences are a perennially fascinating subject that bridges modern medical practice and ancient Greek philosophy. The Greek philosophers Heraclitus, Democritus, and Plato theorized about people known as "revenants" who had supposedly died and came back to life. Heraclitus mused, enigmatically, that the revenant is somehow appointed to watch over the living and the dead. Plato's most famous work, *The Republic*, culminates in the story of Er, a warrior who was apparently killed in battle. At his funeral, however, Er spontaneously revived and told a tale of moving away from his body and entering a complex afterlife world. Plato took stories like Er's seriously as offering some assurance of a life after death.

Democritus, the founder of atomic theory, was also interested in stories of people who had returned from the dead. In his writings, which now survive only in fragments, Democritus tried to explain 'return from the dead stories' in terms of his favorite explanatory principles - atoms and the void.

He noted that there is no such thing as a moment of death. In other words, Democritus held that the experiences of the dying result from the gradual winding down process of the body before death. Clearly people have known about near-death experiences for thousands of years. Such experiences must have been quite rare in antiquity and the medieval periods, since surviving an extreme injury or illness was much more uncommon. Scattered reports exist from those times, but the situation changed dramatically in the late twentieth century.

The last several decades of the twentieth century saw momentous breakthroughs in technology and procedures for cardiopulmonary resuscitation. Widespread use of these new techniques soon dramatically increased the number of people who survived a close brush with death. By the mid-1970s, there were so many individuals who had undergone near-death experiences that the phenomenon was bound to come to the attention of the public. My book, *Life after Life* (1975), an analysis of about 150 cases of near-death experiences was apparently the catalyst that woke the modern world up to this ancient phenomenon.

Since then, numerous physicians and psychologists have interviewed large numbers of patients who recounted near death experiences. These physicians include, for example, cardiologist Michael Sabom, MD, psychiatrist Bruce Greyson, MD, cardiologist Pim Van Lommel, MD, resuscitation specialist Sam Parnia, MD, radiation oncologist Jeffrey Long,MD, psychologist Kenneth Ring, PhD, and others. All these authorities and others have published their findings and a large professional and popular literature on the subject has accumulated. A consensus has emerged among researchers that experiential reports of near-death experiences tend to conform to a discernible, common pattern.

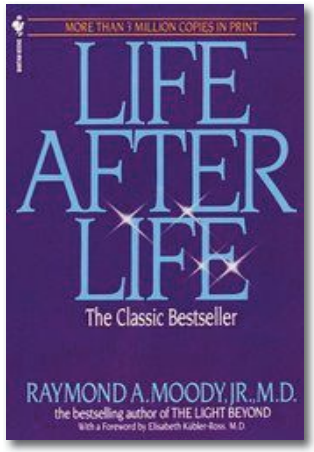
Characteristics of Near-Death Experiences

Survivors of close calls with death usually recount their transcendent experiences in the form of a travel narrative. They tell us that their consciousness leaves their body and rises upward, where they witness the resuscitation procedure going on below. They seem to pass through a dark enclosure they may compare to a brilliant white light. However articulate they may be, they say that the experience is ineffable and indescribable. Words are inadequate. They say that in the bright light they feel comfort, joy, peace and love so intense as to be almost palpable. They say that they perceive the spirits of deceased loved ones, departed relatives, and friends who seem to be there to welcome them. These patients also say that they re-experience in vivid detail the events of their lives in a sort of holographic, full-color panorama. Although it takes only an instant, they report



Socrates Drinking The Conium. Engraved by unknown engraver and published in Pictorial History Of The Worlds Great Nations, United States, 1882.

Book Review



In *Life After Life* Raymond Moody, MD, investigates more than one hundred case studies of people who experienced "clinical death" and were subsequently revived. First published in 1975, this classic exploration of life after death started a revolution in popular attitudes about the afterlife and established Dr. Moody as the world's leading authority in the field of near-death experiences. *Life after Life* forever changed the way we understand both death -- and life -- selling over 13 million copies to a world hungry for a greater understanding of this mysterious phenomenon.

From: Amazon.com
Originally published 1975 republished 2001
175 pages
HarperOne

reviewing the actions of their lives emphatically, from within the consciousness of others with whom they had interacted rather than from their original perspective.

Patients differ as to how they got back. At one moment they were immersed in the light and the next moment they were back in their hospital beds with no sense of a transition. Other patients say that they were told, perhaps by one of their deceased loved ones, that they had to go back; that they had things left to complete. Yet other patients say they were given a choice. They could either stay in the light and continue that experience or return to the life they had been living. Most commonly, these patients say that for themselves they would have preferred to stay in the light, however, they chose to go back for someone else, usually to raise their young children.

Upon returning, these patients remark that their near-death experiences profoundly changed their lives. They say that their experiences convinced them personally that there is an afterlife so they no longer fear death These patients say that whatever they might have been pursuing in their lives before - power, wealth, fame or something else - their experiences convinced them that the most important goal in life is to learn to love. Although they still find that goal as difficult to realize as anyone else, their near-death experiences commit them to pursuing love.

Not everyone who recovers from a near-death event reports a near-death experience Nor does everyone who has a near-death experience report the whole, prototypical series of events. Some recall only a brief out-of-body experience with a view of their own physical body below, followed by a quick return. Others get only as far as the dark passageway, while others proceed all the way into the light. We do not know the reasons for all these variations. Notably, much of what 'common sense' suggests about near-death experiences turns out not to be true.

First, NDEs do not seem to be dreams. Dreams seem less real than ordinary waking reality; NDEs seem hyper-real i.e. "…more real than ordinary waking reality." Patients describe their NDE as almost the antithesis of dreams and deny dream-like qualities.

The occurrence of NDEs does not seem related to patients prior religious training or beliefs. Many people with no prior interest or background in religion report powerful NDEs after surviving grave medical crises. NDEs are not related to specific medical conditions. Patients with infections, trauma, cardiac arrest, complications of childbirth and many other diverse conditions have reported NDEs. There is wide variation in patient ages from the very young to the very old and every age between.

Attempts to explain NDEs in physical or neuro-psychological terms have postulated complex seizures or brain anoxia. One problem with these explanations is that typical NDE phenomena often occur among deathbed bystanders. This is called a "shared death experience. (SDE)" The bystanders are neither ill nor injured. NDE and SDE are not caused by brain hypoxia or atypical seizures.

Shared Death Experiences

Bystanders or onlookers at the death of a patient may include physicians, nurses, other medical personnel, and relatives or friends of the dying. All of these types of bystanders report SDE that are often indistinguishable from near-death experiences. For example bystanders sometimes say they saw a transparent replica of the dying person leave that persons body at the point of death. Or they describe leaving their own bodies and rising up to accompany their dying loved one part way toward the light. Onlookers at someone else's death also sometimes report that a brilliant light filled the room, they heard indescribably beautiful music and/or

they perceived apparitions of the dead person's deceased loved ones. Occasionally, onlookers empathically report that they co-lived the "life review" of the deceased person. (See Editor's note.)

Origins of the Description of Near-Death Experiences

I first heard a shared death experience from one of my professors of medicine in December 1972. Since then, I have heard thousands of such accounts from physicians, nurses, kith and kin attendant at someone's death. I want to re-emphasize that all the same elements of near-death experiences reported by people who almost die are also reported by onlookers at the death of someone else. As incredible as this statement may seem, it is easily confirmable by any thorough investigator who will considerately and sympathetically inquire among people who were present at the death of others. I do not know exactly what the incidence or prevalence of shared death experiences might be but they are common and under-reported.

Near-Death Experiences and Medical Sociology

In the late 1970s, dissemination of knowledge about near-death experiences, both in mass media and in the medical literature, caused a worldwide sensation. Books about NDEs sparked theological debates and speculation about the prospect of life after death. Popular movies and television talk shows enthusiastically took up the banner of near-death experiences. Almost forty years later, near-death experiences are still vigorously debated in every corner of the earth. Numerous physicians have investigated the phenomenon and have been deeply impressed with patients' accounts of their near-death experiences. The topic remains a staple of television documentaries and newspaper and magazine articles.

This continuing fascination with near-death experiences has profound implications for the sociology of medicine. Advances in resuscitation techniques return to life a large number of people experiencing profound states of visionary consciousness at the very edge of absolute death. This is a prime example of how the progress of medicine can affect society in far-reaching and unanticipated ways.

Inevitably near death experience reports have fueled debate on the possibility of life after death. There are no known rational or logical principles that allow reliable inferences about the prospect of an afterlife. Research into near-death experiences that is not rigorously rational may blur the line between medicine and religion. The best practice for physicians is to stick strictly to clinical and research concerns.

Clinical Implications of Near-Death Experiences

What should a physician do when a patient recovers from an almost fatal illness or injury and reports a near-death experience? From talking with thousands of such patients, I find most simply want someone to listen to them noncommittally. They want to talk about what happened to them and to ventilate the powerful emotions and memories associated with their near-death experience. After listening, it also helps to reassure the patient that he or she is not alone, that millions of other individuals have had such experiences. Listening and reassuring them helps set them on a lifelong course of integrating what for most is their most profound transcendent event.

Intervening with their families can often save such patients considerable unnecessary discomfort and interpersonal conflicts. The family should know that the patient is not mentally ill nor are NDEs rare. Patients with near-death experiences are generally convinced from the outset that the experience was real and that they are not 'crazy'. They often worry that other people will make fun of them or doubt their sanity.

Summary

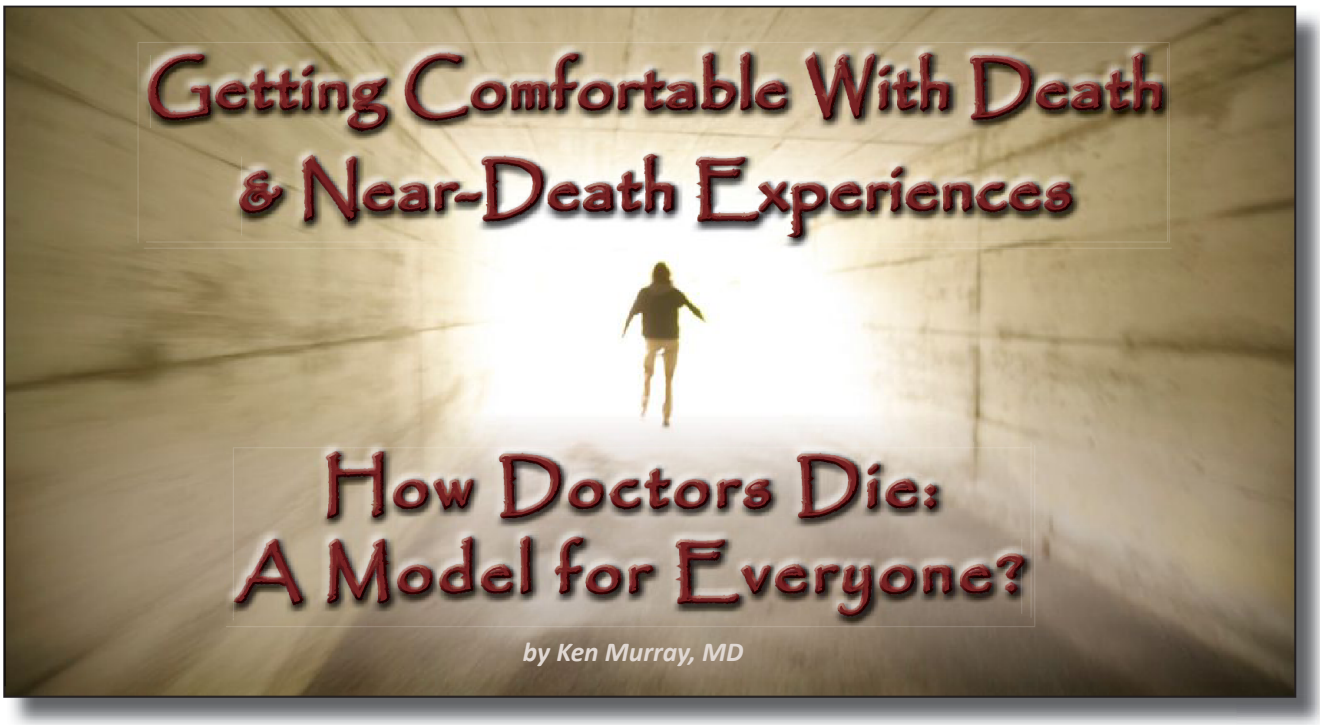
Near-death experiences are an ancient and very common phenomenon that spans from ancient philosophy, religion and healing to the most modern clinical practice of medicine. Probably we are not much closer to an ultimate explanation of NDEs than were early thinkers like Plato and Democritus. Puzzling cases of near-death experiences continue to come to light and the ancient debate about what they mean continues unabated.

[Editor's note: I have a friend of 30 plus years, highly intelligent, educated, non-religious and absolutely truthful and trustworthy who volunteered to seeing a "white mist" rise up from a dying great-grandmother's body and ascent to the corner of the room, linger then disappear through the ceiling. My friend was age six at the time and had not shared this extremely common form of 'shared death experience' with anyone.]

References and Sources

- Moody Jr RA. Life After Life: The 25th Anniversary of the Classic Bestseller. HarperOne; 2001
- Moody Jr RA. Life After Life - Survival of Bodily Death. MMB, Inc. 1975 (later Bantam Books)
- http://www.lifeafterlife.com
- Guthre WKC. History of Greek Philosophy: Volume 2 The Pre-Socratic Tradition from Parmenides to Democritus. Cambridge UK 1979:436-438
- Plato, The Republic. circa 380 BC

MM



For all the time physicians spend fending off the deaths of others, they tend to be fairly serene when faced with death themselves.

Years ago, Charlie, a highly respected orthopedist and a mentor of mine, found a lump in his stomach. He had a surgeon explore the area, and the diagnosis was pancreatic cancer. This surgeon was one of the best in the country. He had even invented a new procedure for this exact cancer that could triple a patient's five-year-survival odds–from 5 percent to 15 percent–albeit with a poor quality of life. Charlie was uninterested. He went home the next day, closed his practice, and never set foot in a hospital again. He focused on spending time with family and feeling as good as possible. Several months later, he died at home. He got no chemotherapy, radiation, or surgical treatment. Medicare didn't spend much on him.

It's not a frequent topic of discussion, but doctors die, too. And they don't die like the rest of us. What's unusual about them is not how much treatment they get compared to most Americans, but how little. For all the time they spend fending off the deaths of others, they tend to be fairly serene when faced with death themselves. They know exactly what is going to happen, they know the choices, and they generally have access to any sort of medical care they could want. But they go gently.

Of course, doctors don't want to die; they want to live. But they know enough about modern medicine to know its limits. And they know enough about death to know what all people fear most: dying in pain, and dying alone. They've talked about this with their families. They want to be sure, when the time comes, that no heroic measures will happen–that they will never experience, during their last moments on earth, someone breaking their ribs in an attempt to resuscitate them with CPR (that's what happens if CPR is done right).



Ken Murray, MD, is a Clinical Assistant Professor of Family Medicine at University of Southern California.
Contact: kmurray@dr.com
Reprinted with permission.This article was originally published at Zócalo Public Square. (link to www.zocalopublicsquare.org on digital edition)

Almost all medical professionals have seen what we call "futile care" being performed on people. That's when doctors bring the cutting edge of technology to bear on a grievously ill person near the end of life. The patient will get cut open, perforated with tubes, hooked up to machines, and assaulted with drugs. All of this occurs in the Intensive Care Unit at a cost of tens of thousands of dollars a day. What it buys is misery we would not inflict on a terrorist. I cannot count the number of times fellow physicians have told me, in words that vary only slightly, "Promise me if you find me like this that you'll kill me." They mean it. Some medical personnel wear medallions stamped "NO CODE" to tell physicians not to perform CPR on them. I have even seen it as a tattoo.

To administer medical care that makes people suffer is anguishing. Physicians are trained to gather information without revealing any of their own feelings, but in private, among fellow doctors, they'll vent. "How can anyone do that to their family members?" they'll ask. I suspect it's one reason physicians have higher rates of alcohol abuse and depression than professionals in most other fields. I know it's one reason I stopped participating in hospital care for the last 10 years of my practice.

How has it come to this–that doctors administer so much care that they wouldn't want for themselves? The simple, or not-so-simple, answer is this: patients, doctors, and the system.

To see how patients play a role, imagine a scenario in which someone has lost consciousness and been admitted to an emergency room. As is so often the case, no one has made a plan for this situation, and shocked and scared family members find themselves caught up in a maze of choices. They're overwhelmed. When doctors ask if they want "everything" done, they answer yes. Then the nightmare begins. Sometimes, a family really means "do everything," but often they just mean "do everything that's reasonable." The problem is that they may not know what's reasonable, nor, in their confusion and sorrow, will they ask about it or hear what a physician may be telling them. For their part, doctors told to do "everything" will do it, whether it is reasonable or not.

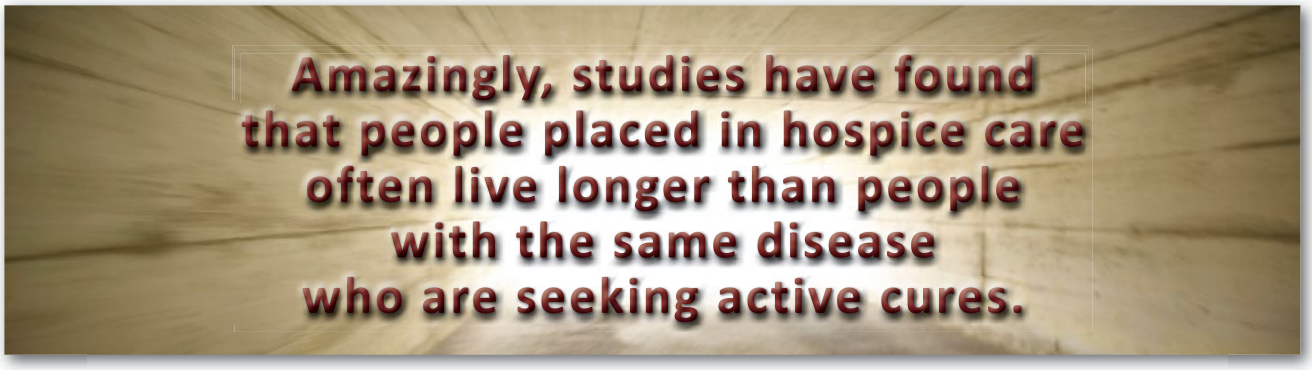
The above scenario is a common one. Feeding into the problem are unrealistic expectations of what doctors can accomplish. Many people think of CPR as a reliable lifesaver when, in fact, the results are usually poor. I've had hundreds of people brought to me in the emergency room after getting CPR. Exactly one, a healthy man who'd had no heart troubles (for those who want specifics, he had a "tension pneumothorax"), walked out of the hospital. If a patient suffers from severe illness, old age, or a terminal disease, the odds of a good outcome from CPR are infinitesimal, while the odds of suffering are overwhelming. Poor knowledge and misguided expectations lead to a lot of bad decisions.

But of course it's not just patients making these things happen. Doctors play an enabling role, too. The trouble is that even doctors who hate to administer futile care must find a way to address the wishes of patients and families. Imagine, once again, the emergency room with those grieving, possibly hysterical, family members. They do not know the doctor. Establishing trust and confidence under such circumstances is a very delicate thing. People are prepared to think the doctor is acting out of base motives, trying to save time, or money, or effort, especially if the doctor is advising against further treatment.

Some doctors are stronger communicators than others, and some doctors are more adamant, but the pressures they all face are similar. When I faced circumstances involving end-of-life choices, I adopted the approach of laying out only the options that I thought were reasonable (as I would in any situation) as early in the process as possible. When patients or families brought up unreasonable choices, I would discuss the issue in layman's terms that portrayed the downsides clearly. If patients or families still insisted on treatments I considered pointless or harmful, I would offer to transfer their care to another doctor or hospital.

Should I have been more forceful at times? I know that some of those transfers still haunt me. One of the patients of whom I was most fond was an attorney from a famous political family. She had severe diabetes and terrible circulation, and, at one point, she developed a painful sore on her foot. Knowing the hazards of hospitals, I did everything I could to keep her from resorting to surgery. Still, she sought out outside experts with whom I had no relationship. Not knowing as much about her as I did, they decided to perform bypass surgery on her chronically clogged blood vessels in both legs. This didn't restore her circulation, and the surgical wounds wouldn't heal. Her feet became gangrenous, and she endured bilateral leg amputations. Two weeks later, in the famous medical center in which all this had occurred, she died.

It's easy to find fault with both doctors and patients in such stories, but in many ways all the parties are simply victims of a larger system that encourages excessive treatment. In some unfortunate cases, doctors use the fee-for-service model to do everything they can, no matter how pointless, to make money. More commonly, though, doctors are fearful of litigation and do whatever they're asked, with little feedback, to avoid getting in trouble.



Even when the right preparations have been made, the system can still swallow people up. One of my patients was a man named Jack, a 78-year-old who had been ill for years and undergone about 15 major surgical procedures. He explained to me that he never, under any circumstances, wanted to be placed on life support machines again. One Saturday, however, Jack suffered a massive stroke and got admitted to the emergency room unconscious, without his wife. Doctors did everything possible to resuscitate him and put him on life support in the ICU. This was Jack's worst nightmare. When I arrived at the hospital and took over Jack's care, I spoke to his wife and to hospital staff, bringing in my office notes with his care preferences. Then I turned off the life support machines and sat with him. He died two hours later.

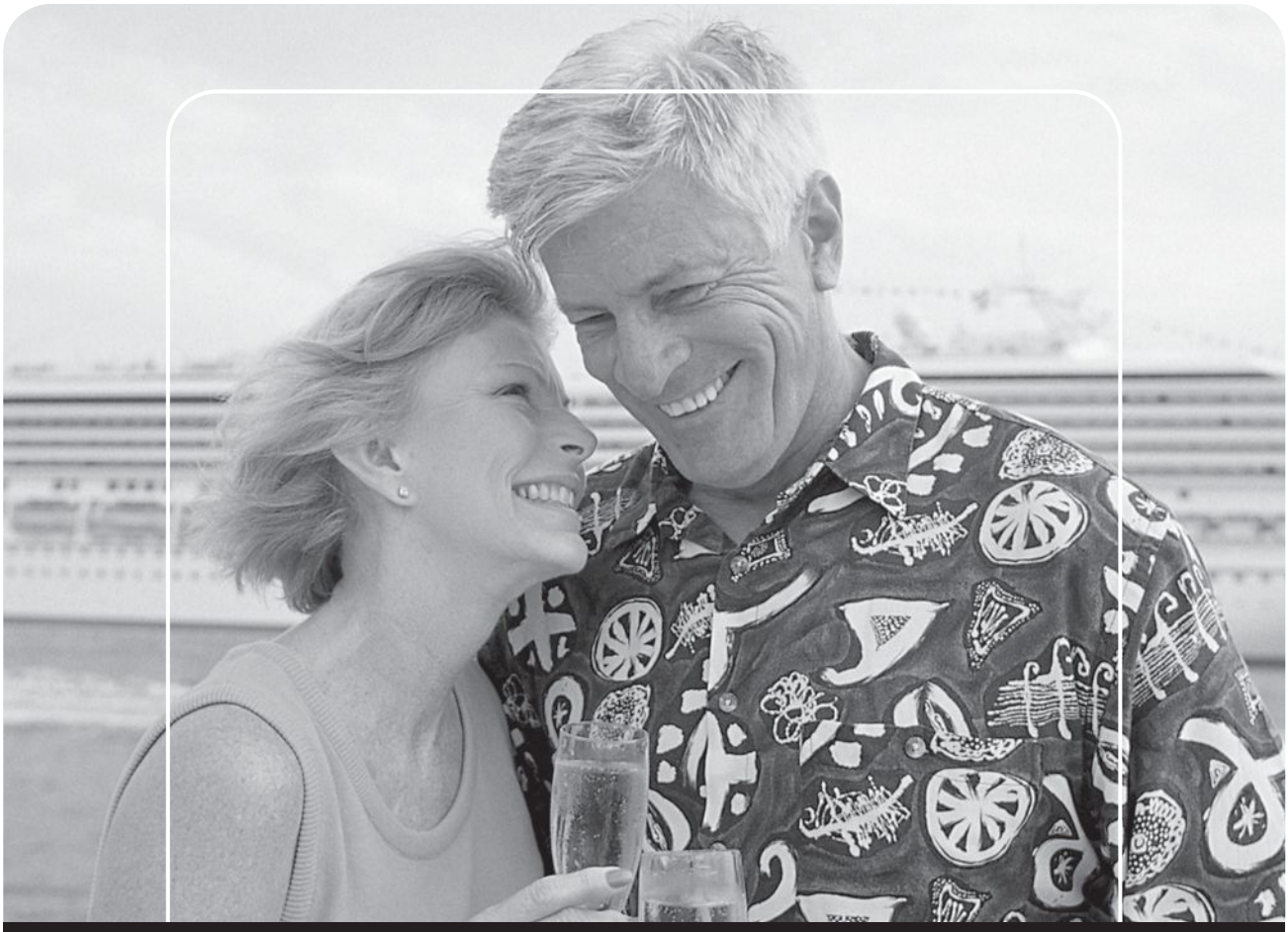
Even with all his wishes documented, Jack hadn't died as he'd hoped. The system had intervened. One of the nurses, I later found out, even reported my unplugging of Jack to the authorities as a possible homicide. Nothing came of it, of course; Jack's wishes had been spelled out explicitly, and he'd left the paperwork to prove it. But the prospect of a police investigation is terrifying for any physician. I could far more easily have left Jack on life support against his stated wishes, prolonging his life, and his suffering, a few more weeks. I would even have made a little more money, and Medicare would have ended up with an additional $500,000 bill. It's no wonder many doctors err on the side of over-treatment.

But doctors still don't over-treat themselves. They see the consequences of this constantly. Almost anyone can find a way to die in peace at home, and pain can be managed better than ever. Hospice care, which focuses on providing terminally ill patients with comfort and dignity rather than on futile cures, provides most people with much better final days. Amazingly, studies have found that people placed in hospice care often live longer than people with the same disease who are seeking active cures. I was struck to hear on the radio recently that the famous reporter Tom Wicker had "died peacefully at home, surrounded by his family." Such stories are, thankfully, increasingly common.

Several years ago, my older cousin Torch (born at home by the light of a flashlight–or torch) had a seizure that turned out to be the result of lung cancer that had gone to his brain. I arranged for him to see various specialists, and we learned that with aggressive treatment of his condition, including three to five hospital visits a week for chemotherapy, he would live perhaps four months. Ultimately, Torch decided against any treatment and simply took pills for brain swelling. He moved in with me.

We spent the next eight months doing a bunch of things that he enjoyed, having fun together like we hadn't had in decades. We went to Disneyland, his first time. We'd hang out at home. Torch was a sports nut, and he was very happy to watch sports and eat my cooking. He even gained a bit of weight, eating his favorite foods rather than hospital foods. He had no serious pain, and he remained high-spirited. One day, he didn't wake up. He spent the next three days in a coma-like sleep and then died. The cost of his medical care for those eight months, for the one drug he was taking, was about $20.

Torch was no doctor, but he knew he wanted a life of quality, not just quantity. Don't most of us? If there is a state of the art of end-of-life care, it is this: death with dignity. As for me, my physician has my choices. They were easy to make, as they are for most physicians. There will be no heroics, and I will go gentle into that good night. Like my mentor Charlie. Like my cousin Torch. Like my fellow doctors. MM



What's Their Secret?

Making good decisions. Seizing opportunities. Committing to the long-term. The secret is, they didn't do it alone — they chose Moneta Group.

At Moneta Group, we work with your family or business to customize a financial plan that fits ***your*** goals. Serving as your Family CFO, our experts build a relationship before we build a portfolio, so you can retire when and how you want.

Now that the secret is out, it's time **for Moneta Group** to help ***you*** live the lifestyle of ***your*** dreams.

STEVE FINERTY | 314-726-2300
ROB HEHMEYER | 314-244-3327
MIKE CARPENTER | 314-244-3260

MONETAGROUP®
www.monetagroup.com

PERSPECTIVE

Non-Assigned Medicare Payment Increases Practice Revenue & Lowers Medicare Costs

by Patrick K. Price, MD

Abandoning Medicare assigned payment renews an old-fashioned relationship between patient and physician.



Patrick K. Price, MD, is a Kansas City ophthalmologist, MSMA member since 1982, and formerly served as Medical Director for Kansas, Nebraska, and Western Missouri between 1993 and 2008.
Contact: pprice@discovervision.com

Summary

Private practice physicians can increase practice revenue and also save Medicare money. What seems like a paradox is instead a choice. The non-assigned Medicare payment option allows physicians to bill 8% more for their services. This also decreases Medicare payment 5%. Selecting the non-assigned payment method does not require permission from Medicare or any Medicare contractor. This is a physician decision and for 2014 must be made between mid-November and year end 2013.

A Decay of Revenue

Cells can die two ways. First, necrosis occurs when an external force depletes cellular energy, which causes, cell disintegration. The second way is apoptosis, a sequence whereby cell death signals open a cascade of executioner proteins like cytochrome c, which then cleave cell organelles and lead to cell death. Necrosis is cell murder; apoptosis is suicide.[1]

Private practice medicine dies one way by decay of revenue. Similar to cells, practice necrosis is caused by external factors. Increased regulations, a litany of auditing metrics (i.e. PQRS, MRUR 1, and MRUR 2), and capital expenditure for electronic health records all add practice expense. In these examples costs are added to avoid future punitive reduced reimbursement consequences. These expenditures are not balanced by greater practice revenue long-term. Cost center audits show practice visits and services can increase and yet the practice can become bankrupt when the practice expenses outpace revenue.[2] Identifying one way to mitigate this margin loss and explain the benefits of financially healthy private primary care practice are the objectives of this paper.

Make a Choice

Following is one policy a private practice may employ to improve its Medicare revenue. Every November the Centers for Medicare and Medicaid Services (CMS) offer physician offices a choice between accepting and not accepting payment through assignment. This ultra-important decision must be made by 12/31/13 for the year 2014.

The difference is illustrated in the Medicare Manual 100-4 Chapter 1, Section 30.3.12. A hypothetical service with a payment fixed by CMS to be $2,185.00 is paid by one of two reimbursement pathways.

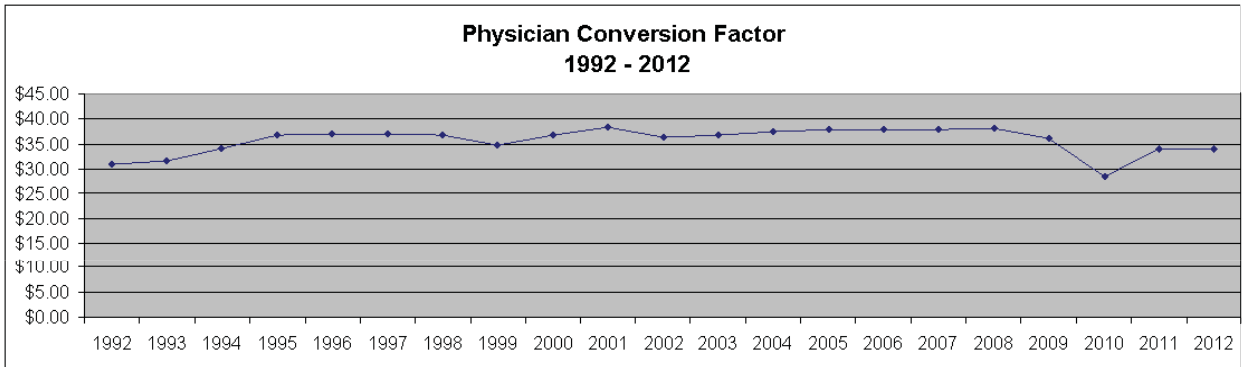
1. Physicians accepting assignment and direct payment from Medicare receive a total amount equal to $2,000.

2. Physicians who do not accept assignment bill the patient. They receive 95% of $2,000 or $1,900 through Medicare. Their total charge is 115% of $1,900 or $2,185.[3]

Medicare pays 5% less and the physician revenue increases 8% when the doctor bills the patient. The patient pays the doctor and Medicare reimburses the patient. Beneficiaries never pay more than the Medicare fixed price. Doctors can adjust charges within the boundaries of a Federal allowed charge based upon the complexity of the service and patient resources.

Figure 1

Years 1993 – 1997 are approximations derived by calculating the average of the surgical, non-surgical, and primary care conversion factors, beginning in 1998 the previous method was abandoned in favor of a single conversion factor.



Medicare paid doctors $20.5 billion for office visits (E&M services) in 2011. By employing a non-assigned billing scenario physicians would have saved Medicare $1.02 billion an increased their revenue $1.64 billion.[4]

No special approval by Medicare or any Medicare carrier or Medicare Administrative Contractor (MAC) is required. Physicians can make a decision to create a direct fee for service relationship with patients.

Why is the Medicare participate/non-participate decision so critically important? Figures 1 and 2 illustrate how the economic underpinnings of private practice have eroded over 20 years as an unintended consequence of Medicare policy between 1992 and today.

Medicare payments for each unit of physician work, the conversion factor (CF), have been nearly flat for a generation.[5] (See Figure 1.)

The Medicare CF is an important determinant of revenue growth. The CF determines Medicare payments per service and can affect private insurance payments if private insurers index their payments to the Medicare fee schedule.

The relationship between the annual percent change in the CF and consumer price index (CPI), which the Bureau of Labor Statistics uses to reflect inflation, is depicted below.[5, 6] (See Figure 2.)

Figure 2

Source: Information from the Centers of Medicare and Medicaid Services and the U.S. Bureau of Labor Statistics.

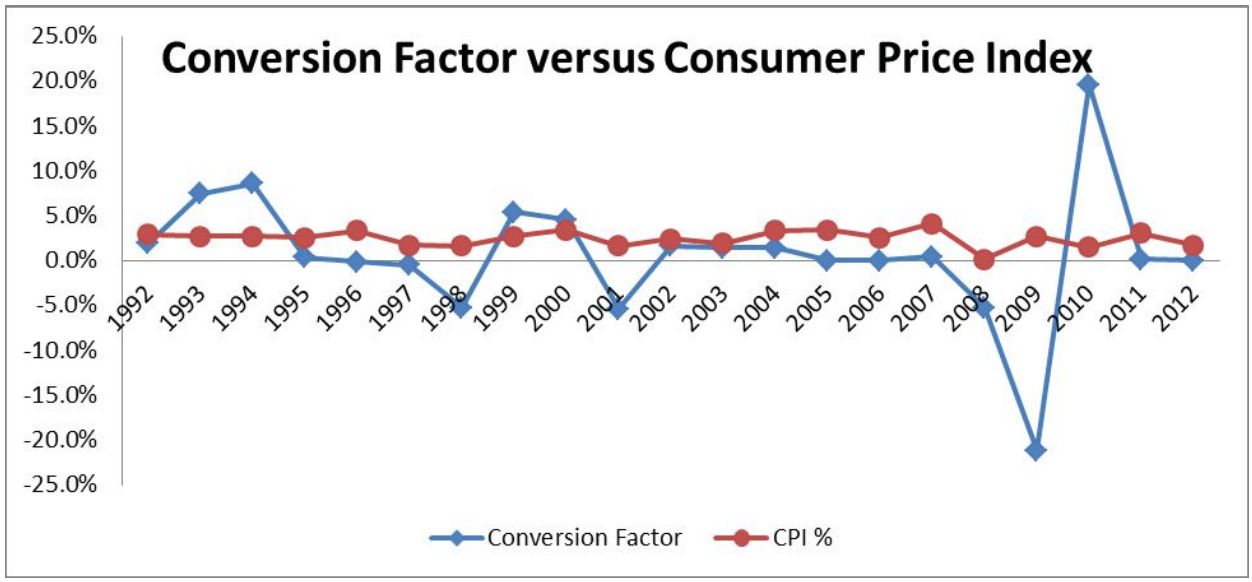
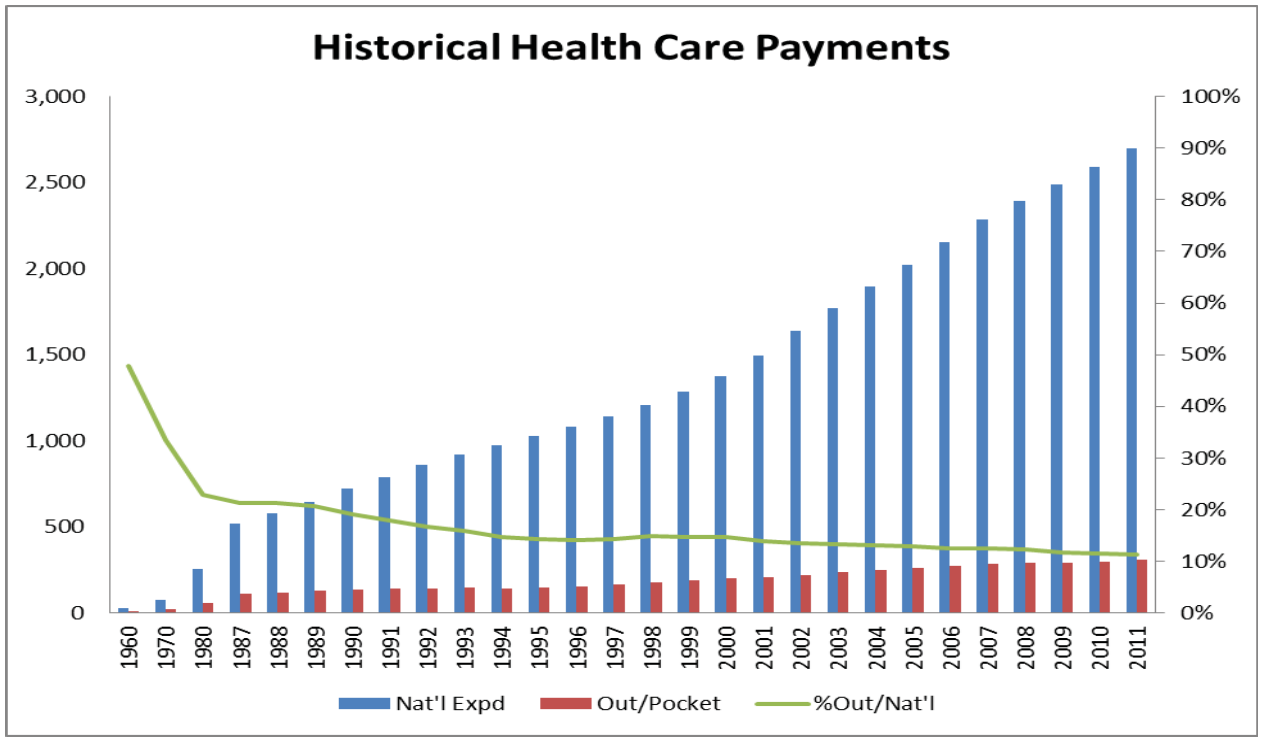


Figure 3
Source: Information from the National Health care Expenditure Accounts.



Annual inflation increases the practice overhead for items like rent, employee salaries, and utilities. Previously referenced practice cost center audits combined with Figure 2 together are warnings. When inflation exceeds revenue growth for a sustained time physicians can be busy and yet move toward bankruptcy.

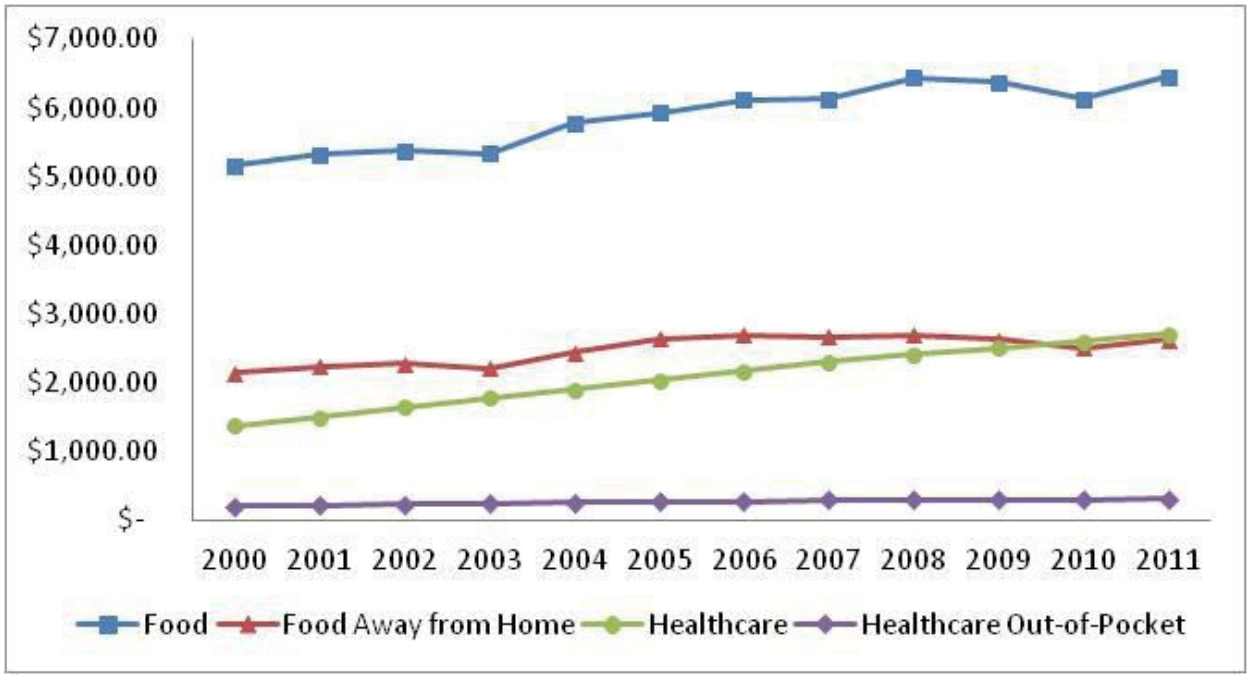
Private practice physicians unable to fund their overhead due to regulation and withering reimbursement often sell out to hospital consortiums. This inevitably increases the total cost of US health care. One day in a private practice office an electrocardiogram (EKG) costs $20.00 and a colonoscopy costs $400.00. The next day the hospital owns the medical practice. Using the same building, equipment, and physician(s) the hospital bills and is paid $35.00 for the EKG and $875.00 for the colonoscopy. Medicare pays more because the hospital bills these services as hospital outpatient services. Not only does Medicare pay more but patient's deductibles are higher as well. In spite of these increased costs hospitals and the federal government argue such acquisitions make care more efficient.[7] (Editor's note: see "Bitter Pill: Analysis of Steven Brill's Time Magazine Article May/June 13 page 166 for further documentation of hospitals being the primary driver of health care costs).

The trend of inflation adjusted income, which decreased 7.1 percent for all physicians and 10.2 percent for primary care physicians between 1995 and 2003, continues.[8] The Association of American Medical Colleges predicts a shortage of 45,000 primary care physicians by 2020.[9] This development is an unintended consequence of Federal policy. Long waiting times for an appointment to see a primary care physician and more expensive hospital outpatient facilities and emergency departments overflowing with patients who do not have timely access to primary care will be the result. This is not a good outcome for patients, physicians, or Medicare.

The Patient-Physician Relationship

Abandoning Medicare assigned payment renews an old-fashioned relationship between patient and physician. The recipient of care pays the person who orders the care and together they make value versus cost judgments. For fifty years the percents of national health care costs paid out-of-pocket have declined and absolute dollar amounts have increased only slightly based upon CMS National Healthcare Expenditure Accounts (NHEA) data on the average annual healthcare expenses of Americans.[10] (See Figure 3.)

Figure 4
Information from the National Healthcare Expenditure Accounts and the U.S. Bureau of labor Statistics



Patient out-of-pocket costs of 11¢ per dollar spent and physician payment by a third party (i.e. Medicare or an insurance company) distills away important incentives for patient and physician collaboration to find efficient care the patient values.

An example illustrates this point. Ophthalmologists use two similar biologic drugs, one a progenitor, to treat exudative "wet" macular degeneration. The Food and Drug Administration (FDA) approved the more expensive drug, which cost $2,000.00 per dose, to treat wet macular degeneration. The much less expensive progenitor biologic drug cost below $150.00 per dose. But the manufacturer has not requested FDA approval for this purpose. Physicians designed a national study and with the cooperation of patients proved the two agents achieved equivalent outcomes. Now about half the patients choose the less expensive equivalent drug for treatment. Patients save hundreds of dollars from lower deductibles and Medicare saves tens of millions of dollars.[11]

Data from BLS and NHEA shows that during the recent recession Americans could quickly adjust the out-of-pocket expense of meals away from home but not on health care.[10,12] (See Figure 4.)

Dollars spent on national health care costs were less than eating away from home prior to the recent recession. The amounts are closer to equal now. Americans adjusted the money spent eating away from home but they were unable to affect their health care costs because government bureaucracies and private insurance control 89¢ of every dollar spent; personal discretion is less a factor.

The Affordable Care Act, "Obamacare", funding depends upon $455 billion coming from cuts in government payments to health-care providers that serve patients on Medicare and two other federal programs.[13] The annual Medicare Trustees Report notes that based upon the Sustainable Growth Rate Formula (SGR) the 2013 conversion factor (CF) should have been $25.5217 for each unit of physician work. But because of legislative manipulation the CF is $34.0230 in 2013.[14] Our federal government does not have enough revenue to continue legislative overrides, create a new health care entitlement, the Affordable Care Act, and pay for services patients' value.

Governments can, and do, offer benefits to constituents before the revenue to pay for them is available. There are many previous examples of unexpected deleterious consequences of bureaucratic policies failing to meet funding goals and/or improve the lives of US citizens. These serve as yellow warning lights - proceed cautiously or red lights - stop and rethink the whole policy. In 2010 the Institute of Medicine published a consensus

committee report, which supported the position that nurse practitioners should be able to lead medical teams and medical homes. Contrary opinions from the American Academy of Family Physicians and the Council of Medical Specialty Societies highlight the association of expert, physician lead best care for each individual and sufficient payment for efficient care.[15]

Governments frequently ask physicians to create value from elements physicians do not control. Alchemists in the 12th century were supported by monarchs and regents in their empiric pursuit of chrysopoeia i.e. creating gold from lead. Our Federal government seeks a modern form of chrysopoeia. Elemental combinations and acronymic formulas for example,: health care organizations, (HMO), SGR, EHR, medical homes, or accountable care organizations (ACO) historically do not mutate into improved quality, availability and lower costs. Physician hard work, long hours, being accessible on call, continuity and rigorous training create the gold standard of health care Americans value.

Practice in a health model of the future.

Mercy in Arkansas, Kansas, Missouri and Oklahoma, is seeking BC/BE physicians to join thriving practices. Positions offer an excellent benefits package including health, dental, and vision benefits, life insurance, vacation and CME, retirement plan and more. Available opportunities may include:

- Anesthesia
- Cardiology
- Dermatology
- Critical Care
- CV/CT Surgery
- Emergency Medicine
- Endocrinology
- Family Medicine
- Gastroenterology
- General Surgery
- Gynecologic Oncology
- Head and Neck Surgery
- Hematology/Oncology
- Hospitalist
- Nocturnist
- Infectious Disease
- Internal Medicine
- Maternal Fetal Medicine
- Neonatology
- Neurology
- Neurosurgery
- OB/GYN – Traditional
- OB/GYN Hospitalist
- Occupational Medicine
- Ophthalmology
- Optometry
- Oral & Maxillofacial Surgery
- Orthopedic Surgery
- Otolaryngology
- Pain Management
- Pathology
- Plastic Surgery
- Podiatry
- Psychiatry
- Pediatrics
- Pediatric Emergency Medicine
- Pediatric Endocrinology
- Pediatric GI
- Pediatric Hem/Onc
- Pediatric Internal Medicine
- Pediatric Neurology
- Pediatric Surgery
- Pediatric Urgent Care
- Physical Medicine and Rehabilitation
- Pulmonology/Critical Care/Sleep Medicine
- Radiation Oncology
- Radiology-Interventional
- Rheumatology
- Robotics
- Trauma Surgery
- Urology
- Vascular Surgery

For more information, please contact: Angie Abraham, MBA
Executive Director of Physician Recruitment • Mercy Clinic
Phone: 877-880-6650 | Fax: 888-290-8300
Email: angie.abraham@mercy.net

AA/EOE

Mercy

Conclusion

Thoughtful adoption of non-assigned payment is not chrysopoeia. It is one step primary care physicians can take to solve a paradox: How to contribute to Medicare's long-term solvency and generate sufficient revenue in private primary care practice to attract the individuals best trained to care for a patient.

References

1. Sedlak T, Snyder S, Messenger Molecules and Cell Death; Therapeutic Implications JAMA.2006;295:81-89
2. Dugel PV, Tong KB, Development of an Activity-based Costing Model to Evaluate Physician Office Practice Profitability. Ophthalmology 2011;118:203-208
3. Centers for Medicare and Medicaid Services, Accessed January 30,2013 at http://www.cms.gov/manuals/downloads/clm104c01.pdf
4. Centers for Medicare and Medicaid Services National Healthcare Expenditure Accounts 2011 chapter 9 table 9.7, Accessed April 21, 2013, at http://www.cms.gov/apps/ama/license.asp?file=/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/MedicareMedicaidStatSupp/Downloads/2012Physician.zip
5. Centers for Medicare and Medicaid Services Estimated Sustainable Growth Rate and Conversion Factor, for Medicare Payments to Physicians in 2013, Accessed February 22, 2013, at http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/SustainableGRatesConFact/Downloads/sgr2013f.pdf
6. Consumer Price Index, U.S. Department of Labor Bureau of Labor Statistics. .Accessed May 18, 2013, at ftp://ftp.bls.gov/pub/special.requests/cpi/cpiai.txt
7. Wilde Mathew A, Same Doctor Visit, Double the Cost The Wall Street Journal, 27 August 2012, pp.B1,B2
8. Bodenheimer T, Primary Care – Will It Survive? N Engl J Med 2006; 355(9): 861-864
9. Briefing, The future of medicine-squeezing out the doctor. The Economist, 2 June 2 012, pp. 29-31
10. Centers for Medicare and Medicaid Services. Accessed April 20, 2013, at http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Downloads/dsm-11
11. Mundy A, Corbett Dooran J, Avastin Savings Get Closer Look The Walls Street Journal, 7 September 2011, pp. B3
12. All Consumer Units, Consumer Expenditure Survey, U.S. Department of Labor Bureau of Labor Statistics. Accessed April 19, 2013 at ftp://ftp.bls.gov/pub/specialrequest/consumerexpendsurvey/ces2011
13. Adamy J, Health Law Augurs Transfer of Funds from Old to Young The Wall Street Journal, 26 July 2010, pp.A1,A12
14. Centers for Medicare and Medicaid Services Estimated Sustainable Growth Rate and Conversion Factor, for Medicare Payments to Physicians in 2013. Accessed February 22, 2013 at http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/SustainableGRatesConFact/Downloads/sgr2013f.pdf
15. Donelan K, DesRoches CM, Dittus RS, Buerhaus P, Perspectives of physicians and nurse practitioners on primary care practice. N Engl J Med 2013;368(20):1898-906

Acknowledgments

I acknowledge the help of Todd Hildreth OD, David Phillips, OD, and Joseph Price, MBA. I only accomplished the writing of this article with their combined editing and formatting assistance.

Disclosure

None reported.

MM



"As physicians, we have so many unknowns coming our way…

One thing I am certain about is my malpractice protection."

Medicine is feeling the effects of regulatory and legislative changes, increasing risk, and profitability demands—all contributing to an atmosphere of uncertainty and lack of control.

What we do control as physicians:
our choice of a liability partner.

I selected ProAssurance because they stand behind my good medicine and understand my business decisions. In spite of the maelstrom of change, I am protected, respected, and heard.

I believe in fair treatment—and I get it.

PROASSURANCE®
Treated Fairly

WARD'S 50 2007-2013 7 Years Running

Professional Liability Insurance & Risk Management Services

ProAssurance Group is rated **A+ (Superior)** by A.M. Best.
ProAssurance.com • 800.282.6242

Accountable Care Organizations: Are We Even at the Table?

by James Wolfe, MD

I heard Joe Flowers, a medical futurist, speak at the Iowa Medical Society this spring. He had some interesting observations.

1. Unless both physician and patients are engaged in real behavior pattern changes ACOs are destined to fail.
2. Unless patients trust the health care representative they are unlikely to change their behaviors. They must believe that the individual is "on their side", knows them, has a relationship with them, and has the "credentials (i.e. an RN, an NP or an MD after their name), implying he/she knows what he/she is talking about. These observations led me to learn more about his thoughts since he is well recognized as an authority on the forces changing health care in the U.S. This led to a Google search for additional articles by Mr. Flowers which revealed that he has been a prolific writer.

A distillation of his major points are enlightening.

1. ACOs that continue to use fee-for-service models are destined for failure because they will be high priced outliers which will result in loss of market share.



James B. Wolfe, MSMA member since 1978, is the 2013-2014 MSMA President and an ENT surgeon from Springfield, Missouri.
Contact: jbwolfemd@hotmail.com

2. None of the various ACO models have been tested. Some will be based on false assumptions which will result in ultimate failure. Other ACOs will fail because they don't implement their business models correctly. Some will fail because they concentrate on cost cutting measures without recognizing the profound effects these efforts will have on the system's cash flow. Programs designed to change patient behaviors are fairly expensive with all of the expense front loaded. If the ACO doesn't have sufficient cash reserves it will not survive long enough to reap the rewards of the patient behavior modification programs.
3. Some ACOs will fail because they fail to understand that they are really in the health insurance business. Several studies have shown that 20% of patients generate 80% of costs; 5% generate 50% of costs; 1% create 20%. Over 50% of these high cost patients have chronic poorly-treated conditions. Programs that implement long-term trusted relationships with "real health professionals working in teams" have shown a 20-25% reduction in costs for the targeted populations. Since these patients generate 50% of total costs, dropping costs for the high-cost target populations by 25% could result in overall drops of 12.5% for the whole population. Unfortunately, these successful programs are front-loaded in the costs so #2 is opervative.
4. Because ACOs are really local insurance companies, their structure requires "significant changes in physicians behaviors such as prescribing patterns, working in true teams, collaboration between specialists, rapid and constant exchange of information." Unfortunately, unsuccessful ACOs use systems that "merely disrupt the physicians' work lives and customer patterns with greater reporting requirements and/or more complicated payment structures without offering them clear direction, incentives or assistance."

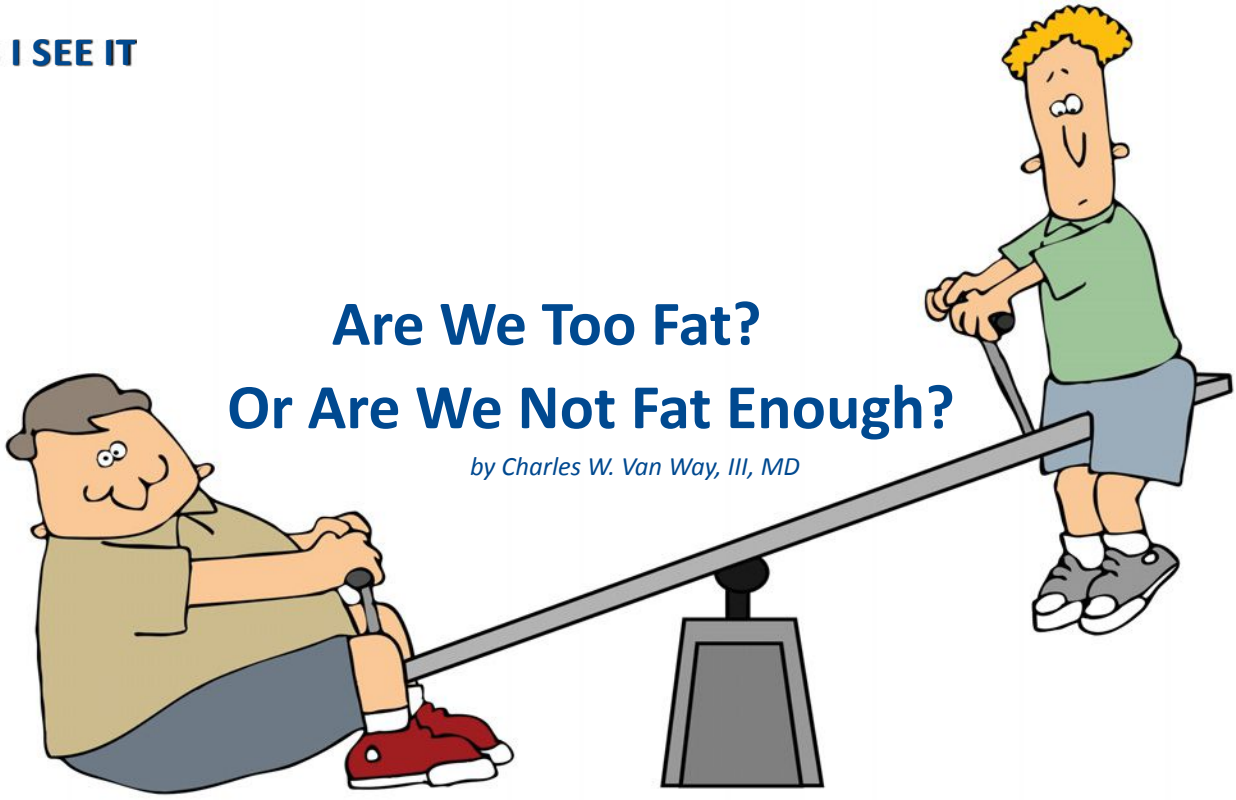


Given that ACOs are really insurance companies, what then, is the real role of large health insurance companies such as Aetna, United Healthcare, or WellPoint? It would appear that at some time in the future if ACOs become successful and widespread, the major insurance companies will morph into national healthcare marketing companies without significant risk for health care costs. Since most health care is local in nature, their major value will reside in their national contracts that allow patients to travel wherever they wish and not worry about health care coverage.

At the same Iowa Medical Society meeting I heard a panel discussion with representatives of the four active ACOs in Iowa. What I found most interesting of all was the fact that in spite of all attesting to the notion that physicians were important in the ground level creation of their organizations, not a single physician was on the panel. All of the participants were either from a business or marketing background. They all agreed that by 2020 none of their organizations would have a fee-for-service model. Transition of care from the acute setting to home was the area viewed by the panel as the greatest area of savings potential.

Once one considers the above facts, it becomes apparent that in the future physicians will need additional skill sets to be successful. In addition to their medical skills, physicians will need to be able to read and fully understand financial statements as well as understand risk management concepts. Future physicians' financial success will hinge on aligning with financially rock solid systems. Those physicians who fail to acquire these financial tools may find that they could be financially liable for monetary shortfalls of the ACO. It is apparent that successful ACOs will have active physician input during the creation of their business models. These physicians will need to possess significant background in business fundamentals as well as an intimate knowledge of the differences in patient flow of the various fields of medicine. The major problem ACOs must solve is how to incorporate specialists into the new payment paradigm. Most of the present ACO business models are "outsourcing" specialty care which is still based on fee-for-service. Based on Mr. Flowers assertions, these models are destined for failure.

So, what does all this mean to Missouri physicians and MSMA? IF ACOs prove successful, we will see further erosion of the independent private practitioner in the years to come. Unless ACOs are formed by independent practitioners they will be frozen out of all panels. Hence, significant pressure will force independent physicians to join groups or systems as employees. In the future the independent practitioner will become extinct. MSMA is preparing for this transition by investigating services and programs unique to employed physicians. I and our staff would certainly welcome any ideas for services etc., from our employed physician members. As always, I am interested in hearing from our members directly. My e-mail address is jbwolfemd@hotmail.com and my home phone number is 417-882-6680. MM



Are We Too Fat? Or Are We Not Fat Enough?

by Charles W. Van Way, III, MD

"For every complex problem there is an answer that is clear, simple, and wrong."
- H. L. Mencken

As we all know, it is important to remain thin. Indeed, thinness is regarded in certain circles as only slightly below Godliness. As witness the tireless efforts of many of my more evangelical colleagues in what we sometimes call the Nutrition Game. In health records today, we record not only height and weight, but also the sacred Body Mass Index, more familiarly known as the BMI.

The BMI is, as you all know, the number obtained by dividing the weight in kilograms by the square of the height in meters (See Figure 1).

This number has the great virtue that it's hard to calculate. You can't calculate it in your head, can you? It's a little bit mysterious, not at all intuitive, and has the same instant believability as many other products of science. And so, it has become an instant measure of the virtue, or lack thereof, of any human on the planet, regardless of age, sex, occupation, or religious preference. The Centers for Disease Control has even published a handy guide to the BMI.[1]

For the high priests of thinness, low BMI is part of the scriptures. (See Figure 2). According to these scriptures, a person's chance of long life is greatly affected by where on this table one is to be found. Mortality, it is said, has a U-shaped curve when plotted against BMI, rising above 30 and below 18. And the range of 18.5 to 25 has long been regarded as the best, and of course the most virtuous. This is a clear and straightforward view of the world, and it has a great deal of appeal, especially for simple-minded folk such as politicians and social activists.

But alas! Many workers in the vineyards of research have risen to contest this revealed wisdom. It is an unfortunate fact that most research for the last 15 years or so has found that it isn't that simple. A recent review by Katherine Flegal, et al., conducted a meta-analysis of 97 studies of mortality risk (hazard ratio, to be technical) versus BMI published over the last 15-20 years, most of them since 2000.[2] Their conclusions have been very unsettling to many people. First, "overweight" people from 25-30 had a lower risk of mortality than did those who were "normal." Second, "obese" people from 30-35 were at no greater risk than those who were "normal," although admittedly a higher risk than those who were 25-30. Those with a BMI over 35 had a significantly higher risk of mortality, upholding the conventional wisdom at the upper end, at least. Putting it very carefully, the study concluded that overweight and mild obesity may not be as harmful by itself as we had thought it was, and may not, by themselves, require treatment.

It should be noted that it has been pretty well established by a number of studies that the mortality risk for those under 18.5 is indeed higher than for those in the 20s. As generations of medical practice have taught us, underweight and weight loss are bad signs to see in a patient. A generation of physical fitness advocates should take note, but most of them won't.

Perhaps the most unsettling thing about this paper, at least to true believers, was its source. It came from the Center for Disease Control. Yes, the same place where

the table above came from. Not only that, the study was supported by the CDC and the National Cancer Institute. It's going to be very hard to claim that the study was biased by the nutritional-industrial complex. Or anyone else. In short, the study was well and meticulously done, and comes from an unimpeachable source.

A number of editorials have followed, many of them deploring or denying the results. This paper, it has been said, has undercut the fight against obesity! Maybe it's true, but it shouldn't be so! We don't care if it's true, it's wrong! However, the accompanying editorial in *JAMA*, by Heymsfeld and Cefalu, was a bit more balanced.[3] To paraphrase, it said that yes, they're right, and we probably need to rethink the whole grade I obesity thing. But they went on to suggest that the results might be explained because the optimum may be in the 22-25 range, in which case including those between 18.5 and 22 might have resulted in the estimates for "normal" being too high. One can explain away anything, I suppose, but there really isn't a shred of evidence for this bit of sophistry.

Figure 1

Body Mass Index (BMI) is not easily determined without a calculator.

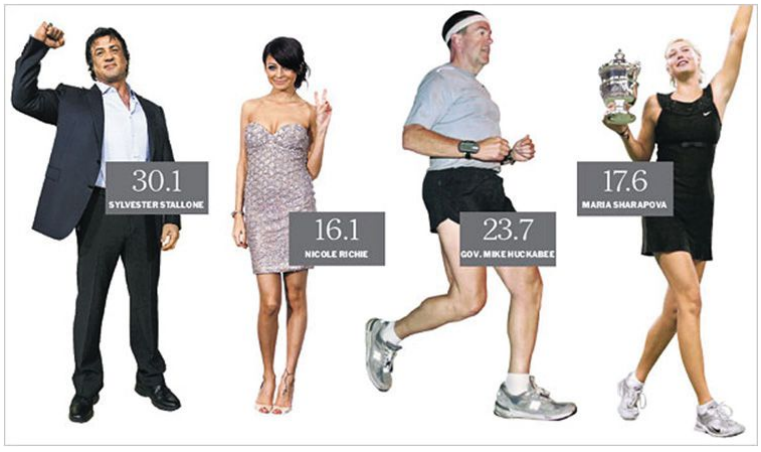
$$BMI = \left(\frac{\text{Weight in Pounds}}{(\text{Height in Inches} \times \text{Height in Inches})}\right) \times 703$$

OR

$$BMI = \left(\frac{\text{Weight in Kilograms}}{(\text{Height in Meters} \times \text{Height in Meters})}\right) \times 703$$

Figure 2

For the high priests of thinness, low BMI is part of the scriptures.



The fact is that many perfectly healthy people, who had BMIs around 23, when they were 20 years old, now have BMIs around 28 or more when they reach the age of 50. It doesn't seem to affect their health or well-being. The idea that one number can be invariant across the entire life span, and in both sexes, was fairly unrealistic to begin with, and it is probably to our discredit that we accepted the BMI without a lot more skepticism. Too many factors contribute to good (or poor) health to simplify things down to a single number measuring a single attribute. But if, as Dr. Flegal and her colleagues have suggested, the "obesity epidemic" should be limited to those who are really at – 35 and above – its worldwide scope will be drastically reduced.

It seems unlikely that we will lose our obsession with thinness. We have a strong cultural esthetic in Western culture to promote thinness, especially in women. As was famously said by Wallis Simpson, Duchess of Windsor, "A woman can never be too thin or too rich." Esthetics are certainly a common and acceptable way to judge such things. But there appears to be a lot less wrong with being somewhat "overweight" than we had previously thought. Perhaps both men and women should lose some of their feelings of guilt, rather than losing some of their weight. It may be true that it is better to be fit than to be fat, but being a bit fat does not appear to be particularly harmful. We physicians can take some guidance from this. There are so many things about which we must nag our patients. Have you taken your anti-hypertensives? Are you taking vitamins? Getting exercise? Perhaps we can lighten up, in this one area at least.

The real lesson of all this is that we can and should regard simple solutions, such as the BMI, with considerably more skepticism than we have in the past. As he frequently was, H. L. Mencken was correct. They didn't call him the Sage of Baltimore for nothing.

Observant readers will note that I've used this particular quotation from the Sage in previous essays. Perhaps I'm just lazy, something I won't entirely deny. But the truth is, this observation applies to so many things that it just keeps coming to mind.

References

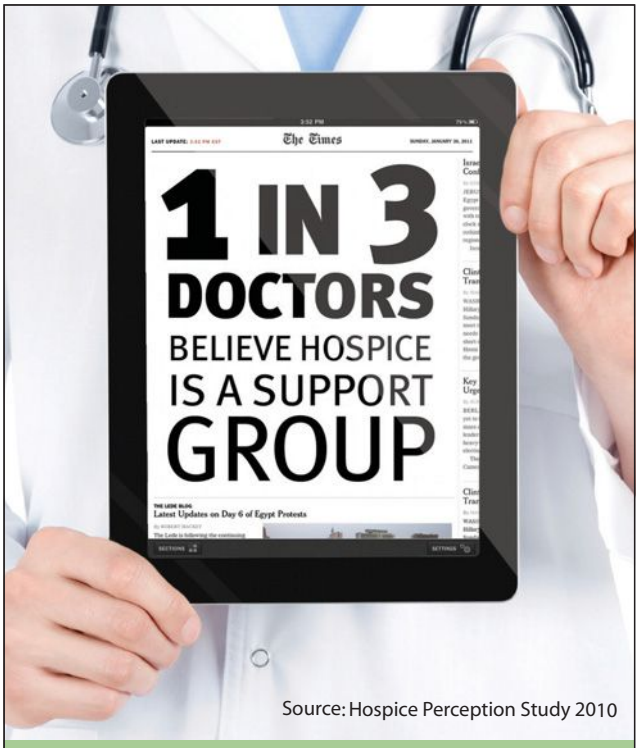
1. Interpretation of BMI for adults. Center for Disease Control and Prevention. http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html
2. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of All-Cause Mortality With Overweight and Obesity Using Standard Body Mass Index Categories: A Systematic Review and Meta-analysis. JAMA 2013;309(1):71-82.
\3. Heymsfield SB, Cefalu WT. Does Body Mass Index Adequately Convey a Patient's Mortality Risk? JAMA 2013;309(1):87-88.

MM

Charles W. Van Way, III, MD, FACS, FCCP, FCCM, MSMA member since 1989 and Missouri Medicine Contributing Editor, is Professor of Surgery, the Sosland/Missouri Endowed Chair of Trauma Services, and the Director of the Shock Trauma Research Center.
Contact: cvanway@kc.rr.com

Reprinted with permission from the Greater Kansas City Medical Bulletin, Spring 2013





Source: Hospice Perception Study 2010

We want to change that statistic.

This is just one of the surprising statistics revealed by a nation-wide survey of physicians. And that's why Crossroads Hospice wants to help medical professionals understand more about hospice and how much patients and families can benefit. To do that, we've sponsored and published a variety of papers like the one written by *Physicians Practice* magazine: What Every Doctor Should Know About Hospice.

3 easy ways to get your free whitepaper.

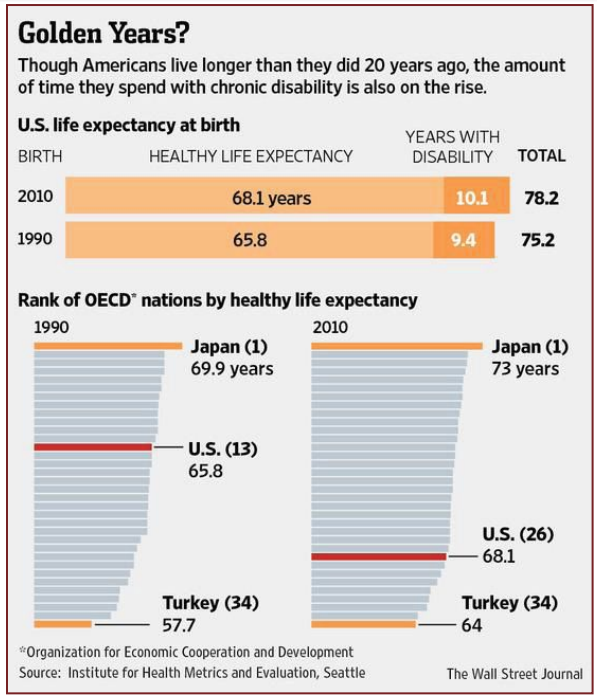
1. Scan this QR code
2. Email info@CrossroadsHospice.com (subject line: Every Doctor)
3. Visit CrossroadsHospice.com/msm

Crossroads HOSPICE

Expect more from us. We do.

Fast, easy referrals: **888-909-6673**
CrossroadsHospice.com/msm

1 Picture = 1,000 Words



Addendum

To "Do Omega-3 Fatty Acids Cause Prostate Cancer?" (July/August 2013). Mark F. McCarty, BA, as stated in About the Authors, is with NutriGuard Research Inc., Encinitas, CA. This firm sells products containing omega-3. This is an Editor's clarification and not a disclosure omission.

156th
MSMA Annual
Convention

April 4-6, 2014
St. Louis Airport Renaissance Hotel

Hotel Reservation Deadline: March 12, 2014
Call the St. Louis Renaissance Airport Hotel
directly at 1-800-468-3571 or
Online at msma.org/annualconvention



A reputation is like trust.

It takes years to grow, but can be ruined in seconds. Make sure your reputation is protected with medical malpractice insurance coverage from PSIC.

Learn more about PSIC at **www.psicinsurance.com.**
Or call us at **1-800-788-8540.**

Malpractice insurance is underwritten by Professional Solutions Insurance Company.
14001 University Avenue | Clive, Iowa 50325-8258 ©2013 PSIC NFL 9549

PSIC | Professional Solutions INSURANCE COMPANY
Protecting Reputations ... One Doctor at a Time®

Missouri Medicine Annual Statement of Ownership, Management & Circulation

1. Publication Title: Missouri Medicine
2. Publication No.: 0355-3800
3. Filing Date: 9/27/13
4. Issue Frequency: Bi-Monthly
5. No. of Issues Published Annually: 6
6. Annual Subscription Price: $75
7. Complete Mailing Address of Known Office of Publication:
   113 Madison Street - Cole County
   Jefferson City, MO 65101
8. Complete Mailing Address of Headquarters or General Business Office of Publisher:
   113 Madison Street - Cole County
   Jefferson City, MO 65101
9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor:
   Publisher-Missouri State Medical Association
   113 Madison Street - Cole County
   Jefferson City, MO 65101
   Editor: John C. Hagan, III, MD
   113 Madison Street - Cole County
   Jefferson City, MO 65101
   Managing Editor: Lizabeth R. S. Fleenor
   113 Madison Street - Cole County
   Jefferson City, MO 65101
10. Owner: Missouri State Medical Association
    113 Madison Street - Cole County
    Jefferson City, MO 65101
11. Known Bondholders, Mortgagees & Other Security Holders: None
12. The purpose, function, and nonprofit exempt status for federal income tax purposes has not changed during the preceding 12 months.
13. Publication Name: Missouri Medicine
14. Issue Date for Circulation Data Below: July/August 2013
15. Extent and Average Actual number nature of number of copies of circulation copies each single issue during published preceding nearest to

	12 Months	Filing Date
15a. Total No. Copies (Net Press Run)	4334	4150
15b. Paid and/or Request Circulation		
(1) Paid/Requested Outside-County Mail Subscriptions	4076	4002
(2) Paid In-County Subscriptions	5	5
(3) Sales Through Dealers and Carriers, Street Vendors	1	1
(4) Other Classes Mailed Through the UPS	0	0
15c. Total Paid and/or Requested Circulation	4082	4008
15d. Free Distribution by Mail	0	0
15e. Free Distribution Outside the Mail	0	0
15f. Total Distribution	4082	4008
15g. Copies Not Distrib.	175	142
15h. Total	4257	4150
15i. Percent Paid	100%	100%

16. This Statement of Ownership is printed in the September/October 2013 issue of this publication.

Pills are *NOT* a Party!

Pills are *NOT* a Party! is a fifteen-minute animated DVD which educates middle school youth on the dangers of indiscriminate drug use. The DVD will encourage discussion and provide teaching opportunities about:

- **The dangers of abusing prescription and over-the-counter (OTC) drugs**
- **The consequences of giving in to peer pressure**
- **The dangers of pill parties**
- **The legal implications of taking drugs prescribed for another person**
- **How to dispose of medications properly**

Proper Prescription Pete, a talking pill bottle, teaches the viewer:

- **How drugs work in the body**
- **The possible side effects and life threatening consequences from taking random medications**
- **To take only prescription drugs that are prescribed for them**
- **Some drugs severely impair your ability to make healthy choices and safe decisions**

PLAYABLE ON DVD PLAYERS ON TELEVISIONS AND MAC AND PC COMPUTERS



Prescription and over-the-counter drug abuse affects your life!

For more information about Greene County Medical Society Alliance Educational DVDs, e-mail director@gcms.us or call 417/887-1017.

Major contributors for **Pills are *NOT* a Party!** include CoxHealth, Ferrell Duncan Clinic, and Mercy Hospital Springfield.

SMOKING MAKES ME UGLY!!!

The "Smoking Makes Me Ugly" DVD takes you on a twelve minute tour highlighting the effects of smoking on the inside and outside of your body. The animated tour is hosted by "CigFree", a sarcastic cigarette. CigFree's approach isn't subtle. He is down right nasty, just like the effects of smoking on your body. The tour will start in your mouth, head through your throat and lungs. You'll see how smoking affects your heart, stomach and intestines. You'll see the effects of smoking on every part of your health.

PLAYABLE ON DVD PLAYERS ON TELEVISIONS AND MAC AND PC COMPUTERS

DVD CONTENTS:

- **12 MINUTE ANIMATED TOUR OF THE EFFECTS OF SMOKING ON THE INSIDE AND OUTSIDE OF THE BODY**
- **CHAPTER MARKS TO EASILY NAVIGATE PORTIONS OF THE TOUR**
- **PRINTABLE HANDOUTS, WORKSHEETS AND TEACHER GUIDES**
- **INTERACTIVE LESSONS: SMOKING AFFECTS MY PIGGY BANK, MY SMOKE AFFECTS EVERYONE, 4,000 CHEMICALS CAN BE WRONG AND SMOKING MAKES ME UGLY!!!**
- **ANIMATED MENUS**





EACH DVD INCLUDES A COMPLETE SET OF PRINTABLE HANDOUTS, WORKSHEETS AND TEACHER GUIDES THAT ACCOMPANY THE DVD.

FOR MORE INFORMATION AND ORDERING VISIT THE OFFICIAL SMOKING MAKES ME UGLY WEBSITE AT WWW.SMOKINGMAKESMEUGLY.COM OR EMAIL INFO@SMOKINGMAKESMEUGLY.COM

Transforming the Future of Medicine



by Larry J. Shapiro, MD

Washington University in St. Louis
SCHOOL OF MEDICINE

Construction began this summer on a new School of Medicine research building that will be dedicated to interdisciplinary research into some of the most complex problems in human biology. The six-story building, which will house 138,000 square feet of highly flexible, open laboratories, has a June 2015 target date for completion.



Larry J. Shapiro, MD, MSMA member since 2006, is Executive Vice Chancellor for Medical Affairs and Dean at Washington University School of Medicine in St. Louis.
Contact: shapirol@wustl.edu

Advancing human health is at the heart of Washington University's plans for the future. Through a strategic planning process that began in 2006, the university identified improvements in human health as one of four key themes, together with preparing the leaders of tomorrow, inspiring innovation and entrepreneurship and enhancing the quality of life. These themes capture the greatest opportunities to enhance the university's contributions to society.

Washington University School of Medicine has a depth of talent, experience, focused vision and combined intellect that position us well to contribute to each of these strategic themes. Our mission is to lead in advancing human health through innovative research, outstanding clinical care and the education of tomorrow's leaders in biomedicine.

Research

The School has been at the forefront of biomedical research and last year received more than $545 million in research grants and contracts from government agencies and private sources. The majority of that annual support, $372 million, is in 678 separate awards from the National Institutes of Health (NIH).

For example, NIH recently renewed its commitment of $50 million to support the Institute of Clinical and Translational Sciences (ICTS) for "Accelerating Discoveries Toward Better Health." ICTS' programs are designed to facilitate discoveries in clinical research and to speed the translation of research findings into improved prevention, diagnosis and therapy in clinical practice.

These endeavors require collaboration among many different disciplines and partners. As part of the university's efforts embodied in our BioMed 21 initiative to translate basic science discoveries into solutions to global health problems, the School of Medicine has partnered with other Washington University schools, including Arts & Sciences and Engineering, and has developed seven new Interdisciplinary Research Centers (IRCs), which conduct disease-focused translational research. Through the

IRCs and other similar research activities, we are discovering and applying solutions to conditions ranging from brain and neurologic disorders, heart disease and cancer to diabetes, obesity and infectious diseases.

Additionally, large-scale research programs are increasingly important to understanding the causes and interrelatedness of diseases. Our investments in gene sequencing, computational sciences and bioinformatics have demonstrated the power and promise of "Big Data," and have changed the way researchers collect, store, manipulate and analyze large, complex data sets to drive discovery. Researchers here are using these powerful methods to unravel the genetic basis of many different cancers including brain, breast, lung and ovary, as well as leukemia.

Patient Care

In partnership with BJC Healthcare, Washington University has the ability to translate laboratory discoveries to clinical care and to extend this care to the broader population to improve overall human health. Medicine will be practiced very differently in the future. Through the application of genomics and other tools, physicians will provide care that is more individualized and personally tailored. In addition, they will be held increasingly responsible for the health of a group of patients and will require the tools for population health management. The university created the Institute for Public Health and the Population Health Sciences Program to complement the efforts of other public health innovators and bring university resources together to focus on the health of communities.

Patient demographics are changing. An aging population suffers from more complex and chronic diseases. Patients are likely to have multiple illnesses, be more culturally diverse and have varying degrees of health literacy. Successful models for clinical care will emphasize health promotion, disease prevention and removing barriers to access. The impact of health-care reform, which includes quality and patient-safety initiatives, also is influencing the care our physicians provide and will reinforce the many programs we already have underway to measure outcomes and continuously improve our methods.

Our faculty practice — Washington University Physicians — together with the activities of our

In Brief

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

- Founded: 1891
- Executive Vice Chancellor for Medical Affairs, Dean and President of Washington University Medical Center: Larry J. Shapiro, MD
- Total Students: 1,364
  - MD, MD/PhD, MA/MD: 598
  - Audiology and Communication Sciences: 72
  - Clinical Investigation: 104
  - Genetic Epidemiology: 29
  - Occupational Therapy: 274
  - Physical Therapy: 274
  - Population Health Sciences: 13
- MD Program Applicants in 2013-14: 4,445 (of them, 122 enrolled)
- Faculty: 1,968
- Non-faculty Assistants and Others: 174
- Staff: 6,708
- Total Employees: 8,850
- Affiliated Private Practice Faculty: 1,349
- Fellows and Trainees: 883
- House Staff: 1,110

WASHINGTON UNIVERSITY MEDICAL CENTER

- Washington University Medical Center Institutions:
  - Alvin J. Siteman Cancer Center
  - Barnes-Jewish Hospital
  - The Rehabilitation Institute of St. Louis
  - St. Louis Children's Hospital
  - Washington University School of Medicine
- Beds: 1,573
- Employees: 21,600 (approximate for all medical center institutions)

WASHINGTON UNIVERSITY PHYSICIANS CLINICAL ACTIVITIES (2012)

- Physician Outpatient Visits: 941,849
- Hospital Admissions (BJH/SLCH): 67,779



As part of the Introduction to Medicine course, Seth Kendler, MD, and MD/PhD student Agata Bielska practice skills on patient Shirley Weatherford under the guidance of Victoria Fraser, MD, Adolphus Busch Professor of Medicine and chair of the Department of Medicine at Washington University.



Mark Manary, MD, the Helene B. Roberson Professor of Pediatrics at the School of Medicine, works with children in Malawi, in sub-Saharan Africa, the epicenter of his intervention efforts and research involving severe malnutrition. Manary, one of several faculty at the School of Medicine whose work aims to improve health globally, introduced more than a decade ago a revolutionary peanut butter-based therapeutic food to battle severe malnutrition, an affliction that contributes to the death of 1 million children each year.

1,300 voluntary clinical faculty and our vital and much-appreciated associations with thousands of referring community physicians, create a platform from which we all, in combination and partnership, can be a force for positive change in patient care.

Education

Our students have the opportunity to learn from a nationally renowned faculty while pursuing their studies in a wide array of academic departments and programs. Our MD program and our programs in occupational therapy, audiology and communication sciences, and physical therapy, are among the highest ranked by *U.S. News & World Report*. Through the work of our admissions office team and our friends across the nation and world who spread the word about Washington University, we most recently had 4,445 applicants for 122 positions in our first-year MD class. Our students are distinguished by outstanding academic credentials, stellar personal characteristics and a commitment to public service. Based on the most common measures of academic excellence (undergraduate GPA and MCAT scores), Washington University's MD program is the most selective in the nation.

This autumn marks the 40th anniversary of our Division of Biology and Biomedical Sciences (DBBS), through which we offer the PhD degree. Over the last six years, applications to the DBBS have increased from 730 to about 1230. Our dual-degree MD/PhD program is the country's largest.

Medical education in the United States is at an exciting crossroads. We will see more changes in the next 5–10 years than we have in the last 50. One of the biggest changes is the move toward competency-based curricula. Our trainees at all levels will be expected to demonstrate proficiency in competency areas that go well beyond traditional domains of medical knowledge and patient care. These include professionalism, interpersonal communication, systems-based practice (practicing medicine within the confines of the national, regional and local regulatory and fiscal environment), and practice-based learning and improvement.

Historically, teaching has been faculty-centric, but here it has been transformed to a student-centric model. Our medical education program is designed to allow students to learn in the manner they prefer. Courses are multidimensional and multimodal. "Anytime and anywhere" learning occurs. The MD degree and residency years are appreciated by our students as just the beginning of a lifelong learning process.

Challenges Ahead

The School of Medicine has made progress toward

many of its goals, yet new challenges will require further innovation and novel approaches. Health care reform, while increasing the focus on quality, effectiveness and safety, also portends reductions in reimbursement for physicians. Federal research budget constraints effectively reduce National Institutes of Health (NIH) grant awards at a time when we are at the brink of harnessing translational research to create new, personalized treatments. Both our workforce and our student body must become more diverse if we are to reach our maximum potential as an institution that serves the best interests of society. We invite you to join us as we plan for our future. We look forward to any suggestions that you, the physicians across the great state of Missouri, have regarding how our institution can better fulfill its missions and work more closely and effectively with you.



David J. Murray, MD, the Carol B. and Jerome T. Loeb Professor of Anesthesiology (right), works with (from left) Luke Lowry, Daniel Seitz, Antonina Frolova and Gregory Bryant, all recent School of Medicine graduates, in the Howard and Joyce Wood Simulation Center. Murray has been credited with developing the simulation center into one of the leading clinical simulation programs in the United States.

To learn more about the many initiatives in research, patient care and education at Washington University School of Medicine, and to keep up to date with the promising work being done here, please visit http://medicine.wustl.edu.

MM

Why choose between national resources and Missouri clout?

The Doctors Company protects you with **both.**

As a member of the nation's largest physician-owned medical malpractice insurer, you won't have to choose. You will benefit from our financial strength and stability—with 74,000 members and $4 billion in assets—that enables us to protect you now and in the future.

You also benefit from our long-standing relationships with Missouri's leading attorneys and litigation experts. As one of the early leaders of the tort reform movement, we will work tirelessly to reinstate limits in Missouri. And we'll help you reduce the likelihood of a claim with the state's only dedicated Patient Safety Department.

Founded by doctors for doctors, we are fiercely committed to rewarding our members. The Tribute® Plan is an unrivaled financial benefit that rewards you for your loyalty to The Doctors Company and for your commitment to superior patient care. No other Missouri insurer offers a benefit of this magnitude.

To learn more about our benefits for Missouri members, call our Springfield office at (800) 865-0650 or visit www.thedoctors.com.

We relentlessly defend, protect, and reward the practice of good medicine.

THE DOCTORS COMPANY

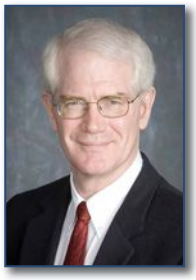
www.thedoctors.com

Knight ADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

Neurodegenerative Disorders of Aging: The Down Side of Rising Longevity

by John C. Morris, MD

The exact causes of neurodegeneration remain the focus of much investigation, but as nerve cells have some of the highest metabolic rates in the human body, one possibility links the lifetime "wear and tear" on these cells.



John C. Morris, MD, MSMA member since 2007, is the Friedman Distinguished Professor of Neurology and the Director of the Knight Alzheimer's Disease Research Center at the Washington University School of Medicine in St. Louis.
Contact: morrisj@abraxas.wustl.edu

The United States (U.S.) population is undergoing a demographic revolution, with ever-growing numbers of adults living to age 65 and beyond such that the proportion of older adults in our society will increase from 13% in 2010 to 20% by 2040. All-race U.S. life expectancies, also increasing, already are 81 years for women and 76 years for men. There thus not only are many more older adults, they are living longer. Longevity brings increasing risk for neurodegenerative disorders, in which nerve cells (neurons) deteriorate and die.

The exact causes of neurodegeneration remain the focus of much investigation, but as nerve cells have some of the highest metabolic rates in the human body, one possibility links the lifetime "wear and tear" on these cells to a failure to produce sufficient bioenergetics and to successfully neutralize byproducts of metabolism, such as free radicals, necessary to maintain neuronal health. Such a notion is consistent with the marked association with increasing age of the most common (and most feared) neurodegenerative disorder, Alzheimer disease (AD).

AD already is a public health menace of the highest order, as the disease costs over $200 billion a year in the U.S. to care for its victims. It is by far the most common cause of dementia and, alone among the leading causes of death, lacks any effective therapy to materially slow or halt its course or to prevent its occurrence. It is a disorder unique to humans, as the most highly developed brain cells in higher order association cortex are most vulnerable to the disease process. As synapses and neurons gradually degenerate and die, their brain functions become gradually impaired and eventually lost.

Hence, the clinical presentation of the illness is reflected in the gradual onset and inevitable progression of the clinical manifestations of the deteriorating function of higher order association cortex: impaired memory, insight, attention, reasoning, language, and personality. As the disease progresses over the typical 7-10 years from onset to death (AD is universally fatal), eventually other brain areas are affected and the individual loses the ability to control sphincters, swallow, talk, or walk. It is so feared because the affected individual gradually but

Alzheimer disease is so feared because the affected individual gradually but steadily loses their autonomy and their very personhood, becoming ever more dependent and disabled.

steadily loses their autonomy and their very personhood, becoming ever more dependent and disabled.

Alzheimer disease currently is diagnosed based on its dementia syndrome: the gradual onset and progression of memory and other cognitive impairment, representing a decline for that individual from previously attained abilities, which is sufficient to interfere with the performance of accustomed activities. However, this diagnostic process is time-consuming and inexact; it is estimated that 50% of all individuals with AD dementia remain to be diagnosed by their physicians. Our faculty outpatient group, the Memory Diagnostic Center at Washington University Medical Center in St. Louis, is working to improve dementia diagnosis and management and to translate these improvements to our clinician colleagues throughout Missouri. In addition, our Knight Alzheimer's Disease Research Center (ADRC) is conducting translational research to not only enhance the tools needed to accurately identify persons with AD but also to develop and evaluate mechanism-based therapies that one day may provide truly effective therapy for this disorder.

The accompanying series of articles is contributed by members of the Memory Diagnostic Center and the Knight ADRC. The article written by Erik Musiek and Suzanne Schindler is focused on a high level but very practical approach to the clinical diagnosis and management of AD dementia. The paper from Suzanne Schindler, Jonathan McConathy, Beau Ances, and Marc Diamond extends the current clinical approach to the coming era of diagnostic testing for AD using molecular imaging and fluid biomarkers, which in the very near future are expected to allow us to move from a syndromic diagnosis to one that is supported by objective test results.

Not all dementia is caused by AD. In older adults, Parkinson disease also is a leading cause of dementia. The article by Allison Willis summarizes the most modern clinical approach to Parkinson disease and its management, and points to its role as another important neurodegenerative dementing disorder. In younger adults (e.g., <60 years), frontotemporal dementia (FTD) is equal to AD as a cause of dementia. The paper by Nupur Ghoshal and Nigel Cairns reviews this fascinating and informative group of disorders and illustrates how specific clinical disease phenotypes reflect the specific brain regions involved. Taha Bali and Timothy Miller link the FTD disorders to the spectrum of neurodegenerative motor neuron diseases (e.g., amyotrophic lateral sclerosis) and discuss a new genetic basis for this linkage. Finally, the previously under-recognized conditions that are characterized by rapidly progressive dementia (in contrast to the gradual onset and progression of neurodegenerative dementias) are reviewed by Robert Bucelli and Beau Ances as more state-of-the-art diagnostic tools are available for their recognition. The importance of this group of disorders is that some are responsive to selected therapies and thus the dementia potentially is reversible.

We provide these articles in hope that they will benefit the readers of Missouri Medicine with a better appreciation of the neurodegenerative dementing disorders and related diseases. Better recognition ultimately will translate to better management, and better management will lead to better understanding of the responsible etiologies. In this way, we hope together to develop the clinical infrastructure that will result in truly effective treatments for these devastating diseases.

Acknowledgments

This series of articles would not have been accomplished without the organizational and editorial efforts of Krista Moulder, PhD, who expertly oversaw the entire conceptual and writing process. Linda Krueger provided excellent editorial assistance. Dr. Morris, Dr. Moulder, and Ms. Krueger are supported by National Institute on Aging grants P50AG05681, P01AG03991, P01AG026276, and U19AG032438.

MM

Knight ADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

Alzheimer Disease: Current Concepts & Future Directions

by Erik S. Musiek, MD, PhD & Suzanne E. Schindler, MD, PhD

Alzheimer Disease is a devastating neurodegenerative disease which affects millions of people, and threatens to become a public health crisis in coming years.





Erik S. Musiek, MD, PhD, (left) is a an Assistant Professor of Neurology, and Suzanne E. Schindler, MD, PhD, is a Clinical and Postdoctoral Research Fellow in Neurology. Both are with the Knight Alzheimer's Disease Research Center at the Washington University School of Medicine in St. Louis.
Contact: musieke@neuro.wustl.edu

Abstract

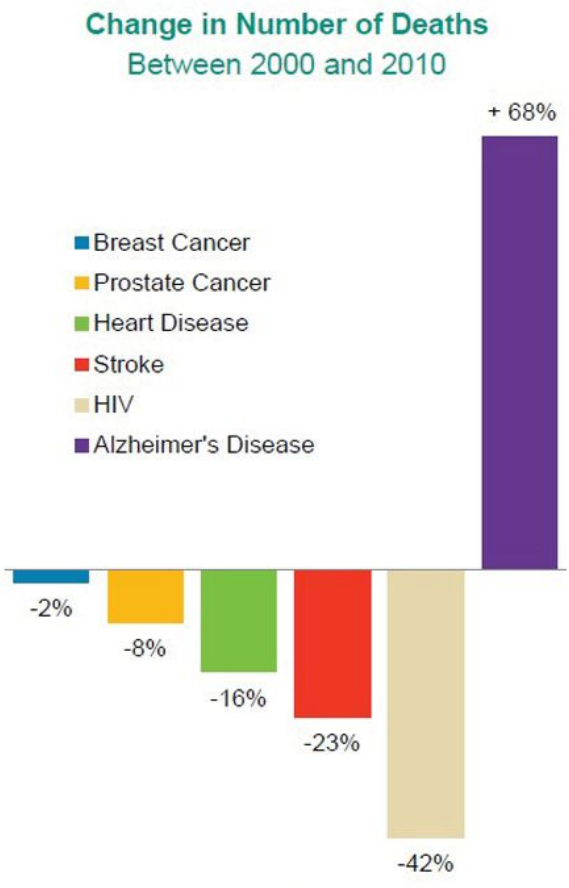
Alzheimer disease (AD) is the most common cause of dementia in individuals over age 65, and is expected to cause a major public health crisis as the number of older Americans rapidly expands in the next three decades. Herein, we review current strategies for diagnosis and management of AD, and discuss ongoing clinical research and future therapeutic directions in the battle against this devastating disease.

Introduction and Epidemiology

Alzheimer disease (AD) is a major public health problem in the United States and throughout the world. AD is the most common cause of dementia in people over the age of 65 and affects well over five million people in the United States (U.S.), including 110,000 people in Missouri[1]. As the population ages, the number of American AD cases is projected to explode to 16 million by 2050, with an estimated annual cost of 1 trillion dollars.[1] Aside from its devastating effect on affected individuals, AD also takes an enormous toll on caregivers, as caring for an Alzheimer's patient has been associated with financial stress, depression, and increased risk for other medical problems. Moreover, while the numbers of deaths caused by the other major killer diseases in the U.S., such as heart disease, cancer, and HIV, have declined in the past decade, deaths caused by AD continue to increase (See Figure 1). While no curative therapies have yet been developed, diagnosis of AD early in the disease course is important in that it allows for optimal initiation of symptomatic therapy and lifestyle modification, provides the opportunity for the patient to make plans for her own future, and may someday facilitate the preservation of cognition through disease-modifying therapy.

Alzheimer disease is characterized clinically by an insidious onset and progressive decline of cognitive function, usually beginning with impairment of short term memory. The classic neuropathologic hallmarks of AD are amyloid plaques, which are formed by aggregation of the amyloid-beta (Aβ) peptide, and neurofibrillary tangles, which consist of misfolded tau protein (See Figure 2). Autopsy data demonstrate that amyloid plaques begin forming in the brain many years before the onset of any symptoms. Amyloid plaques likely initiate a pathological cascade of events, including tau misfolding, oxidative stress and synaptic injury that eventually lead to neuronal death

Figure 1
Percent change in number of deaths caused by major diseases in the US, 2000-2008. Source: The Alzheimer's Association.



and brain dysfunction.[2] The medial temporal lobe, which plays a critical role in short term memory, is particularly affected in AD, explaining the early characteristic deficits in short term memory.

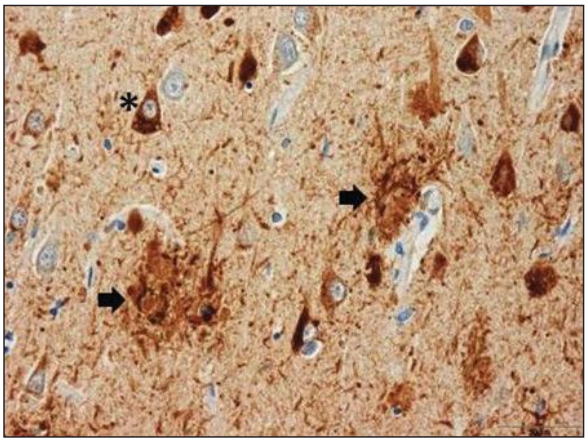
Age is the strongest risk factor for the development of AD. At age 65, 13% of Americans have AD and by age 85 over 45% are affected.[1] Family history impacts AD risk, as individuals with an affected first degree relative (parent or sibling) have a two-three fold increased risk of developing AD. The vast majority of AD cases (99%) are sporadic, following no clear Mendelian genetic inheritance pattern. For sporadic AD, Apolipoprotein E (*APOE*) genotype is the major genetic susceptibility factor. *APOE* ε3 is the most common genotype in the overall population. In comparison to ε3, the ε2 allele imparts a decreased risk of AD, while the ε4 allele is associated with an increased risk. Two copies of the ε4 allele increase the risk of AD by 12-fold, and about half of all AD patients harbor at least one *APOE* ε4 allele.[3] Recent evidence suggests that *APOE* is important in Aβ metabolism and amyloid plaque formation.[3] Several other genes have recently been identified which modulate the risk of sporadic AD, and ongoing research is investigating their functions. In less than 1% of cases, a dominantly inherited familial form of AD is caused by mutations in amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), or presenilin 2 (*PSEN2*). Disease-causing mutations have been shown to influence production of Aβ peptide.[4] Most patients with dominantly inherited AD present with symptoms between age 30-50.

Proposed environmental risk factors for AD include traumatic brain injury, low educational attainment, diabetes, obesity, and cardiovascular risk factors such as high cholesterol and coronary artery disease.[1] Women have a significantly higher lifetime risk of AD than men, due in part to their longer average lifespan. Caucasians have lower rates of AD than do African Americans or Hispanic Americans, though the reason for this is unknown. Exercise, healthy diet (including high intake of fish, fruits, and vegetables), and remaining cognitively involved and stimulated are all associated with lower risk of AD, although it has not been proven that any specific food or activity can prevent AD or slow its course. While a variety of over the counter agents have been purported to bolster cognition or prevent AD, most of these have not been rigorously tested, and none have been proven efficacious in randomized controlled clinical trials in humans.

Phenotype

The typical clinical course of AD dementia is characterized by an insidious onset and slow progression of symptoms over years.[5] The initial symptoms are often related to short term memory deficits, such as repeating questions or statements, forgetting appointments, misplacing items, or forgetting important details about events. In the early stages, these symptoms can be very subtle, and can manifest simply as slight decline in the patient's ability to perform complex tasks. Problems with orientation, including confusion about the date or getting lost, are often seen early in AD dementia. As the disease progresses, patients often require assistance managing finances, shopping, driving, and keeping track of their schedule. In moderate AD dementia, patients depend heavily upon a caregiver and often require assistance

Figure 2
Amyloid plaques and neurofibrillary tangles within neurons in a silver-stained brain section from an Alzheimer's disease patient (see asterisk and black arrows below).



maintaining their hygiene. At the end stages of AD dementia, patients are completely dependent on others, may forget the identities of their closest friends and family members, and may become bed-bound. The proximate cause of death is usually aspiration or infection.

Diagnostic Methods

The goals of the initial history, exam, laboratory work-up and imaging are 1) to rule-out causes of cognitive dysfunction not related to neurodegenerative disease and 2) to diagnose the presence or absence of a neurodegenerative disease based on the history, exam, any available psychometric data, labs and imaging data.

History and exam

The majority of the history should be obtained from a collateral source familiar with the patient's daily life, as patients with cognitive impairment often have poor insight into their condition. The focus of the history should be on changes in the patient's memory and thinking over time, as individuals vary greatly in their baseline abilities and habits. For example, are there certain abilities the patient has lost because of a decline in memory or thinking? Although most people can describe occasional lapses in memory, the history should probe for problems that are consistent and worsening over time. The AD-8 Dementia Screening Interview can be helpful, as it is sensitive to early cognitive changes associated with dementia[6] and is brief, reliable, and available at no cost. The AD-8 does not definitively diagnose dementia, but it can be helpful in identifying patients who require further evaluation (See Figure 3).

Common causes of cognitive dysfunction, particularly in the elderly, include depression and cognitive side effects of medications. It is important to directly ask the collateral source and patient about symptoms of a possible mood disorder because this information is often not immediately offered. The patient's medication list should be scrutinized for psychoactive medications, such as benzodiazepines, anti-cholinergics, pain medications, and sleep aids that can cause or exacerbate cognitive dysfunction. Any association between the patient's symptoms and alcohol consumption should be assessed. A family history of dementia can suggest the patient is at higher risk, especially in cases of early onset dementia. Finally, it is helpful to screen for obstructive sleep apnea (OSA), as OSA is associated with a higher rate of developing dementia and is often treatable.[7] In patients with dementia, disrupted sleep-wake cycles are common and may be a major cause of caregiver stress.

The patient should undergo a screening neurological examination. Verbal fluency should be noted, as certain dementias are associated with prominent language difficulties. A neurologic exam should be performed to exclude focal signs, which might suggest stroke, demyelination, or a mass lesion. The examiner should also evaluate for increased muscle tone, tremor, slowness, abnormal gait, or poor balance, which may indicate a Parkinsonian syndrome. Most patients presenting with AD dementia have normal neurological exams except for evidence of cognitive impairment.

Psychometric testing can be helpful in some circumstances: 1) Quantifying a subtle deficit 2) Identifying which cognitive domains are affected 3) Providing a baseline against which future testing can be compared. In addition to the informant-based AD8, short instruments that can be administered to the patient in an office setting include the Mini Mental State Exam (MMSE),[8] the Short Blessed Test[9] and the Montreal Cognitive Assessment (MOCA, available at www.mocatest.org).[10] Interpretation of the tests must take into account educational level and any other factors that could affect the result, including decreased vision or hearing. A poor result on a test does not definitively diagnose dementia, but may lend support to the diagnosis. Complete evaluation performed by a licensed clinical neuropsychologist can be helpful in complex or atypical cases.

Laboratory work-up and imaging:

Since cognitive dysfunction may be caused by a large number of medical and neurological causes, a thorough evaluation to rule-out potentially treatable causes of dementia is needed. Blood tests to be ordered include

blood chemistries (including liver function test and creatinine), complete blood cell count, thyroid stimulating hormone (TSH) and vitamin B12 level. In patients with early onset dementia, atypical dementia, or risk factors for sexually transmitted infections, it is also appropriate to check a rapid plasma reagin (RPR) and HIV antibody. At this time, it is not recommended that patients routinely be tested for *APOE* isoform or mutations associated with autosomal dominant Alzheimer's disease.[11]

Practice parameters developed by the American Academy of Neurology recommend that brain imaging be performed on all patients with cognitive decline.[11] A brain MRI both with and without contrast and including diffusion sequences is the most sensitive test. In patients with renal dysfunction the MRI can be performed without contrast. In patients who cannot undergo an MRI because of contraindications such as an implanted pacemaker, a head CT is acceptable but may not visualize more subtle findings. In cases of early onset dementia, atypical dementia or dementia of uncertain diagnosis, cerebrospinal fluid (CSF) and advanced imaging techniques may help clarify the diagnosis. These methods, including recently-developed tests for CSF Aβ and tau and PET-based imaging of brain amyloid plaques (amyloid imaging) allow for more specific and earlier diagnosis of AD. These tests are described further in the article entitled, "Advances in Diagnostic Testing for Alzheimer Disease."

Patients with onset of dementia prior to age 60, rapid progression of dementia over months, or atypical forms of dementia may benefit from seeing a dementia specialist for further evaluation. Symptoms of atypical dementias may include early and prominent changes in behavior, language, visuospatial function or movement.

Management

Two classes of medications are FDA approved for the treatment of AD. Acetylcholinesterase inhibitors, including donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Razadyne®) are approved for symptomatic treatment of mild to moderate AD, and are intended to support memory by increasing the amount of available acetylcholine in the synaptic cleft by preventing its breakdown. All of these agents are available in generic forms for oral administration. These drugs can cause gastrointestinal side effects including nausea, vomiting, and diarrhea, as well as cardiovascular effects such as bradycardia. Donepezil is the most commonly prescribed, and is usually initiated at 5 mg daily for four to six weeks, then increased to 10 mg daily if tolerated. A 23mg dosage has been approved that may impart slight increases in efficacy, but it is associated with significantly higher risks of gastrointestinal side effects[12]. Rivastigmine is available as a patch (not yet available as a generic), which may have lower incidence of nausea and can be helpful in more advanced AD patients who have difficulty remembering to take their pills.

The second class of FDA approved AD medication is N-methyl-D-aspartate (NMDA) glutamate receptor antagonists. Memantine (Namenda®) has been approved for use in moderate to severe AD. The initial postulated mechanism of action was reduction in glutamatergic excitotoxicity, but several studies have shown this is not the case. Memantine is also a non-competitive antagonist of serotonin $5HT_3$ and nicotinic acetylcholine receptors, and activates dopamine D2 receptors, though it is unclear if these actions mediate its effects. Side effects from memantine are quite rare, but can include confusion, drowsiness, headache, agitation, insomnia, and hallucinations.[13] Generic memantine is not yet available in the U.S. Generally, memantine is added to the regimen after the patient has already reached a stable dose of an acetylcholinesterase inhibitor, though it can be used as monotherapy in patients who do not tolerate acetylcholinesterase inhibitors.

In more advanced disease, patients can become aggressive and violent. Atypical antipsychotic medications are sometimes indicated, but should be used carefully because of studies showing that antipsychotics increase mortality in elderly dementia patients. Benzodiazepines should also be used with great caution, as they can cause paradoxical increases in agitation, as well as dependence and withdrawal. Non-pharmacologic strategies for behavioral management include keeping the environment consistent, non-threatening, and calm, avoiding cues which may precipitate agitation, and simplifying the daily routine. Depression and anxiety are very common in AD patients, and physicians and caretakers must be vigilant for these conditions and treat them appropriately. The Alzheimer's Association (www.alz.org) provides a wealth of valuable resources for both patients and caregivers, and in many areas provides a variety of informational sessions, support groups, and referral services.

Regarding safety, assessment of driving skills by a professional is recommended for any individuals with notable cognitive impairment, and restricting or eliminating driving is encouraged if there is substantial concern. Firearms in the home should be secured. Patients may need oversight with meals and with their medications, as well as

Figure 3: 8-item Informant Interview to Differentiate Aging and Dementia*
(Positive Predictive Value = 87% for CDR 0 vs CDR ≥ 0.5)

Report only a change caused by memory and thinking difficulties		
	Yes	**No**
1. Is there repetition of questions, stories, or statements?		
2. Are appointments forgotten?		
3. Is there poor judgment (e.g., buys inappropriate items, poor driving decisions)?		
4. Is there difficulty with financial affairs (e.g., paying bills, balancing checkbook)?		
5. Is there difficulty in learning or operating appliances (e.g., television remote control, microwave oven)?		
6. Is the correct month or year forgotten?		
7. Is there decreased interest in hobbies and usual activities?		
8. Is there overall a problem with thinking and/or memory?		
TOTAL AD8 SCORE		

*Adapted from Galvin et al, "The AD8: A Brief Informant-Interview to Detect Dementia", *Neurology*. 2005;65:559-564.

with personal finances, and in some cases access to banking and investment accounts must be restricted. Patients with moderate disease may not be safe to leave unattended at home, as dangerous situations such as leaving water or a gas stove on are quite common. As the disease progresses, patients are likely to wander, and may need constant supervision, as well as a SafeReturn® bracelet, available through the Alzheimer's Association.

Future Directions

It is an exciting time for research in AD and other dementias, as over 70 clinical trials of experimental therapies are ongoing. Large-scale clinical studies of dementia and healthy aging, including the Memory and Aging Project at Washington University and the nationwide Alzheimer's Disease Neuroimaging Initiative, have provided critical insights into how AD begins and progresses, and have shown that the pathological process leading to clinical AD begins at least a decade prior to the onset of any cognitive symptoms.[2] With the advent of new biomarkers, very early and even presymptomatic diagnosis is now possible. Unfortunately, at this point in time, all efforts at therapeutic intervention in the symptomatic disease course have failed. Thus, it appears that treatment strategies for AD must be initiated as early in the disease course as possible, to prevent ongoing neurodegeneration.[2] Ideally, asymptomatic individuals could be screened and treated presymptomatically, thereby preventing or delaying dementia. At present, there is no such therapeutic "prevention" option and thus presymptomatic screening cannot be encouraged.

The majority of current experimental therapeutic strategies for AD focus on eliminating Aβ, as Aβ accumulation appears to precede neurodegeneration and symptom onset by years, and likely initiates the pathogenic cascade in AD. Passive immunization with antibodies that bind Aβ is an attractive paradigm, and a number of monoclonal antibodies are in various stages of clinical trials in humans.[1]. Small molecule inhibitors of beta- and gamma-secretases, enzymes which play critical roles in the generation of Aβ, have also been developed, and several are in late stage clinical trials.[15, 16] As mentioned above, there have been several well-publicized failures of anti-amyloid therapies in phase III clinical trials in the past few years, including both Aβ antibodies and gamma secretase inhibitors. It is likely that these failures were due to multiple issues including poor efficacy of the drug in reducing Aβ levels, treatment too late in the disease process, and dilution of the trial population with non-AD dementias. A second generation of therapeutics is now entering phase III trials, and clinical trial methodology is being refined, so there is hope that an effective Aβ-targeted therapy will be identified. The first clinical trials providing presymptomatic therapy for rare early onset familial AD patients are beginning this year, including the Dominantly Inherited Alzheimer's Network (DIAN) treatment trial,

and the Alzheimer's Prevention Initiative (API). The DIAN trials will employ two distinct anti-Aβ antibodies and API will use another Aβ antibody.[17, 18] While they focus on rare autosomal dominant AD, success of these trials may set the stage for future preventative trials in sporadic (late onset, non-familial) AD. Indeed, a third trial, entitled the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) study, will evaluate presymptomatic therapy with anti-Aβ antibodies in 70+ year old participants with no cognitive symptoms, but with amyloid imaging evidence of presymptomatic AD. Thus, the era of presymptomatic anti-amyloid experimental therapy is at hand (but far from ready for clinical use), and these important trials likely will have major impact on the AD field for years to come.

While these initial trials all employ therapies targeting Aβ, non- Aβ therapies are also in development, including agents which aim to reduce tau aggregation, suppress neuroinflammation, prevent oxidative injury, augment neuronal metabolism, and modulate *APOE* levels. Small molecule activators of α7 nicotinic acetylcholine receptor and nasally-inhaled insulin have entered clinical trials, both of which have been show to enhance cognition in AD in smaller studies, providing new possible avenues of symptomatic therapy.[19, 20] Intravenous immunoglobulin (IVIG) has shown promise in stabilizing cognition in small cohorts of symptomatic AD patients, though the mechanisms are unclear, and a larger trial has reportedly failed. Preclinical studies in mouse models have identified dozens more potential therapeutic targets, which await validation in humans but will hopefully keep the drug development pipeline stocked for years to come.

Conclusion

Alzheimer disease is a devastating neurodegenerative disease which affects millions of people, and threatens to become a public health crisis in coming years. Great strides have been made in our understanding of the underlying disease mechanisms and in early diagnosis, and the first experimental efforts to treat AD presymptomatically are beginning, potentially heralding a new era of AD management.

References

1. Alzheimer's Association. 2012 Alzheimer's Disease Facts and Figures, Alzheimer's & Dementia.; 8: 131-168
2. Perrin RJ, Fagan AM, Holtzman DM. Multimodal techniques for diagnosis and prognosis of Alzheimer's disease. Nature. 2009; 461:916-922
3. Verghese PB, Castellano JM, and Holtzman DM. Apolipoprotein E in Alzheimer's disease and other neurological disorders. Lancet Neurology. 2011, 10:241-252
4. Mayeux R. Clinical practice. Early Alzheimer's disease. N Engl J Med. 2010; 362:2194-2201.
5. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011; 7:263-269.
6. Galvin JE, Roe CM, Xiong C, Morris JC. Validity and reliability of the AD8 informant interview in dementia. Neurology. 2006; 67:1942-1948.
7. Yaffe K, Laffan AM, Harrison SL, Redline S, Spira AP, Ensrud KE, Ancoli-Israel S, Stone KL. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. JAMA. 2011; 306:613-619.
8. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J. Psychiat Res. 1975; 12:189–198.
9. Katzman R, Brown T, Fukd P, Peck A, Schechter R, Shimmel H. Validation of a short orientation-memory-concentration test of cognitive impairment. Am J Psychiat. 1983; 140:734-739.
10. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment (MoCA©): A Brief Screening Tool For Mild Cognitive Impairment. J Am Geriatr Soc. 2005; 53:695–699.
11. Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2001; 56:1143-1153.
12. Farlow MR, Salloway S, Tariot PN, Yardley J, Moline ML, Wang Q, Brand-Schieber E, Zou H, Hsu T, Satlin A. Effectiveness and tolerability of high-dose (23 mg/d) versus standard-dose (10 mg/d) donepezil in moderate to severe Alzheimer's disease: A 24-week, randomized, double-blind study. Clin Therapy. 2010; 32:1234-1251.
13. Areosa Sastre A, Sherriff F, McShane R. Memantine for dementia. The Cochrane Database of Systematic Reviews. 2005; Issue 3. Art. No.: CD003154. DOI: 10.1002/14651858.CD003154.pub4.
14. Panza F, Frisardi V, Imbimbo BP, Seripa D, Solfrizzi V, Pilotto A. Monoclonal antibodies against β-amyloid (Aβ) for the treatment of Alzheimer's disease: the Aβ target at a crossroads. Expert Opin Biol Ther. 2011; 11:679-686.
15. Ghosh AK, Brindisi M, Tang J. Developing β-secretase inhibitors for treatment of Alzheimer's disease. J Neurochem. 2012; 120 Suppl 1:71-83
16. Wolfe MS. γ-Secretase inhibitors and modulators for Alzheimer's disease. J Neurochem. 2012; 120 Suppl 1:89-98.
17. Morris JC, Aisen PS, Bateman RJ, Benzinger TL, Cairns NJ. Et al. Developing an international network for Alzheimer research: The Dominantly Inherited Alzheimer Network. Clin Investig (Lond). 2012; 2:975-984.
18. Reiman EM, Langbaum JB, Fleisher AS, Caselli RJ, Chen K, Ayutyanont N, Quiroz YT, Kosik KS, Lopera F, Tariot PN. Alzheimer's Prevention Initiative: a plan to accelerate the evaluation of presymptomatic treatments. J Alzheimers Dis. 2011; 26 Suppl 3:321-329.
19. Haydar SN, Dunlop J. Neuronal nicotinic acetylcholine receptors - targets for the development of drugs to treat cognitive impairment associated with schizophrenia and Alzheimer's disease. Curr Top Med Chem. 2010; 10:144-152.
20. Craft S, Baker LD, Montine TJ, Minoshima S, Watson GS, Claxton A, Arbuckle M, Callaghan M, Tsai E, Plymate SR, Green PS, Leverenz J, Cross D, Gerton B. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Arch Neurol. 2012; 69:29-38.

Disclosure

None reported.

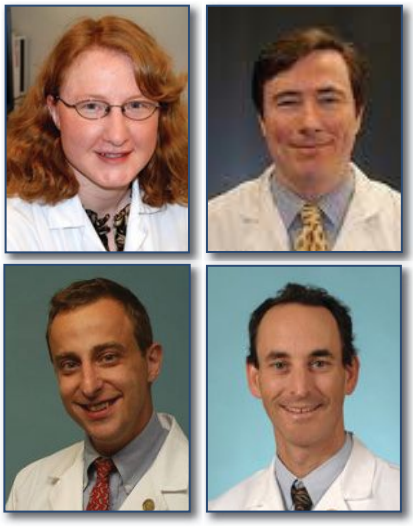
MM

Knight ADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

Advances in Diagnostic Testing for Alzheimer Disease

by Suzanne E. Schindler, MD, PhD, Jonathan McConathy, MD, PhD, Beau M. Ances, MD, PhD & Marc I. Diamond, MD

Confirming diagnosis encourages patients and caregivers to join organizations, such as the Alzheimer's Association, that offer resources to manage the illness.



Top, from left: Suzanne E. Schindler, MD, PhD, is a Clinical and Research Postdoctoral Fellow. Jonathan McConathy, MD, PhD, Assistant Professor, Radiology. Bottom, from left: Beau M. Ances, MD, PhD, is an Associate Professor, Neurology. Marc I. Diamond, MD, is the David Clayson Professor of Neurology. All are at the Knight Alzheimer's Disease Research Center at the Washington University School of Medicine in St. Louis.
Contact: schindlers@neuro.wustl.edu

Abstract

The diagnosis of Alzheimer disease (AD) dementia is based primarily on the clinical history and examination, but advances in understanding the pathophysiology of AD have led to new diagnostic methods. When used appropriately, the tests can provide strong positive or negative evidence AD dementia. This article described which patients may benefit from additional testing using Cerebrospinal Fluid (CSF) biomarkers, amyloid imaging, quantitative structural magnetic resonance imaging (MRI), and fluoro-deoxyglucose positron emission tomography (FDG-PET).

Introduction

The development of biomarkers and imaging techniques for the diagnosis of Alzheimer disease (AD) has progressed considerably in the last several years. This article will describe the advanced diagnostic methods for AD that are currently available in clinical practice and when they are helpful.

A clear diagnosis of AD dementia can be helpful to patients in many ways. The diagnosis validates and explains the difficulties that patients have been experiencing and that caregivers have been noticing. Patients and caregivers may find comfort and support in educating themselves about the disease. Confirming diagnosis encourages patients and caregivers to join organizations, such as the Alzheimer's Association, that offer resources to manage the illness. Knowledge of their loved one's diagnosis may help caregivers to make plans that include choosing an appropriate living situation, completing legal paperwork and making a plan for supportive care. Patients with a clear diagnosis may also be more likely to start medications that help with the symptoms of disease.

Despite advances in diagnostic testing, AD dementia remains a clinical diagnosis. The available tests are not perfect and should be used by a clinician to help choose between diagnoses or, in some cases, to provide greater confidence in the diagnosis of AD dementia. There is no indication for testing in asymptomatic

individuals, particularly because we have no effective preventative therapy. A positive result also has not been demonstrated to inevitably result in dementia, and even if it did, it cannot predict the time frame within which the individual may develop symptoms, i.e. whether he or she will develop dementia in 1 year or 20 years. An asymptomatic individual who tests positive is likely to experience anxiety about developing dementia, but cannot significantly change their risk of dementia or predict when they will first manifest symptoms. Therefore, testing is not offered to asymptomatic individuals.

Indications for Referral and/or Advanced Diagnostic Testing

Alzheimer disease is a progressive neurodegenerative disease characterized neuropathologically by amyloid plaques, neurofibrillary tangles, and loss of neurons. The clinical syndrome of cognitive decline that accompanies AD pathology is termed AD dementia.[1] Practice parameters developed by the American Academy of Neurology,[2] as described by an article in this issue entitled "Alzheimer disease," allow accurate diagnosis in many cases. The work-up consists of a detailed history from someone who knows the patient well, a screening neurological examination, routine laboratory testing, and brain imaging. The evaluation focuses on ruling out reversible causes of dementia and establishing a clinical history typical of AD dementia.

After a complete initial evaluation, it is still sometimes unclear whether a patient has AD dementia or some other cause of cognitive dysfunction. A referral to a dementia specialist may be indicated for a patient with unusual or complex cognitive problems, particularly if primary care physicians do not have the time or resources to perform a very detailed evaluation. A patient that falls into the following categories may particularly benefit from an evaluation by a dementia specialist and/or advanced diagnostic testing:

1. Early Onset Dementia

A patient younger than 65 with symptoms of dementia and no additional conditions explaining his or her cognitive decline may benefit from either cerebrospinal fluid (CSF) testing or an amyloid-PET scan to help support the diagnosis. Since AD dementia is unusual in patients before age 65,[3] and because the diagnosis of AD dementia will likely have a more devastating impact on a younger patient's life, a supporting laboratory test can reassure both the patient and clinician that the diagnosis is correct. Additionally, in patients with a strong family history of AD dementia and a very early age of onset (before age 55), genetic testing may be considered in cases with an appropriate pedigree demonstrating autosomal dominant inheritance over several generations.

2. Prominent Behavioral or Language Problems

A patient who develops prominent behavioral changes and/or language problems early in the course of disease may have a frontotemporal dementia (FTD). Additional history of the patient's behavioral changes and a detailed examination of the patient's language function are important. FDG-PET is sometimes used to evaluate patterns of regional hypometabolism and to help discriminate between dementia caused by FTD or by other diseases, including a rare "frontal variant" of AD[4]. When indicated, the presence of AD pathology can be established using either CSF testing or an amyloid-PET scan.

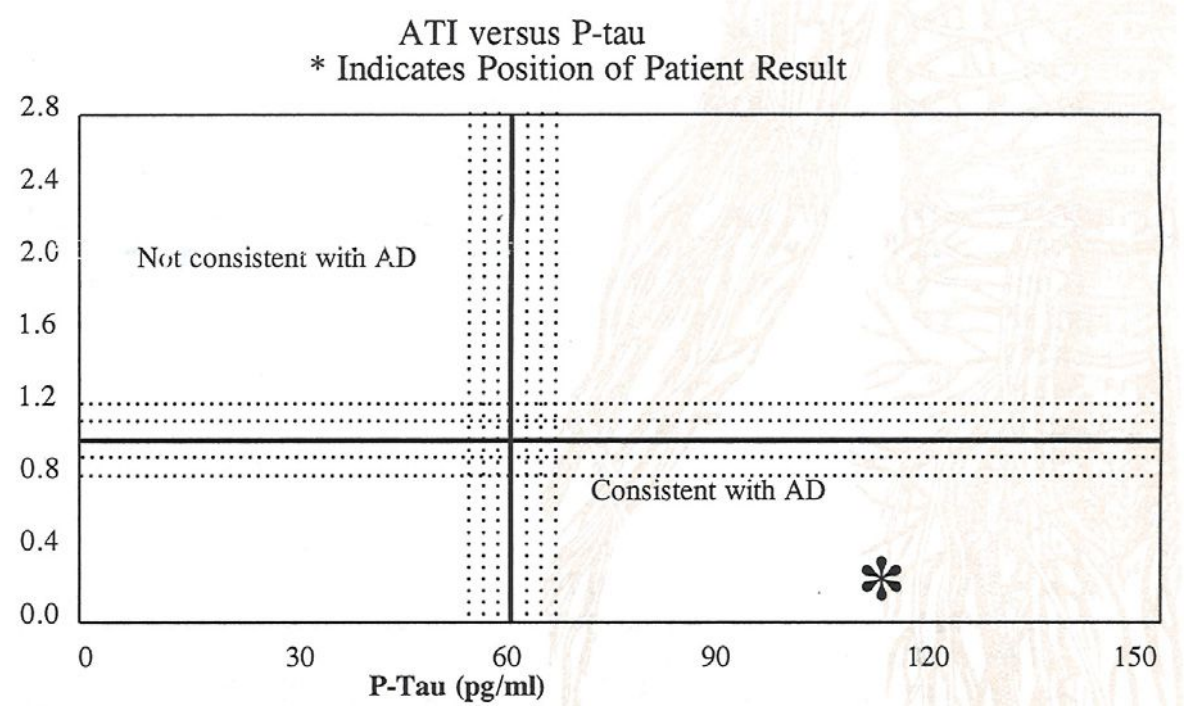
3. Prominent Visuospatial Dysfunction

A rare form of AD dementia, posterior cortical dysfunction, presents with prominent visuospatial problems.[5] The patient's eye exam may appear normal, but the patient may have deficits in processing visual information that can render him or her functionally blind. A detailed neurological examination is required to evaluate the extent of the visual deficits. A positive CSF test or an amyloid-PET scan supports the diagnosis of AD. Other causes of posterior cortical dysfunction include Parkinson disease and Creutzfeldt-Jakob disease.

4. Rapidly Progressive Dementia

Alzheimer disease dementia usually causes a very slowly progressive decline in memory and thinking and rarely results in an appreciable change from one week to the next or even one month to the next. When cognition rapidly worsens in a patient with pre-existing AD dementia, it may indicate a medical problem such as an infection. In a patient without pre-existing dementia, a sudden decline in memory and thinking over weeks to months may be caused by a number of different etiologies, some of which may be treatable. The work-

Figure 1
Athena Diagnostics® is a commercial laboratory that performs the assays that provide a graphical interpretation of the results as consistent with AD.



up is often complex and may require hospitalization (see article in this series on rapidly progressive dementia).

5. Uncertain Dementia

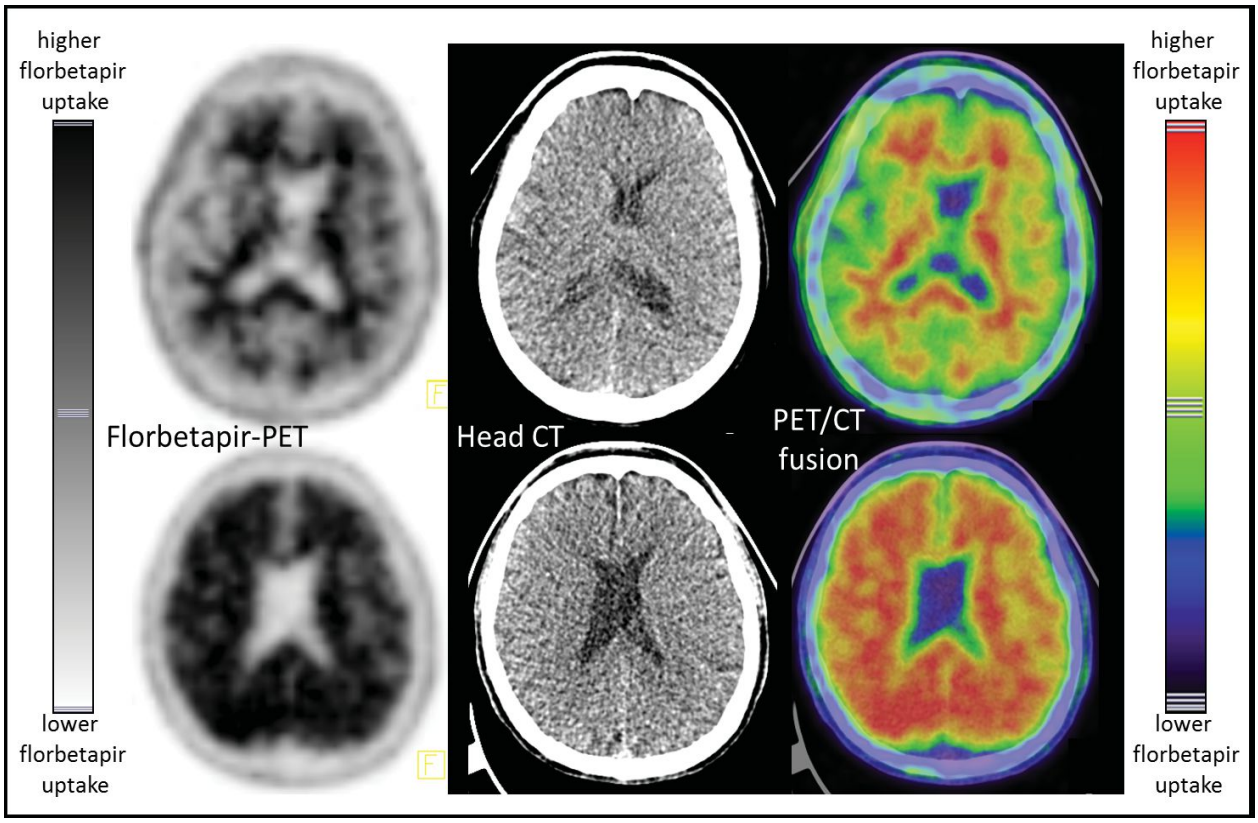
A patient with very mild memory changes consistent with AD dementia and no complicating factors usually has incipient AD dementia. Further testing is typically not necessary; instead, following the patient clinically over the next year or two usually provides information leading to a diagnosis. In a patient with very mild but consistent cognitive decline who has medical or psychiatric problems that complicate the diagnosis, further testing can help establish whether AD-related brain pathology is present. Positive CSF testing or amyloid-PET supports the diagnosis of AD, but does not rule-out other contributors to cognitive dysfunction. Quantitative MRI allows evaluation for disproportionate cortical or hippocampal atrophy suggestive of AD or another neurodegenerative disease.

6. Individual Factors

Some patients may need a more certain diagnosis. For example, high functioning individuals with very mild AD symptoms may request confirmatory tests because an AD diagnosis would precipitate irreversible career changes (e.g. retiring, selling a company, etc.). The clinician must consider the degree of additional certainty that would be contributed by the test, and whether the results would definitely change an individual's decisions. To date, insurance companies and Medicare usually do not cover such additional studies.

The new diagnostic tests for AD dementia have resulted from advances in our understanding of AD.[6] We have learned that deposition of amyloid-β (Aβ) protein into neuritic plaques begins many years prior to the onset of symptoms and is accompanied by decreases in the 42 amino acid form of Aβ (A42) in CSF. Tau, a protein involved in neuronal structure, increases in the CSF prior to the onset of symptoms, possibly reflecting neuronal injury. Radiolabeled chemicals that bind amyloid in the brain have been developed that allow measurement of the total amount of amyloid in the brain via a PET scan. FDG-PET, which images the metabolism of the brain, can be used to evaluate the pattern of brain hypometabolism. Quantitative structural brain MRI can be used to evaluate for cortical and hippocampal atrophy

Figure 2
Following intravenous injection of florbetapir, a PET scan is performed that is interpreted as either positive, indicating moderate to frequent neuritic amyloid plaques, or negative, indicating no to sparse neuritic amyloid plaques.



due to neuronal death, which also begins prior to the onset of dementia.

Cerebrospinal Fluid Biomarkers

Cerebrospinal Fluid (CSF) biomarkers for AD require collection of the CSF via a lumbar puncture (spinal tap), a procedure which is very safe and reliable when performed by experienced personnel. CSF levels of three AD-related proteins are measured: Aβ42, tau, and tau phosphorylated at position 181. Patients with AD have low levels of CSF Aβ42 and high levels of CSF tau and phospho-tau, leading to elevated ratios of tau:Aβ42 and phosphotau:Aβ42.[7] Most patients with even very mild AD dementia have elevated ratios of tau:Aβ42 and phosphotau:Aβ42.[8] Athena Diagnostics® is a commercial laboratory that performs the assays (http://www.athenadiagnostics.com/content/test-catalog/find-test/service-detail/q/id/310) and provides a graphical interpretation of the results as consistent with AD (See Figure 1), not consistent with AD, and borderline. Some private insurance companies and Medicare may cover the costs of the lumbar puncture and CSF testing.

Amyloid Imaging

Several positron emission tomography (PET) tracers have been developed to non-invasively image fibrillary beta-amyloid plaques in the brain.[9] One of these PET tracers, florbetapir (Amyvid™), is currently FDA-approved and commercially available[10, 11] and others are likely to be approved soon. The levels of radioactivity in the cerebral cortex measured through florbetapir-PET are correlated with the frequency of neuritic amyloid plaques at autopsy.[12] Following intravenous injection of florbetapir, a PET scan is performed that is interpreted as either positive, indicating moderate to frequent neuritic amyloid plaques, or negative, indicating no to sparse neuritic amyloid plaques (See Figure 2).

A positive scan supports the diagnosis of AD dementia, but is not diagnostic because a substantial number of older individuals have neuritic plaques but are cognitively normal.[13] A negative scan makes the diagnosis of AD less likely, but does not completely rule it out. Florbetapir-PET is not currently reimbursed by the Centers for Medicare and Medicaid Services (CMS) or by most private insurance companies. Imaging centers that provide Amyvid-PET are listed at the following website: https://www.amyvidimagingcenterlookup.com/.

Quantitative Structural MRI

Nearly all patients evaluated for AD undergo structural brain imaging, usually MRI. Patients with AD usually have cortical and hippocampal atrophy.[14-16] A number of commercially available software packages exist that can perform quantitative volumetric imaging analysis to determine whether an individual's regional or whole brain volume is within the range of age- and education-matched normal older adults. Some neuroradiologists perform quantification of the degree of atrophy versus established norms using commercial packages or methods developed within the institution. Serial MRI also may be instructive, as AD is associated with progressive cerebral atrophy.

Fluorodeoxyglucose (FDG)-PET

The relative rates of glucose metabolism of different brain regions can be measured non-invasively with PET using the fluorine-18 labeled glucose analogue 2-deoxy-2-fluoro-D-glucose (FDG). FDG is intravenously injected and a PET scan is performed. Brain regions that are metabolically active preferentially take up FDG while brain regions with neuronal loss or synaptic dysfunction do not. The reader evaluates the scan to determine whether the metabolic activity is normal or whether some brain regions show evidence of hypometabolism. AD typically has a pattern of posterior temporal and parietal hypometabolism while FTD usually has frontal and anterior temporal hypometabolism.[4, 17] FDG-PET is used routinely for oncologic and neurologic imaging and is available at many PET imaging centers. Brain-FDG/PET is usually reimbursed by Medicare and private insurers when the clinical indication is to help differentiate between AD and FTD.

References

1. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association 2011; 7(3): 263-9.
2. Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001; 56(9): 1143-53.
3. Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. Lancet 2005; 366(9503): 2112-7.
4. Foster NL, Heidebrink JL, Clark CM, et al. FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. Brain 2007; 130(Pt 10): 2616-35.
5. Crutch SJ, Lehmann M, Schott JM, Rabinovici GD, Rossor MN, Fox NC. Posterior cortical atrophy. Lancet Neurol 2012; 11(2): 170-8.
6. Jack CR, Jr., Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol 2013; 12(2): 207-16.
7. Galasko D, Chang L, Motter R, et al. High cerebrospinal fluid tau and low amyloid beta42 levels in the clinical diagnosis of Alzheimer disease and relation to apolipoprotein E genotype. Archives of neurology 1998; 55(7): 937-45.
8. Fagan AM, Roe CM, Xiong C, Mintun MA, Morris JC, Holtzman DM. Cerebrospinal fluid tau/beta-amyloid(42) ratio as a prediction of cognitive decline in nondemented older adults. Archives of neurology 2007; 64(3): 343-9.
9. Rowe CC, Villemagne VL. Brain amyloid imaging. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2011; 52(11): 1733-40.
10. Doraiswamy PM, Sperling RA, Coleman RE, et al. Amyloid-beta assessed by florbetapir F 18 PET and 18-month cognitive decline: a multicenter study. Neurology 2012; 79(16): 1636-44.
11. Clark CM, Pontecorvo MJ, Beach TG, et al. Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-beta plaques: a prospective cohort study. Lancet Neurol 2012; 11(8): 669-78.
12. Clark CM, Schneider JA, Bedell BJ, et al. Use of florbetapir-PET for imaging beta-amyloid pathology. JAMA 2011; 305(3): 275-83.
13. Rodrigue KM, Kennedy KM, Devous MD, Sr., et al. beta-Amyloid burden in healthy aging: regional distribution and cognitive consequences. Neurology 2012; 78(6): 387-95.
14. Kesslak JP, Nalcioglu O, Cotman CW. Quantification of magnetic resonance scans for hippocampal and parahippocampal atrophy in Alzheimer's disease. Neurology 1991; 41(1): 51-4.
15. Fotenos AF, Snyder AZ, Girton LE, Morris JC, Buckner RL. Normative estimates of cross-sectional and longitudinal brain volume decline in aging and AD. Neurology 2005; 64(6): 1032-9.
16. van de Pol LA, Hensel A, Barkhof F, Gertz HJ, Scheltens P, van der Flier WM. Hippocampal atrophy in Alzheimer disease: age matters. Neurology 2006; 66(2): 236-8.
17. Mosconi L. Brain glucose metabolism in the early and specific diagnosis of Alzheimer's disease. FDG-PET studies in MCI and AD. Eur J Nucl Med Mol Imaging 2005; 32(4): 486-510.

Disclosure

None reported.

MM

Knight ADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

Parkinson Disease in the Elderly Adult

by Allison W. Willis, MD, MSCI

As the disease progresses, partnering with a Parkinson disease specialist is helpful for both the increased complexity of disease management and to assure that proper management of non-PD medical illnesses can continue.



Allison W. Willis, MD, MSCI, is an Assistant Professor of Neurology, in the Movement Disorders Division, at the Knight Alzheimer's Disease Research Center at the Washington University School of Medicine in St. Louis.
Contact: willisa@neuro.wustl.edu

Abstract

Parkinson disease is the second most neurodegenerative disease, after Alzheimer disease, that affects up to two million Americans, the overwhelming majority of whom are aged 60 and older. The changing demographics of the country place more Americans at risk for Parkinson disease (PD) than ever before. Primary care physicians treat the majority of PD patients in the United States. Here I review diagnosis and treatment strategies for idiopathic Parkinson disease in the elderly adult.

Parkinson Disease Epidemiology

Parkinson disease (PD) is a common neurodegenerative disease of older adulthood. Population-based data on 36 million Medicare beneficiaries over the age of 65 suggests that 1.6% of Americans are treated yearly for PD, approaching the rate of stroke or migraine. The cardinal clinical symptoms of Parkinson disease - limb tremor, shuffling gait, slowness, stiffness, and postural instability - can be accompanied by autonomic nervous system dysfunction, depression, dementia and psychosis. In addition to physical disability, PD is associated with an increased likelihood of death.[1-3] The shifting demographics of the U.S. population due to the aging of the Baby Boomers has placed more adults at risk of PD than ever before, underscoring the need for increased understanding of PD diagnosis, clinical course and management.

Demographic and Geographical Variation in PD Diagnosis

Although the cause of PD remains unknown, environmental factors are suspected.[4-7] PD diagnoses cluster in the Midwest and Northeast United States, even after adjustment for population characteristics and physician density (See Figure 1).[8] PD risk also varies across demographic groups, suggesting differential susceptibility to PD-type neurodegeneration. Parkinson disease has been consistently diagnosed more often in men compared to women, and the neuroprotective effects of estrogen have been evidenced by increased risk of PD in women with early menopause.[9-11] In a nationwide Medicare beneficiary study, Asian and African Americans had almost half the risk of PD as whites (See Figure 2), and an excess of diagnoses among whites has been found in most mixed race populations worldwide.[8] Proposed biological mechanisms for this include increased baseline neuromelanin, the antioxidant that

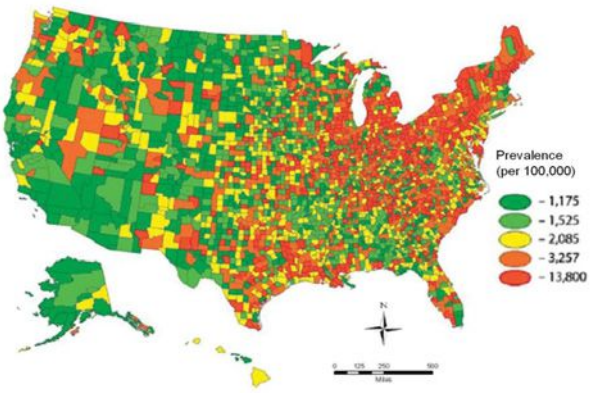


Figure 1: Predicted Age, Race, and Sex Adjusted Prevalence of Parkinson Disease among U.S. Medicare Beneficiaries, 2003.

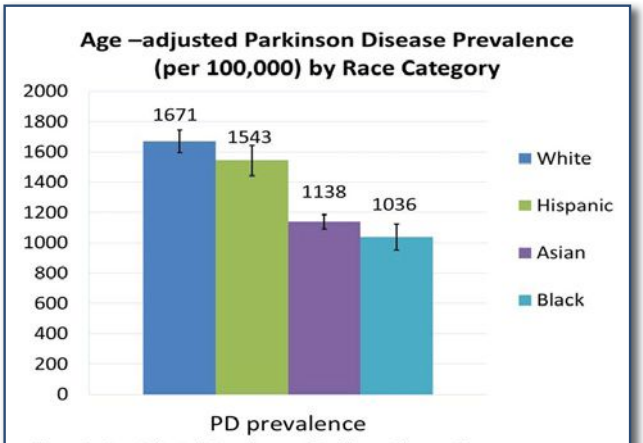


Figure 2: Age-Adjusted Prevalence of Parkinson Disease Diagnoses among Medicare Beneficiaries ≥ 65 by Race/ Ethnic Category, 2003.

protects from free radical damage in people of color, increased resilience to age-related degeneration and lower prevalence of common PD-causing genes.[12-15]

Parkinson Disease Symptoms and Diagnosis

Despite recent efforts to develop predictive imaging tests, PD remains a clinical diagnosis. Motor-related complaints or symptoms include tremor, decreased arm swing, shuffling walk, stopped posture, shortened steps, decreased facial expressiveness, stiffness, overall slowing of movement compared to peers, difficulty in rolling over in bed or in rising from a seated position. Autonomic symptoms include constipation, urinary disturbance (frequency, urgency), hyperhidrosis, nausea, flushing, orthostasis. Non-motor symptoms are highly prevalent, may predate motor symptoms, and may be under-assessed and undertreated.[16] These include anxiety, depression, difficulty thinking or concentrating, fatigue, anosmia, and sleep disturbance.

Diagnostic Criteria

A clinical PD diagnosis requires a minimum of two of the following four cardinal signs of parkinsonism:

1) Tremor: distal resting tremor of 3 to 6HZ or higher frequency. Postural/ kinetic tremors may also occur.

2) Muscle rigidity (a velocity independent resistance to passive movement).

3) Bradykinesia (slowness and poverty of movement).

4) Postural instability (not caused by primary visual, cerebellar or proprioceptive dysfunction).

Although bilateral motor findings often are present by the time a diagnosis is made, presentations with asymmetric motor signs (one side being worse than the other) are supportive of PD. A history of gradual onset of symptoms is also supportive, but this relies heavily on patient perception.

The final criterion is a sustained and robust response to a dopaminergic challenge. The equivalent of levodopa titrated up to 1,000-1,500 mg/day is considered an adequate challenge.

Exclusion Criteria for PD

Parkinsonism (including resting tremor and mild asymmetry of motor findings) can be seen in essential tremor, tardive dyskinesia, and Parkinson plus syndromes. Therefore, assessment for the following historical and clinical features is part of the standard initial evaluation for PD, and their presence suggests an alternative diagnosis:

Secondary Parkinsonism

- History of dopamine receptor blockade drug exposure (metoclopramide, haloperidol, atypical antipsychotics, promethazine, tricyclic antidepressants)
- Repeated strokes with stepwise progression of symptoms
- Repeated head injury with loss of consciousness
- History of preceding encephalitis
- Transient symptoms or remission in absence of treatment

Parkinson-Plus Syndrome (Dementia with Lewy Bodies, Multiple Systems Atrophy, Progressive Supranuclear Palsy, Corticobasal Degeneration), ALS with Parkinsonism, Alzheimer-Type Dementia with Parkinsonism

- Lack of subjective and objective response to levodopa (when titrated to at least 1200mg/day-1500mg/day with no evidence of gastrointestinal malabsorption)

- Prominent hallucinations, psychosis, bizarre personality changes early in the disease course
- Dementia on presentation or early in the disease course
- Early or prominent dysautonomia (orthostatic hypotension, incontinence, erectile dysfunction, inorgasmia, syncope)
- Double vision, supranuclear gaze palsy, eyelid opening apraxia
- Early or prominent gait impairment or postural instability
- Cerebellar signs, spasticity, Babinski sign
- Spasticity, fatigability, shortness of breath, fasciculations
- Limb apraxia, "alien limb" phenomenon, aphasia

Parkinson Disease Management

Multilevel engagement of the medical community by industry has been necessary to evaluate the multitude of PD treatments that have come to market in the past two decades. However, this practice has also resulted in conflicting information regarding treatment strategies. Below are principles of treatment for PD in the elderly, based on the least biased data:

1. No drugs have been proven to slow PD progression: In spite of many clinical trials, there is no convincing evidence that any currently available medications (rasagiline) or supplements (Co-Q 10) alter disease progression.

2. In the elderly, immediate release levodopa is the best initial treatment choice for PD symptoms that result in functional impairment. Levodopa is the most effective treatment for the motor symptoms of PD, and may also improve mood and bradyphrenia. Carbidopa/levodopa (Sinemet®) is the most widely used levodopa preparation as it is well tolerated and inexpensive, with several available generic preparations. Levodopa needs to be taken on an empty stomach (one hour before or two hours after meals) for maximum uptake. Carbidopa prevents peripheral metabolism of dopamine, and is included in all formulations of levodopa to minimize gastrointestinal and peripheral vasculature effects. However, flushing, sweating, and most commonly, nausea can occur with use of carbidopa/levodopa. Levodopa-induced nausea should be treated with supplemental carbidopa to allow titration to best motor benefit to continue. Entacapone (Comtan®) is peripherally acting catechol-*O*-methyltransferase (COMT) inhibitor that is taken with levodopa to extend its clinical benefit (it has no effect on its own). Entacapone is most useful for patients who have optimal/near optimal peak motor benefit, but wearing off between doses in spite of q.i.d. levodopa dosing. Branded combinations of Sinemet® and entacapone (Stalevo®) make individualized titration of levodopa and carbidopa to maximum benefit impossible, and are associated with higher patient out of pocket costs. The extended and controlled release forms of Sinemet® have unpredictable bio-availability that limits their daytime use as a primary therapy, but may be useful for overnight wearing off, generally described as awakening due to the return of PD symptoms.

Dopamine agonists are less potent than levodopa, and are associated with compulsive behaviors (gambling, shopping, hypersexuality, fetishism), paranoia, cognitive impairment that resembles dementia and sleep attacks.[17] These side effects are worse among the elderly. In our practice, dopamine agonist use is the most common cause of reversible cognitive impairment in the elderly PD patient. Low dose dopamine agonists are useful as an add-on therapy for patients on a stable dose of levodopa who are experiencing wearing off that is resistant to frequent dosing and a COMT inhibitor (entacapone).

Anticholinergic medications (trihexyphenidyl, benztropine) provide the least amount of motor benefit and are among the most harmful medications one can use in an elderly person with PD. Total anticholinergic burden is associated with a dose–response decline in cognitive function in the elderly.[18,19]

Monoamine oxidase B (MAO-B) inhibitors (rasagiline, selegiline) block the breakdown of dopamine in the brain, and can therefore provide a modest dopaminergic effect. However, this chemical class interferes with many common medications, including almost all commonly used antidepressant classes, narcotics, muscle relaxants, over-the-counter cold medications, and general and local anesthetics, thus limiting their usefulness in a group of people with common comorbid diseases.

4. Some medications should be avoided in PD patients: Common causes of hospitalizations, emergency department visits, and mortality in PD are polypharmacy, drug-drug interactions, and "drug-disease" interactions. For example, dysautonomia is almost universal in PD, and can be present before motor symptoms are manifest. Continuing or failing to reduce blood pressure medications when initiating or increasing levodopa may cause syncope. Sitting and standing blood pressure measurements should be obtained at all office visits, with reduction of antihypertensive medications

(and in severe cases, addition of a hypertensive agent to prevent syncope) as needed. Hallucinations may be part of the disease in later stages, but may also be levodopa-induced or a sign of infection. Narcotic, anticholinergic, hypnotic and benzodiazepine associated falls and confusion are also common triggers of an emergency department visit or hospitalization. Table 1 lists common medications that should be avoided in PD.

Table 1. Medications to Avoid in Patients with Parkinson Disease

Medication Class	Examples	Interaction/Binding Site	Clinical Result
Typical Antipsychotics	Chlorpromazine, Haloperidol, Fluphenazine, Loaxapine Thiothixene, Pimozide Thioridizine	Dopaminergic blockade	PD symptoms worsen
Antiemetic	Chlorpomazine, Metoclopramide, Droperidol Promethazine, Prochlorperazine	Dopaminergic blockade	PD symptoms worsen
Antihypertensive	All	Dopaminergic blockage (reserpine, methyldopa) Increased orthostasis (all)	PD symptoms worsen Syncope, Hypotension-associated organ ischemia
Antihistamine Anticholinergic	Diphenhydramine, hydroxyzine oxybutynin, trihexyphenidyl, buproprion, dextromethorophan,	Cholinergic blockade	Confusion, falls, dry mouth, blurred vision, incontinence
Benzodiazepine Hypnotic	Alprazolam, clonazepam, diazepam, lorazepam, triazolam, eszopiclone, zolpidem	Gamma-aminobutyric acid (GABA) receptor	Confusion, falls, excess sedation, paradoxical agitation
Narcotic	Codeine, morphine, hydromorphone	Opioid receptor	Confusion, falls, paradoxical agitation

5. Motor fluctuations such as the loss of sustained benefit from levodopa ("wearing off"), dystonia, and dyskinesias, occur at some point in nearly all PD patients due to disease progression, *not* because of initial medication choice. Despite past suggestions made by industry-sponsored studies, there is no benefit to "saving" or storing motor benefit by treating PD patients with a dopamine agonist instead of levodopa. This usually results in under-treatment and risk of complications, including lower mood, cognitive slowing, falls, and more rapid functional disability, which may not be reversible once proper treatment begins. Motor fluctuations in the elderly can be managed by frequent dosing and the use of the following adjunct therapies: COMT inhibitors, extended release carbidopa/levodopa combinations, dopamine agonists, and MAO-B inhibitors.

Table 2: Patient, Family and Physician Resources for Parkinson Disease

Organization Name	Web address
American Parkinson Disease Foundation	www.apdaparkinson.org
National Parkinson Foundation	www.parkinson.org
Movement Disorders Society	www.movementdisorders.org
Michael J. Fox Foundation	www.michaeljfox.org
Parkinson Disease Foundation	www.pdf.org

6. Neurology referral and Deep Brain Stimulation. Levodopa associated side effects, most commonly chorea, psychosis and symptomatic orthostasis, may occur rarely in newly diagnosed patients on low dose therapy, but more generally occur in advanced disease and indicate advanced neurodegeneration. They are treated by dose adjustment, use of atypical antipsychotics (clozapine, quetiapine), and hypertensive agents (caffeine, midodrine, fludrocortisone). Referral for neurologist care is appropriate at any time the diagnosis is considered, but especially when symptoms and signs substantially improve after treatment with levodopa (suggesting undertreatment or an alternative diagnosis). Deep Brain Stimulation (DBS) is an effective surgical treatment for motor fluctuations in PD only when strict inclusion exclusion criteria are followed, as not all clinical forms of PD respond to DBS. Referral for DBS is appropriate when significant motor fluctuations persist in spite of optimal medical management and is best performed at an experienced multidisciplinary center that incorporates neurosurgical, neurological, neuropsychological testing in the evaluation and treatment process.

7. Cognitive impairment is common. Cognitive impairment or dementia is diagnosed

in nearly seventy percent of elderly diagnosed PD patients.[3, 20] Dementia phenotype varies, depending on the primary cause (progression of PD, concomitant Alzheimer or vascular dementia). However, iatrogenic cognitive impairment in neurodegenerative populations is increasingly recognized. Limiting exposure to centrally acting medications known to cause confusion in the elderly (narcotics, antihistamines, sedatives, hypnotics, anticholinergics), and adequate dopaminergic therapy is prudent to retain as much cognitive function as possible. Acute cognitive impairment or sudden change in motor benefit in a PD patient may signal an occult infection or metabolic disturbance.

8. Exercise may be neuroprotective. If the cardio-protective, cancer-fighting, mood-elevating, and dementia-preventing effects of regular exercise are not sufficient, yet another reason to treat PD motor symptoms is to allow for exercise. A decreased risk of PD has been demonstrated among those who exercise, and several specific types of exercise have associated with better function and motor preservation in person with PD symptoms.[21-23]

Exercise booklets and tutorial videos, and iphone/ipad applications are wide available for download on the world wide web for PD.

Partnership with a Specialist

Neurologists, particularly those who specialize in movement disorders, can be helpful at all stages of PD patient care. They have clinical experience with the various causes of parkinsonism and phenotypes of PD. As the disease progresses, partnering with a specialist is helpful for both the increased complexity of PD management, consideration of DBS, and to assure that proper management of non-PD medical illnesses can continue.

Where To Go For Help

Several national PD outreach groups exist and provide education, community support, research funding, patient and caregiver programs. Clinical trials of experimental therapies for PD are listed at www.clinicaltrials.gov. The organizations in Table 2 have many patient booklets available for download, educational DVDs, physician information, local support groups, dance and exercise classes, caregiver respite care, fundraising opportunities, and movement disorder specialist referral lists.

References

1. CE CL. Mortality from Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2000;68:254-255.
2. Chen H, Zhang SM, Schwarzschild MA, Hernan MA, Ascherio A. Survival of Parkinson's disease patients in a large prospective cohort of male health professionals. *Mov Disord* 2006;21:1002-1007.
3. Willis AW, Schootman M, Kung N, Evanoff BA, Perlmutter JS, Racette BA. Predictors of survival in patients with Parkinson disease. *Arch Neurol* 2012;69:601-607.
4. Ascherio A, Chen H, Weisskopf MG et al. Pesticide exposure and risk for Parkinson's disease. *Ann Neurol* 2006;60:197-203.
5. Tanner CM, Ottman R, Goldman SM et al. Parkinson disease in twins: an etiologic study. *JAMA* 1999;281:341-346.
6. Uversky VN, Li J, Bower K, Fink AL. Synergistic effects of pesticides and metals on the fibrillation of alpha-synuclein: implications for Parkinson's disease. *Neurotoxicology* 2002;23:527-536.
7. Wang A, Costello S, Cockburn M, Zhang X, Bronstein J, Ritz B. Parkinson's disease risk from ambient exposure to pesticides. *Eur J Epidemiol* 2011;26:547-555.
8. Wright WA, Evanoff BA, Lian M, Criswell SR, Racette BA. Geographic and ethnic variation in Parkinson disease: a population-based study of US Medicare beneficiaries. *Neuroepidemiology* 2010;34:143-151.
9. Yadav R, Shukla G, Goyal V, Singh S, Behari M. A case control study of women with Parkinson's disease and their fertility characteristics. *J Neurol Sci* 2012;319:135-138.
10. Rocca WA, Bower JH, Maraganore DM et al. Increased risk of parkinsonism in women who underwent oophorectomy before menopause. *Neurology* 2008;70:200-209.
11. Shulman LM. Gender differences in Parkinson's disease. *Gend Med* 2007;4:8-18.
12. Ross OA, Wilhoite GJ, Bacon JA et al. LRRK2 variation and Parkinson's disease in African Americans. *Mov Disord* 2010;25:1973-1976.
13. Alladi PA, Mahadevan A, Yasha TC, Raju TR, Shankar SK, Muthane U. Absence of age-related changes in nigral dopaminergic neurons of Asian Indians: relevance to lower incidence of Parkinson's disease. *Neuroscience* 2009;159:236-245.
14. Muthane UB, Chickabasaviah YT, Henderson J et al. Melanized nigral neuronal numbers in Nigerian and British individuals. *Mov Disord* 2006;21:1239-1241.
15. Muthane U, Yasha TC, Shankar SK. Low numbers and no loss of melanized nigral neurons with increasing age in normal human brains from India. *Ann Neurol* 1998;43:283-287.
16. Shearer J, Green C, Counsell CE, Zajicek JP. The impact of motor and non motor symptoms on health state values in newly diagnosed idiopathic Parkinson's disease. *J Neurol* 2012;259:462-468.
17. Bastiaens J, Dorfman BJ, Christos PJ, Nirenberg MJ. Prospective cohort study of impulse control disorders in Parkinson's disease. *Mov Disord* 2013.
18. Ehrt U, Broich K, Larsen JP, Ballard C, Aarsland D. Use of drugs with anticholinergic effect and impact on cognition in Parkinson's disease: a cohort study. *J Neurol Neurosurg Psychiatry* 2010;81:160-165.
19. Kolanowski A, Fick DM, Campbell J, Litaker M, Boustani M. A preliminary study of anticholinergic burden and relationship to a quality of life indicator, engagement in activities, in nursing home residents with dementia. *J Am Med Dir Assoc* 2009;10:252-257.
20. Buter TC, van den Hout A, Matthews FE, Larsen JP, Brayne C, Aarsland D. Dementia and survival in Parkinson disease: a 12-year population study. *Neurology* 2008;70:1017-1022.
21. Shulman LM, Katzel LI, Ivey FM et al. Randomized Clinical Trial of 3 Types of Physical Exercise for Patients With Parkinson Disease. *Arch Neurol* 2012;1-8.
22. Liu T, Lao L. Tai chi for patients with Parkinson's disease. *N Engl J Med* 2012;366:1737.
23. Li F, Harmer P, Fitzgerald K et al. Tai chi and postural stability in patients with Parkinson's disease. *N Engl J Med* 2012;366:511-519.

Disclosure

None reported.

MM

Knight ADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

Unravelling the Mysteries of Frontotemporal Dementia

by Nupur Ghoshal, MD, PhD & Nigel J. Cairns, PhD

Although DNA may be obtained to identify genetic causes in about one-third of Frontotemporal Dementia cases, neuropathology remains the 'gold standard' diagnosis.



Nupur Ghoshal, MD, PhD, (left) is an Assistant Professor, Department of Neurology, and Nigel J. Cairns, PhD, FRCPath, is a Research Professor in the Department of Neurology and in the Department of Pathology and Immunology. Both are at the Knight Alzheimer's Disease Research Center at Washington University School of Medicine in St. Louis.
Contact: cairns@wustl.edu

Abstract

Frontotemporal dementia (FTD) is a clinical term that encompasses the neurodegenerative diseases that selectively affect the frontal and anterior temporal lobes of the brain. FTD, which is underdiagnosed in clinical settings, presents with behavioral changes or deficits in language. The last two decades have seen tremendous advances in the appreciation of the clinical assessment, genetics, and molecular pathology of this group of enigmatic diseases, thus offering hope for the development of rational therapeutic strategies.

Introduction

In 1892, Arnold Pick, a Czech neurologist, described a 71-year-old patient with progressive language and behavioral difficulties. Neuropathologic examination of the brain revealed focal atrophy of the frontal and anterior temporal lobes and characteristic inclusion bodies, called Pick bodies. Pick's disease subsequently has been recognized as a prototypical form of what now is known as "frontotemporal dementia" (FTD), but because of the rarity of Pick's disease there were minimal advances in the understanding of this family of disorders until the work of Arne Brun and colleagues in the 1980s.[1] Since that time there have been tremendous advances in our understanding of the clinical features, genetics and molecular pathology of FTD. Although caused by several distinct pathological entities, they all have a predilection for involvement of the frontal and temporal lobes of the brain and thus have similar clinical phenotypes.[2-4] FTD is the second most common cause of dementia in individuals under age 65, after Alzheimer disease (AD).[5-7] About one-third of all cases of FTD appear to be familial. Typical age at onset of symptoms is between 45-65 years, but may be as young as 30 and as old as 80 years. Men and women are both affected. The FTDs have a world-wide distribution.

In the last decade there have been huge strides made in the classification of these clinically and neuropathologically heterogeneous diseases (See Figure 1). Of particular note, it is now appreciated that there is an overlap between amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, and FTD such that ALS and FTD represent different

Table 1

Frontotemporal dementia subtypes	
Syndrome	**Features**
Behavioral variant FTD	• Personality changes • Lack of insight • Socially inappropriate
Semantic dementia	• Language predominant deficit • Fluent speech, loss of word meaning
Progressive nonfluent aphasia	• Language predominant deficit • Nonfluent, hesitant speech • Retain word meaning • Agrammatical speech and writing
Corticobasal degeneration	• Asymmetric rigidity • Difficulty with learned movements and actions (apraxia) • Visuospatial deficits
Progressive supranuclear palsy	• Symmetric, rigidity of trunk>limbs • Impairment ability to look down • Falling backwards

ends of an FTD spectrum (see ALS paper by Drs. Bali and Miller in this Science of Medicine Series). Many individuals with ALS will develop the clinical features of FTD, and persons with FTD are at greater risk of developing ALS.[8] The most common cause of FTD/ALS is a mutation in the *C9ORF72* gene.[9] Salient features of these FTD disorders are focal atrophy of the frontal and anterior temporal lobes (See Figure 2), neuronal loss, gliosis, and the pathological aggregation of misfolded proteins, either in neurons or glial cells, or both.[2-4] Although it now is possible to determine the underlying pathology in nearly all cases of FTD, there currently is no effective treatment of this group of diseases.

Clinical Phenotypes

In contrast to AD where cognitive deficits (particularly memory loss) predominate, FTD is characterized by language dysfunction or by a behavioral syndrome (See Table 1). There are three clinical subtypes of FTD[6,7]:

1) behavioral variant FTD (bvFTD)
2) Semantic Dementia (SD)
3) Progressive Nonfluent Aphasia (PNFA)

PNFA affects women 2-to-1 over men while for bv FTD and SD, men are affected 2-to-1 over women.[7] The bases for these gender differences are unknown.

Behavioral variant FTD (bvFTD) individuals have florid personality changes and a dramatic loss of insight into their behaviors early in the disease course. They are socially inappropriate and may be disinhibited (hyperorality and sexual disinhibition), apathetic, and less empathetic. Mental rigidity, obsessions, and compulsions are also seen in these patients. While language dysfunction may develop, there is relative sparing of memory, at least early in the disease course. Structural imaging usually reveals focal atrophy of both the frontal and temporal lobes.

Semantic dementia (SD) is primarily a language disorder in which patients have fluent speech, but display word finding difficulty and experience the loss of word meaning. For example, if asked "Can a fork eat a lion?", they may answer affirmatively, indicating that they do not appreciate the meaning of "fork", "eat", "lion", or all three. Memory changes occur later in the disease. Structural imaging often reveals focal atrophy of the anterior left temporal lobe with relative sparing of the frontal lobes; bitemporal atrophy also may be present.

Progressive nonfluent aphasiaalso (PNA) is a language disorder and can be considered a "dementia" of the language system. Patients with PNFA have nonfluent and hesitant speech but they retain knowledge about word meaning. Their speech and writing are agrammatical (i.e., stripped of modifying and connecting words) and may display increased spelling errors. The neural substrate of PNFA involves the left superior temporal lobe, the left inferior frontal lobe, and the left anterior insula. With disease progression, the parietal lobe also is affected.[10]

Although other neurodegenerative disorders have histopathological phenotypes that are distinct from the FTDs and usually have a different topography of cerebral involvement, rarely they may preferentially affect frontal and temporal lobes and thus present as FTD:

1) Corticobasal Degeneration (CBD)
2) Progressive Supranuclear Palsy (PSP)
3) Frontal variant of AD

Figure 1
Molecular and genetic classification of FTD. Three abnormal proteins define the major FTD entities: (1) FTD-Tau (Pick's disease, corticobasal degeneration and progressive supranuclear palsy and those patients who harbor mutations in the MAPT gene), (2) FTD-TDP (sporadic and familial cases with mutations in several genes), and (3) FTD-FUS (rare neurological diseases with FUS-containing inclusions: basophilic inclusion body disease (BIBD) and neuronal interfilament inclusion diseases (NIFID)). Other rare disorders also exist.

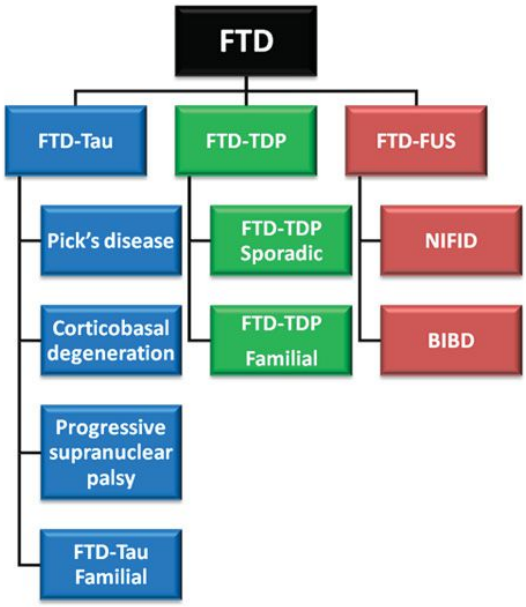
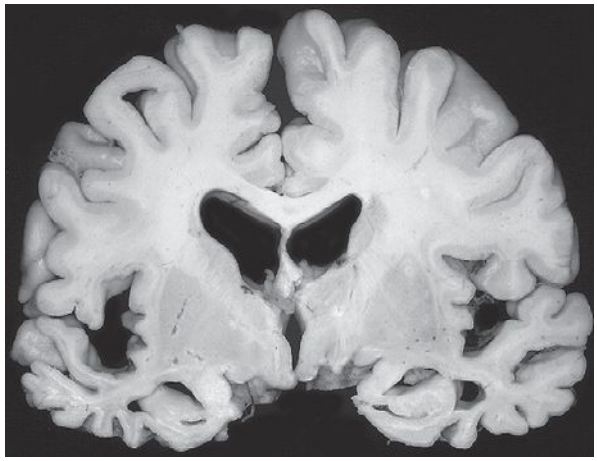


Figure 2
Focal atrophy in FTD. There is marked atrophy of the temporal lobes and moderate atrophy of the frontal lobes. The lateral ventricles are dilated and there is increased space in the inferior horns of the lateral ventricles and expansion of the lateral sulcus in a case of a FTD-TDP.



Corticobasal degeneration (CBD) is a condition in which asymmetric rigidity is present as is seen in Parkinson disease (PD); however, patients are typically less responsive to standard PD treatment. These individuals may have difficulties with learned motor tasks (apraxia). Frontotemporal Dementia-like features may be also present in CBD, including executive dysfunction and visuospatial and number processing deficits. They may have a PNFA-like language deficit as well.

Progressive supranuclear palsy (PSP) is a condition in which symmetric rigidity is present and also is less responsive to standard PD treatment. These individuals have difficulties with looking up and down (supranuclear palsy), resulting in marked propensity to fall backwards. FTD-like features may be also present in PSP, such as impulsivity and executive dysfunction (i.e., impaired reasoning).

Frontal variant AD individuals initially present with social disinhibition, emotional blunting, stereotyped verbal utterances and therefore are often diagnosed with FTD. However, at autopsy these individuals may have a particularly heavy burden of AD pathology in their frontal lobes. Presumably their atypical clinical presentation is due to the topographical distribution of pathology in their frontal lobes.

Finally, another "variant" is dominantly inherited FTD, representing up to one third of all FTD. A careful interview and ascertainment of family history for the presence of FTD should prompt the consideration of dominantly inherited FTD. Causative mutations resulting in FTD have been identified (See Figure 1); the most commonly occurring are in the *C9ORF72*, *MAPT*, and *GRN* genes (see the Neuropathologic Phenotypes section in this article). The earlier the age of symptomatic onset, the greater risk that an underlying autosomal dominant mutation is responsible. In the appropriate context, including a suggestive family history for dominantly inherited dementias, genetic counseling and genetic testing may be considered.

Management

Currently, there are no FDA-approved medications for the treatment of FTD.[11,12] The bulk of FTD management speaks to providing supportive care and symptomatic treatment. Initial management should focus on minimizing polypharmacy, especially centrally acting prescription and non-prescription drugs as well as herbal supplements. Many centrally acting medications such as stimulants, sedatives, and anxiolytics may have paradoxical effects and result in exacerbated behavioral or cognitive symptoms.

Figure 3
Neuropathology of FTD-Tau. A swollen achromatic neuron (arrow) in a case of CBD (A). Tau-containing (brown stain) neurofibrillary tangles in the hippocampus (B) and brain stem (C). Tau-immunoreactive glial inclusions (astrocytic plaque (asterisk), thread (arrowhead) and oligodendroglial inclusion (arrow)) in CBD. Globose intraneuronal tau-immunoreactive inclusions "Pick bodies" in a case of Pick's disease (E). Neurofibrillary tangles in a case of tangle-only dementia (F). A, hematoxylin and eosin stain; B-E, phosphorylated tau immunohistochemistry; F, Bielschowsky silver stain.

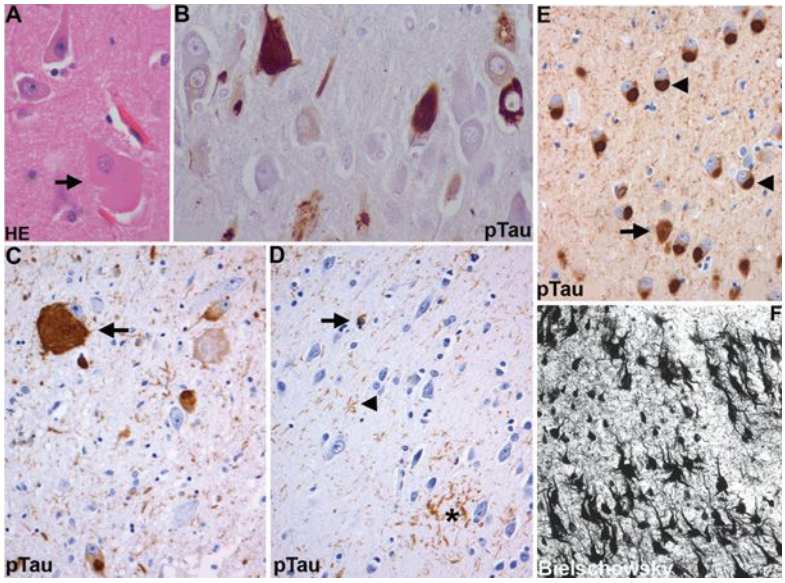
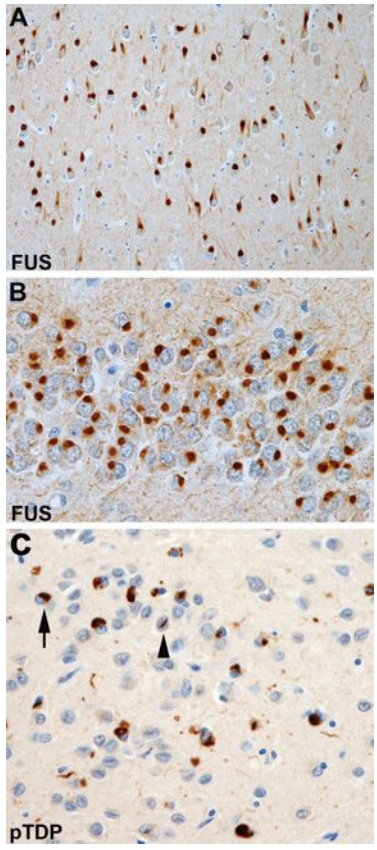


Figure 4
Neuropathology of FTD-TDP and FTD-FUS. FUS-containing neuronal inclusions (brown stain) in the hippocampus (A) and dentate gyrus (B) of a case of NIFID. TDP-immunoreactive neuronal cytoplasmic (arrow) and intranuclear (arrowhead) inclusions in a case of FTD-TDP. A and B, FUS immunohistochemistry; C, phosphorylated TDP immunohistochemistry.



Selective serotonin reuptake inhibitors (SSRIs) have been shown to improve behavioral disinhibition, perseverative behavior, hyperorality, and compulsions. Antipsychotics have been shown to address behavioral disinhibition as well. Stimulants may either reduce or increase compulsive risk taking behavior depending on the mechanism of action.

Frontotemporal dementia patients are not uncommonly treated off-label with approved AD medications. Studies of cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) in FTD have yielded no conclusive evidence for cognitive or behavioral benefit.[13] However, these agents are still often prescribed in the absence of FDA-approved medications for FTD and in some cases to minimize caregiver stress. NMDA antagonists (memantine) were initially thought to be beneficial in FTD based on small studies, but the benefit was not found in a rigorous multicenter, randomized, double-blind, placebo-controlled trial.[11] SD and PNFA patients may benefit from speech therapy with the goal of providing them with assistive devices such a communication board or laptop to allow them to maintain or extend their language capabilities.

With recent advances in understanding the molecular underpinnings of FTD and its subtypes (See Figure 1), it is anticipated that protein-specific, disease-modifying therapies will emerge that will target one mechanistic pathway or another.[11,12]

Neuropathologic Phenotypes FTD-Tau

The recognition of distinct misfolded proteins within neurons and glial cells has transformed the classification of FTD entities within recent years.[2-4,14] About half of FTD cases have abnormal intracellular cytoplasmic accumulations of the microtubule-associated protein tau (MAPT) (See Figure 3). The term "tauopathies" has been applied to this family of apparently unrelated group of diseases which includes: Pick's disease (PiD), corticobasal degeneration

(CBD),[15] progressive supranuclear palsy (PSP),[16] other rare entities, and familial FTD with mutations in the *MAPT* gene. Several families with FTD with and without movement disorder have been identified with mutations in the *MAPT* gene on chromosome 17.[17] *MAPT* gene mutations account for up to 10% of all FTD cases. Microscopically, neuronal loss, astrocytosis, microvacuolation, and swollen neurons are found in affected areas together with a spectrum of tau pathology including intraneuronal neurofibrillary tangle (NFT)-like inclusions, neuronal globose tangle-like inclusions, intraneuronal Pick body-like inclusions, astrocytic tangle-like inclusions and oligodendroglial inclusions resembling coiled bodies and dystrophic neurites (See Figure 3). An extraordinarily wide-range of tau pathology has been observed in these familial cases.[2,14]

FTD-TDP

Frontotemporal dementia with ubiquitinated inclusions accounts for roughly the remaining half of FTD cases. The identification of two RNA-binding proteins within the ubiquitinated inclusions, TDP-43 (TDP)[18] and the fused-in sarcoma (FUS) proteins,[19] led to a further expansion in the number of distinct FTD entities. The majority of FTD with ubiquitin inclusion cases contain inclusion bodies made up largely of TDP-43 protein; a very small proportion (less than 5%) contain the protein FUS. FTD-TDP has been observed in both sporadic cases and dominantly inherited FTD cases with mutations in either an expansion in a hexanucleotide repeat in the *C9ORF72*[20] (10% of FTD) gene or in the *GRN* (10% of FTD) gene.[21] Mutations in other genes including *VCP and TARDBP* [3] are very rare causes of FTD. The neuronal and glial inclusions containing TDP are indistinguishable from those seen in most patients with ALS who later develop dementia, suggesting that FTD and ALS are two ends of the same spectrum of FTD-TDP proteinopathy.

FTD-FUS

Mutations have been identified in the *FUS* gene in rare cases of familial ALS and FTD.[20] The inclusion bodies in these cases contain variable amounts of FUS protein (See Figure 4). Also, FUS has been identified as a component of the inclusions of some less frequent FTD entities, including neuronal intermediate filament inclusion disease (NIFID), atypical FTD with ubiquitin-immunoreactive inclusions (aFTD-U), and basophilic inclusion body disease (BIBD).[2,3]

Future Directions

In an effort to determine the mechanisms by which neurons and glial cells die in FTD, *in vitro* and *in vivo* transgenic models have been generated by over-expressing human tau, TDP, or FUS proteins in mice. However, these mice only variably show the features of the human disease they are designed to model.[22] In one more successful model, a mutation (P301L) in the human *MAPT* gene, led to the development of transgenic mice that develop age- and gene dose-dependent accumulation of tau tangles in the brain and spinal cord with associated nerve cell loss and gliosis as well as behavioral abnormalities. The tau inclusions were composed of only mutant human tau, thus implicating the P301L mutation in the aggregation of mutant tau. Various aspects of human tauopathies, TDP-43 and FUS proteinopathies, have been modelled which show some features of the human disease. Recently, in *in vivo* models, it has been shown that small protein aggregates may be taken up by neurons and hijack the machinery of the cell to generate more misfolded protein, similar to that seen in prion diseases.[23] Thus, a spectrum of models is being developed that recapitulates various features of human pathology and these models will facilitate understanding of the molecular mechanisms underlying neurodegeneration in FTD. These data also indicate how abnormal proteins may propagate throughout the brain, potentially providing a promising target for therapeutic intervention.

The Importance of Autopsy

An autopsy, even when limited to examination of the brain, is essential to determine the underlying cause of the clinical symptoms. Although DNA may be obtained to identify genetic causes in about one-third of FTD cases, neuropathology remains the 'gold standard' diagnosis. Neuropathology is essential to determine the underlying cause and the contribution, if any, of other pathologies including vascular disease or co-existing AD. Academic research centers can coordinate and manage the autopsy in those patients who participate in on-going studies. This is an option that should be considered in any patient who shows symptoms of an FTD-like disorder. Support organizations and information on brain donation are listed in this article.

Resources

When to consider FTD and refer patients? Initial symptoms: behavioral changes and language difficulties with or without Parkinsonian features. Age at onset: under the age of 65. Family history of young onset dementia with or without Parkinsonian features. Imaging: focal, not global, atrophy of the brain predominantly involving frontal and temporal lobes

Support Groups

- Association for Frontotemporal Dementias
  (866) 507-7222 (toll free)
  http://www.theaftd.org
- Alzheimer's Association
  (800) 272-3900 (toll free)
  http://www.alz.org

Research, Including Brain Donation

- Knight Alzheimer's Disease Research Center at Washington University in St. Louis
  Research, Participation, and Questions
  (314) 286-2683
  http://www.adrc.wustl.edu/

Acknowledgments

Support for this work was provided by grants from the National Institute on Aging of the National Institutes of Health, USA (P01 AG003991and P50 AG005681). We would also like to thank the staff of the Knight Alzheimer's Disease Research Center Neuropathology Core, Washington University School of Medicine, for their technical support, and the many patients studied and their families for making the research reviewed here possible.

References

1. Brun A. Frontal lobe degeneration of non-Alzheimer type. I. Neuropathology. Archives of gerontology and geriatrics. Sep 1987;6(3):193-208.
2. Cairns NJ, Bigio EH, Mackenzie IR, et al. Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration. Acta neuropathologica. Jul 2007;114(1):5-22.
3. Mackenzie IR, Neumann M, Bigio EH, et al. Nomenclature for neuropathologic subtypes of frontotemporal lobar degeneration: consensus recommendations. Acta neuropathologica. Jan 2009;117(1):15-18.
4. Cairns NJ, Ghoshal N. FUS: A new actor on the frontotemporal lobar degeneration stage. Neurology. Feb 2 2010;74(5):354-356.
5. Liscic RM, Storandt M, Cairns NJ, Morris JC. Clinical and psychometric distinction of frontotemporal and Alzheimer dementias. Archives of neurology. Apr 2007;64(4):535-540.
6. Ratnavalli E, Brayne C, Dawson K, Hodges JR. The prevalence of frontotemporal dementia. Neurology. Jun 11 2002;58(11):1615-1621.
7. Yener GG, Rosen HJ, Papatriantafyllou J. Frontotemporal degeneration. Continuum. Apr 2010;16(2 Dementia):191-211.
8. Lomen-Hoerth C. Characterization of amyotrophic lateral sclerosis and frontotemporal dementia. Dementia and geriatric cognitive disorders. 2004;17(4):337-341.
9. Rademakers R, Neumann M, Mackenzie IR. Advances in understanding the molecular basis of frontotemporal dementia. Nature reviews. Neurology. Aug 2012;8(8):423-434.
10. Rohrer JD, Warren JD, Modat M, et al. Patterns of cortical thinning in the language variants of frontotemporal lobar degeneration. Neurology. May 5 2009;72(18):1562-1569.
11. Boxer AL, Knopman DS, Kaufer DI, et al. Memantine in patients with frontotemporal lobar degeneration: a multicentre, randomised, double-blind, placebo-controlled trial. Lancet neurology. Feb 2013;12(2):149-156.
12. Boxer AL, Gold M, Huey E, et al. Frontotemporal degeneration, the next therapeutic frontier: molecules and animal models for frontotemporal degeneration drug development. Alzheimer's & dementia : the journal of the Alzheimer's Association. Mar 2013;9(2):176-188.
13. Kerchner GA, Tartaglia MC, Boxer A. Abhorring the vacuum: use of Alzheimer's disease medications in frontotemporal dementia. Expert review of neurotherapeutics. May 2011;11(5):709-717.
14. Miller BL, Cummings JL. The human frontal lobes : functions and disorders. 2nd ed. New York, NY: Guilford Press; 2007.
15. Gibb WR, Luthert PJ, Marsden CD. Corticobasal degeneration. Brain : a journal of neurology. Oct 1989;112 (Pt 5):1171-1192.
16. Steele JC, Richardson JC, Olszewski J. Progressive Supranuclear Palsy. A Heterogeneous Degeneration Involving the Brain Stem, Basal Ganglia and Cerebellum with Vertical Gaze and Pseudobulbar Palsy, Nuchal Dystonia and Dementia. Archives of neurology. Apr 1964;10:333-359.
17. Goedert M. Tau gene mutations and their effects. Movement disorders : official journal of the Movement Disorder Society. Aug 2005;20 Suppl 12:S45-52.
18. Neumann M, Sampathu DM, Kwong LK, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science. Oct 6 2006;314(5796):130-133.
19. Vance C, Rogelj B, Hortobagyi T, et al. Mutations in FUS, an RNA processing protein, cause familial amyotrophic lateral sclerosis type 6. Science. Feb 27 2009;323(5918):1208-1211.
20. Renton AE, Majounie E, Waite A, et al. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron. Oct 20 2011;72(2):257-268.
21. Mukherjee O, Pastor P, Cairns NJ, et al. HDDD2 is a familial frontotemporal lobar degeneration with ubiquitin-positive, tau-negative inclusions caused by a missense mutation in the signal peptide of progranulin. Annals of neurology. Sep 2006;60(3):314-322.
22. Ghoshal N, Dearborn JT, Wozniak DF, Cairns NJ. Core features of frontotemporal dementia recapitulated in progranulin knockout mice. Neurobiology of disease. Jan 2012;45(1):395-408.
23. Kfoury N, Holmes BB, Jiang H, Holtzman DM, Diamond MI. Trans-cellular propagation of Tau aggregation by fibrillar species. The Journal of biological chemistry. Jun 1 2012;287(23):19440-19451.

Disclosure

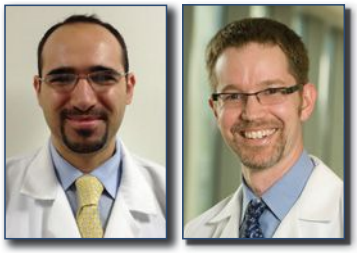
N Cairns has no disclosures. N Ghoshal has participated, or is currently participating, in clinical trials of anti-dementia drugs sponsored by Elan/Janssen, Eli Lilly and Company, Wyeth, Pfizer, Novartis, and Bristol-Myers Squibb. MM

Knight ADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

Management of Amyotrophic Lateral Sclerosis

by Taha Bali, MD & Timothy M. Miller, MD, PhD

Amyotrophic Lateral Sclerosis is a fatal neurodegenerative disease that currently remains incurable, but can be managed symptomatically over the disease duration to maintain the highest quality of life possible.



Taha Bali, MD, (left), is a Fellow, Neuromuscular Disease Division, and Timothy M. Miller, MD, PhD, is an Assistant Professor of Neurology at the Washington University School of Medicine in St. Louis.
Contact: millert@neuro.wustl.edu
http://millerlab.wustl.edu/

Abstract

Motor Neuron Diseases (MNDs) are neurological disorders characterized by the selective and progressive degeneration of motor neurons. Amyotrophic Lateral Sclerosis (ALS), commonly known as Lou Gehrig's disease, is the most common. ALS causes diffuse muscle weakness and death secondary to respiratory failure. The diagnosis is made clinically, supported by electrodiagnostic testing. Although medications are limited, careful attention to breathing, nutrition, and patient mobility can have a major, positive impact on the course of the disease.

Introduction

Motor Neuron Diseases (MNDs) are a group of progressive disorders that are invariably fatal and affect the motor system, involving the upper, lower motor neurons, or both. The most common entity under the umbrella of MNDs is Amyotrophic Lateral Sclerosis (ALS). ALS is a progressive neurodegenerative disease that affects both upper and lower motor neurons, with pathology spanning the primary motor cortex, corticospinal tracts, brainstem and spinal cord, and causing diffuse muscle weakness, atrophy, spasticity and eventually death, typically due to respiratory failure. Other, less common subtypes of MND include Progressive Muscular Atrophy (PMA), which affects only the lower motor neurons; Primary Lateral Sclerosis (PLS), which affects only the upper motor neurons; and Progressive Bulbar Palsy (PBP), which involves both upper and lower motor neurons but remains confined to bulbar muscles (i.e. brainstem centers responsible for facial movements, swallowing, speech, chewing and breathing). MNDs also include hereditary diseases such as Spinal Muscular Atrophy (SMA) and Spinal-Bulbar Muscular Atrophy (SBMA), etc. This review will focus mainly on ALS.[1]

The incidence of ALS is estimated to be 1.7 cases per 100,000 per year,[2] with the cumulative lifetime risk of developing the disease by age 75 being approximately 1:1000.[3] The median age of onset is approximately 64 years for men and 67 for women with the male to female ratio estimated to be 1.8:1.[4] ALS is associated with a family history in approximately 10-20% of cases. Familial ALS (FALS) is defined as the presence of a first degree relative also affected by the disease and most commonly follows an autosomal dominant inheritance pattern. As many as one-third of familial ALS cases are caused by a recently discovered repeat expansion that is also linked to Frontotemporal Dementia (FTD), and hence, a careful family history exploring the presence of a dementia

syndrome and/or other neurodegenerative disorders in any family members should always be performed.[5]

Clinical Presentation

The hallmark of ALS is progressive development of motor symptoms and signs, with no accompanying sensory involvement.

Symptoms

Onset typically is gradual, occurring over a period of months, and is characterized by speech, breathing, or swallowing difficulty and weakness or loss of dexterity in one limb. Symptoms inevitably progress to involve other regions. Other features may include muscle wasting, muscle twitching (fasciculations), cramps, stiffness, and slowness. Fasciculations that are unaccompanied by wasting or weakness generally are due to benign causes rather than ALS. Bulbar onset with dysarthria and dysphagia occurs in one quarter to one third of cases.[6,7] Bulbar disease can also manifest with voice hoarseness, sialorrhea, or "pseudobulbar affect," i.e. mood instability characterized by insuppressible crying or laughter in response to emotional stimuli. Weight loss can occur with bulbar dysfunction or respiratory involvement.

Signs

The neurological exam for the diagnosis of ALS should focus on testing for upper motor neuron signs (UMN) and lower motor neuron signs (LMN). UMN signs are spasticity, hyperreflexia, and slowed movements of arms or legs. LMN signs include weakness, muscle atrophy (See Figure 1) and fasciculations.

Symptoms/Signs that Typically Do Not Appear in ALS and Suggest Another or Additional Diagnosis

Although symptomatic stabilization in a certain affected body region is occasionally observed, remission of symptoms and signs is rare, and when present should cast doubt over the ALS diagnosis. Similarly, bowel and bladder sphincter function, extraocular muscles and the sensory system are all typically spared, and when involved should trigger further investigation into other potential causes of the patient's illness.

Disease Course

Typical survival time from diagnosis is three to five years, although there is wide variation with some patients surviving for as little as six months and others for up to 20 years. For most patients, the pace of the disease remains relatively constant. A rapid increase in the rate of disease progression should provoke examination of other possible causes of worsening (e.g. infection).

Figure 1
Intrinsic hand muscle atrophy commonly seen in ALS patients.



Disease Variants

While ALS is typified by the combination of both upper and lower motor dysfunction without sensory or cognitive disturbances, there are distinct variants of ALS that do not follow this pattern. Progressive muscular atrophy (PMA) is a lower motor neuron only variant of ALS. These patients have progressive muscle atrophy and weakness, but not the hyperreflexia, spasticity, and slowness typical of ALS. Many, though not all, patients with PMA eventually develop the UMN signs and symptoms. It is this variant that symptomatically overlaps most closely with multifocal motor neuropathy, a treatable ALS mimic.

Primary lateral sclerosis (PLS) is an upper motor neuron variant. These patients have severe spasticity, hyperreflexia, slowness, but do not have the muscle atrophy and weakness. Central nervous system disorders such as multiple sclerosis, strokes, and other structural lesions can give a similar presentation and are typically excluded by MRI imaging. Some of these patients do develop LMN signs and symptoms and more typical ALS.

Frontotemporal Dementia with ALS (FTD/ALS): A variant of ALS that suggests a hereditary disease is Frontotemporal Dementia with ALS (FTD/ALS). Patients develop a dementia syndrome distinguished by prominent deterioration in language and behavior, concomitant with, and occasionally years preceding the typical ALS motor symptoms (see "Unravelling the Mysteries of Frontotemporal Dementia" by Ghoshal and Cairns).[7] Unlike Alzheimer's disease, memory is typically preserved early in the course

Table 1
Tests indicated in the evaluation of patients suspected to have ALS
AChR acetylcholine receptor; EMG/NCS: Electromyogram and nerve conduction studies; HSP: Hereditary Spastic Paraplegia; MuSK: muscle specific kinase; OPMD: oculopharyngeal muscular dystrophy; SBMA: Spinal-Bulbar Muscular Atrophy; SMA: Spinal Muscular Atrophy; SOD1: Superoxide dismutase 1; RNS: Repetitive nerve stimulation; VGCC: voltage-gated calcium channel.

TESTS THAT SHOULD BE OBTAINED FOR ALL PATIENTS
MRI imaging (of brain, spine, and occasionally brachial or lumbosacral plexi)
EMG/NCS
Anti-GM1 and anti-NS6S antibodies
Serum immunofixation, quantitative immunoglobulins
Copper, B12, TSH
TESTS THAT SHOULD BE CONSIDERED IN CERTAIN CLINICAL SCENARIOS
CSF studies (protein, glucose, cell count and differentiation, inflammation markers, West Nile serology)
Muscle biopsy
CK, aldolase (only mildly elevated in ALS)
Myasthenic syndromes work up (RNS, anti-AChR antibodies, anti-MuSK antibodies, anti-VGCC antibodies)
Myelopathy work up (RPR, HIV, HTLV, Lyme serology, rheumatologic labs)
Paraneoplastic antibodies
Heavy metal panel
Genetic studies to rule out other MNDs or MND-like diseases when suspected (SMA, SBMA, OPMD, HSP, etc)
Genetic studies to work up familial ALS (SOD1, C9orf72, TDP-43, FUS)

of dementia. While up to 40% of individuals with ALS may have some evidence of FTD on careful neuropsychiatric testing, only about 5-10% have fully developed FTD that manifests with behavioral changes noticed by the physician or caregivers. As noted previously, a recently reported autosomal dominant inherited expansion of a region of chromosome 9 underlies most of recognized FTD/ALS cases.[5]

When To Refer

Since ALS is rare and many physicians are unfamiliar with its presentation, the diagnosis is often delayed. Common clinical features that should prompt early referral to a neuromuscular specialist include: atrophy/weakness of muscles in a limb with increased deep tendon reflexes in that same limb, atrophy/weakness of muscles in one area with complaint of more widespread fasciculations and cramps, and progressively slurred speech with an unremarkable MRI of the brain.

Diagnostic Testing

The disease ALS is diagnosed clinically based on the presence of UMN signs and LMN signs while excluding other possible causes. Formal criteria for ALS have been established (the El Escorial Criteria).[8] Laboratory investigation is focused on defining other causes (possible ALS mimic syndromes) which may be amenable to therapy. Testing for patients with suspected ALS typically consists of electrodiagnostic tests (electromyography [EMG] and nerve conduction studies [NCS]), MRI brain imaging, and laboratory testing (See Table 1).

Imaging

Magnetic resonance (MR) imaging is used to exclude any structural lesions that could potentially account for the patient's presentation. Cervical spine disease with wasting and weakness in the arms or hands at the level of the lesion and spasticity in the legs typically is the most important condition to exclude. For presentations with speech abnormalities, excluding structural lesions (e.g., stroke) with brain MRI is important.

Electrodiagnostic Testing and Lab Work

EMG and NCS evidence of denervation in three body regions with normal sensory responses is the hallmark of ALS. Treatable motor neuropathies that mimic ALS such as multifocal motor neuropathy (MMN) are the most important diagnoses to exclude and can often be recognized on these tests.

Laboratory tests are focused on excluding autoimmune-mediated neuropathy, such as Multifocal Motor Neuropathy (MMN). Anti-GM1 or NS6S antibodies are present in up to 64% of MMN patients[9] and combined with characteristic changes on EMG/NCS strongly suggest MMN, a disorder that often is responsive to immunomodulatory therapy. A low vitamin B12 level or thyroid disorders may complicate management and thus should be identified and corrected. Low copper can present with motor greater than sensory disturbances, although the sensory complaints provide a clue that ALS is unlikely.

Genetic Testing

Genetic testing is recommended for patients with a family history of ALS. The most common genetic cause for familial ALS known to date is the hexanucleotide repeat expansion in the C9ORF72 gene, which is also known to be associated with FTD. A family history of FTD, even without an associated motor syndrome might spark testing for a C9ORF72 mutation.[5] Genetic counseling before testing is appropriate for patients and is strongly recommended before asymptomatic family members are tested.

Management

Following a diagnosis of ALS, the patient and care providers should receive regular support from a multidisciplinary care team. While the medications available to slow the progression of ALS are limited, careful attention to breathing, nutrition, and patient mobility can have a positive impact on the course of the disease.

Riluzole

Riluzole (Rilutek®) is the only FDA approved drug for ALS, and has been shown to prolong survival in ALS patients by three to six months. The modest benefit and high cost of the medication has limited enthusiasm for this treatment among some neurologists and patients, but the medication should be discussed with each patient. Riluzole is well tolerated overall, but patients should be monitored for liver toxicity. Elevation of hepatic enzymes to three to five times the upper limit of normal can occur but is typically self-limited and transient.[10] It is generally recommended to monitor liver enzymes at one week, one month and every six months after the initiation of riluzole, and to stop the drug if liver enzymes are elevated to more than five times the upper limit of normal. Riluzole typically is given at 50 mg twice per day.

Respiration

Respiratory function should be assessed by measuring forced vital capacity (FVC)[11] and maximal inspiratory pressure (MIP; a.k.a. negative inspiratory force (NIF)), and nocturnal oximetry[12]. The potential need for non-invasive ventilation (NIV) should be discussed with patients early in disease, and offered when FVC is less than 50%.[13] Patients using NIV have been shown in a randomized controlled study to have a median survival benefit of 205 days.[14]

Nutrition

Dysphagia is a common problem for ALS patients, leading to choking, aspiration, poor nutrition, and weight loss. At the first signs of dysphagia, a swallowing study should be obtained by a speech pathologist. A change in diet to soft consistency, high caloric foods may initially ameliorate the problem, but in many ALS cases, oral intake becomes insufficient. Supplementation, via percutaneous endoscopic gastrostomy (PEG), is often required. PEG placement in ALS patients results in the stabilization, and occasionally partial regain, of weight[15] and may prolong survival [16]. In discussing PEG tube it is important to emphasize that that oral feeding does not have to completely stop. The decision for a PEG placement should be made early in the course of the disease as restricted pulmonary function (FVC < 50%) increases the chances of procedure-related complications.[17]

Sialorrhea

Sialorrhea and drooling in ALS is not related to saliva overproduction, but results from an inability to adequately handle and swallow saliva. In some cases, a suction machine is sufficient to alleviate the problem. Traditional pharmacologic treatment of sialorrhea involves the use of anticholinergic agents, including glycopyrrolate (Robinul®), amitriptyline (Elavil®), benztropinemesylate (Cogentin®), trihexyphenidyl (Artane®), transdermal hyoscine (Scopolamine®), and atropine drops in mouth[13]. Common side effects include excessive drying of the nasopharynx, constipation, urinary retention, confusion, and sedation, particularly in the elderly. Other treatments include Botox injections and low dose radiation therapy to the salivary glands.

Pseudobulbar Affact

Antidepressants have been historically the mainstay of treatment for management of pseudobulbar affect. Both selective serotonin reuptake inhibitors (SSRIs) and tricylic antidepressants (TCAs) may be helpful, with TCAs superior in treating concomitant sialorrhea when present[18]. More recently, a fixed-dose combination of dextromethorphan (DM)/quinidine (Q) (30 mg DM/30 mg Q BID) has been shown to be effective in a randomized trial.[19] Possible side effects include dizziness, nausea, and somnolence.

Emotional Support

The diagnosis of ALS can be emotionally difficult for patients and their caregivers. Many patients find antidepressants (SSRI) medications helpful for mood even

Web Resources for ALS

- http://neuromuscular.wustl.edu/motor.html
- http://mda.org/disease/amyotrophic-lateral-sclerosis
- http://www.alsa.org/
- http://millerlab.wustl.edu/

when not meeting the full definition of depression. Support groups, available in most areas, can be very important for families and caregivers (see web resources at end of article).

End of Life Issues

A discussion regarding end of life planning should be initiated relatively early in disease. For example, code status should be clarified. Most patients do not inquire about assisted suicide, though physicians should be prepared to discuss this issue.

Other Problems

Patients with ALS may develop other complaints related to the disease pathology, directly or indirectly, such as pain, spasticity, cramps, fatigue, depression and sleep difficulty. There are limited data focused on treatment of these problems in ALS patients, therefore standard management as with other conditions is recommended. Spasticity is generally treated with baclofen or tizanidine as first line agents. Agents of choice for treatment of cramps are gabapentin and phenytoin,[20] while quinine has been recently restricted to treatment of malaria by the Food and Drug Administration (FDA) given its serious cardiac side effects profile.

Summary

Amyotrophic Lateral Sclerosis is a fatal neurodegenerative disease that currently remains incurable, but can be managed symptomatically over the disease duration to maintain the highest quality of life possible. Management is focused on controlling the symptoms, improving patient safety and maintaining autonomy to the extent possible. Multidisciplinary care in a coordinated ALS clinic setting is recommended. A careful family history is important to determine the presence of disease in other family members, and increase the likelihood of finding a genetic cause of the patient's ALS syndrome. Vigorous clinical and basic research in ALS may ultimately bring about treatments to successfully alter the disease course.[1]

References

1. Bedlack RS, Mitsumoto H. *Amyotrophic lateral sclerosis : a patient care guide for clinicians*.

2. Sorenson EJ, Stalker AP, Kurland LT, Windebank AJ. Amyotrophic lateral sclerosis in Olmsted County, Minnesota, 1925 to 1998. *Neurology.* Jul 23 2002;59(2):280-282.

3. Johnston CA, Stanton BR, Turner MR, et al. Amyotrophic lateral sclerosis in an urban setting: a population based study of inner city London. *J Neurol.* Dec 2006;253(12):1642-1643.

4. Traynor BJ, Codd MB, Corr B, Forde C, Frost E, Hardiman O. Incidence and prevalence of ALS in Ireland, 1995-1997: a population-based study. *Neurology.* Feb 1999;52(3):504-509.

5. Renton AE, Majounie E, Waite A, et al. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. *Neuron.* Oct 20 2011;72(2):257-268.

6. Chio A, Calvo A, Moglia C, Mazzini L, Mora G. Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study. *J Neurol Neurosurg Psychiatry.* Jul 2011;82(7):740-746.

7. Lomen-Hoerth C, Anderson T, Miller B. The overlap of amyotrophic lateral sclerosis and frontotemporal dementia. *Neurology.* Oct 8 2002;59(7):1077-1079.

8. Brooks BR. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial "Clinical limits of amyotrophic lateral sclerosis" workshop contributors. *J Neurol Sci.* Jul 1994;124 Suppl:96-107.

9. Pestronk A, Chuquilin M, Choksi R. Motor neuropathies and serum IgM binding to NS6S heparin disaccharide or GM1 ganglioside. *J Neurol Neurosurg Psychiatry.* Jul 2010;81(7):726-730.

10. Lacomblez L, Bensimon G, Leigh PN, Guillet P, Meininger V. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis/Riluzole Study Group II. *Lancet.* May 25 1996;347(9013):1425-1431.

11. Czaplinski A, Yen AA, Appel SH. Forced vital capacity (FVC) as an indicator of survival and disease progression in an ALS clinic population. *J Neurol Neurosurg Psychiatry.* Mar 2006;77(3):390-392.

12. Jackson CE, Rosenfeld J, Moore DH, et al. A preliminary evaluation of a prospective study of pulmonary function studies and symptoms of hypoventilation in ALS/MND patients. *J Neurol Sci.* Oct 15 2001;191(1-2):75-78.

13. Miller RG, Rosenberg JA, Gelinas DF, et al. Practice parameter: The care of the patient with amyotrophic lateral sclerosis (An evidence-based review). *Muscle Nerve.* Aug 1999;22(8):1104-1118.

14. Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. *Lancet Neurol.* Feb 2006;5(2):140-147.

15. Kasarskis EJ, Scarlata D, Hill R, Fuller C, Stambler N, Cedarbaum JM. A retrospective study of percutaneous endoscopic gastrostomy in ALS patients during the BDNF and CNTF trials. *J Neurol Sci.* Oct 31 1999;169(1-2):118-125.

16. Mazzini L, Corra T, Zaccala M, Mora G, Del Piano M, Galante M. Percutaneous endoscopic gastrostomy and enteral nutrition in amyotrophic lateral sclerosis. *J Neurol.* Oct 1995;242(10):695-698.

17. Mathus-Vliegen LM, Louwerse LS, Merkus MP, Tytgat GN, Vianney de Jong JM. Percutaneous endoscopic gastrostomy in patients with amyotrophic lateral sclerosis and impaired pulmonary function. *Gastrointest Endosc.* Jul-Aug 1994;40(4):463-469.

18. Miller RG, Rosenberg JA, Gelinas DF, et al. Practice parameter: the care of the patient with amyotrophic lateral sclerosis (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology: ALS Practice Parameters Task Force. *Neurology.* Apr 22 1999;52(7):1311-1323.

19. Brooks BR, Thisted RA, Appel SH, et al. Treatment of pseudobulbar affect in ALS with dextromethorphan/quinidine: a randomized trial. *Neurology.* Oct 26 2004;63(8):1364-1370.

20. Miller TM, Layzer RB. Muscle cramps. *Muscle Nerve.* Oct 2005;32(4):431-442.

Disclosures

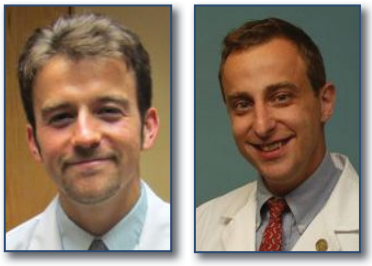
T Bali has no disclosures. T Miller receives research support from the following: NIH/NIA, NIH/NINDS, Project 5 for ALS, Tau Consortium, ALS Association, Muscular Dystrophy Association, , Mallinckrodt Foundation, Hope Center for Neurological Disorders at Washington University, Washington University ICTS, Cure PSP, Isis Pharmaceuticals, Regulus Therapeutics and has filed patents in conjunction with Washington University regarding use of antisense oligonucleotides based therapeutic strategies for neurodegenerative diseases. MM

Knight ADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

Diagnosis and Evaluation of a Patient with Rapidly Progressive Dementia

by Robert C. Bucelli MD, PhD & Beau M. Ances MD, PhD

A thorough, systematic approach is needed to evaluate an RPD patient in order to rule out possible treatable disorders.



Robert C. Bucelli, MD, PhD, (left) is an Assistant Professor in the Department of Neurology. Beau Ances, MD, PhD, is an Associate Professor in the Departments of Neurology, Microbiology and Biomedical Engineering. Both are at the Washington University School of Medicine in St. Louis.
Contact: bances@wustl.edu

Abstract

While the most common dementia is Alzheimer disease (AD), a detailed history is needed to rule out rapidly progressive dementias (RPDs). RPDs are less than two years in duration and have a rate of progression faster typical neurodegenerative diseases. Identification of RPDs is important as some are treatable. This review focuses on the spectrum of RPDs, with special emphasis on paraneoplastic disorders and Creutzfeldt-Jakob disease (CJD).

Introduction

While most causes of dementia are neurodegenerative and are characterized by a gradually progressive course, it is increasingly recognized that less common causes may have a more rapid course. In some instances, an apparent rapid course in fact represents the failure of observers to recognize subtle but progressive cognitive impairment that has been present for several years. Commonly, an evaluation in these instances is precipitated by crisis or a specific event (e.g. motor vehicle accident). The most common etiology is Alzheimer's disease (AD) and a careful history will assist in the diagnosis (Please see previous article on AD). It is extremely important to rule out more common etiologies before considering other rare causes.

However, rare sources of dementia that may have rapid progression, moving from asymptomatic to severe stages in the course of weeks to months are increasingly recognized. It is important to be aware of these more rapidly progressive dementias (RPDs) because some are treatable (e.g. autoimmune encephalopathies) while others are not [e.g. Creutzfeldt-Jakob disease (CJD)]. This review focuses on the spectrum of RPDs, with emphasis on those that are potentially treatable. In contrast, CJD is an inevitably fatal, irreversible disease that requires public health reporting.

Rapidly Progressive Dementias

While no formal diagnostic criteria have been established to define RPDs, most experts use clinical criteria similar to those proposed for CJD. In general, the course of RPD is two years or less in duration and the rate of progression is much faster than observed for more common neurodegenerative diseases.[1] Typically the mode of onset is more acute to subacute (i.e. days to weeks), in stark contrast to many neurodegenerative disorders where an exact date of onset is often difficult to identify. Beyond

this duration requirement, no unifying features exist that are common to all RPDs. A simple pneumonic for helping organize a framework for possible etiologies of RPD is "VITAMIN C"

- V= Vascular
- I=Infectious
- T= Traumatic
- A=Autoimmune
- M=Metabolic
- I= Idiopathic/Iatrogenic
- N=Neoplasm
- C=Congenital

These multiple potential etiologies engender a broad differential diagnostic approach (Please see websites listed at the end of the article). At Washington University in St. Louis (WUSTL) we use a systematic, multi-tiered, approach to evaluate RPD (See Figure 1). In this review we focus on two primary etiologies of RPD, the autoimmune dementing disorders and CJD. The former represents a treatable form of dementia and the latter is of significant importance from a public health perspective.

Autoimmune Dementias

Immune-mediated dementias represent a variety of disorders, ranging from neuropsychiatric lupus to paraneoplastic encephalopathies associated with anti-tumor antibodies to neural antigens.[2] These disorders can affect patients of all ages and until recently were considered a relatively rare cause of RPDs. Cognitive impairment in a young individual (< 50 years old) with a history of a dementing disorder should warrant an extensive evaluation for possible autoimmune disorders. Despite being less common, autoimmune etiologies should also be considered in the elderly population when there is a history of RPD. Some clues that may suggest an autoimmune encephalopathy include a history of an acute /subacute onset of symptoms, new onset seizures, sudden psychosis, respiratory impairment, concurrent involvement of other portions of the nervous system (e.g. peripheral neuropathy, myelopathy), or recently diagnosed cancer.[3] The history of present illness is the cornerstone of the clinical diagnosis. As detailed a history as possible should be obtained from the patient, when possible, and always from collateral source(s). In the absence of a reliable history or an available collateral source, the physician should have a low threshold for considering an autoimmune encephalopathy as this class of disorders is treatable and cognitive impairment may be reversed.

When considering paraneoplastic etiologies a defining feature of these disorders is that the signs/symptoms cannot be attributed to toxicity of chemotherapy or radiation therapy, infection, coagulopathy or other toxic or metabolic causes. While various mechanisms are likely responsible for the nervous system pathology in paraneoplastic syndromes (beyond the scope of this review), the general pathophysiology is associated with an immune-mediated injury to the nervous system due to a shared antigen, expressed on both tumor cells and within the nervous system.[4] The immune system therefore attacks both the cancer cells and the nervous system in its attempt to clear the antigen. The term "paraneoplastic" is commonly applied to any syndrome associated with anti-neuronal antibodies. While many of these disorders occur in the central nervous system (CNS), auto-autoantibodies can also develop in the peripheral nervous system (PNS).[2]

Figure 1
Work-up of a patient with rapidly progressive dementia (RPD).

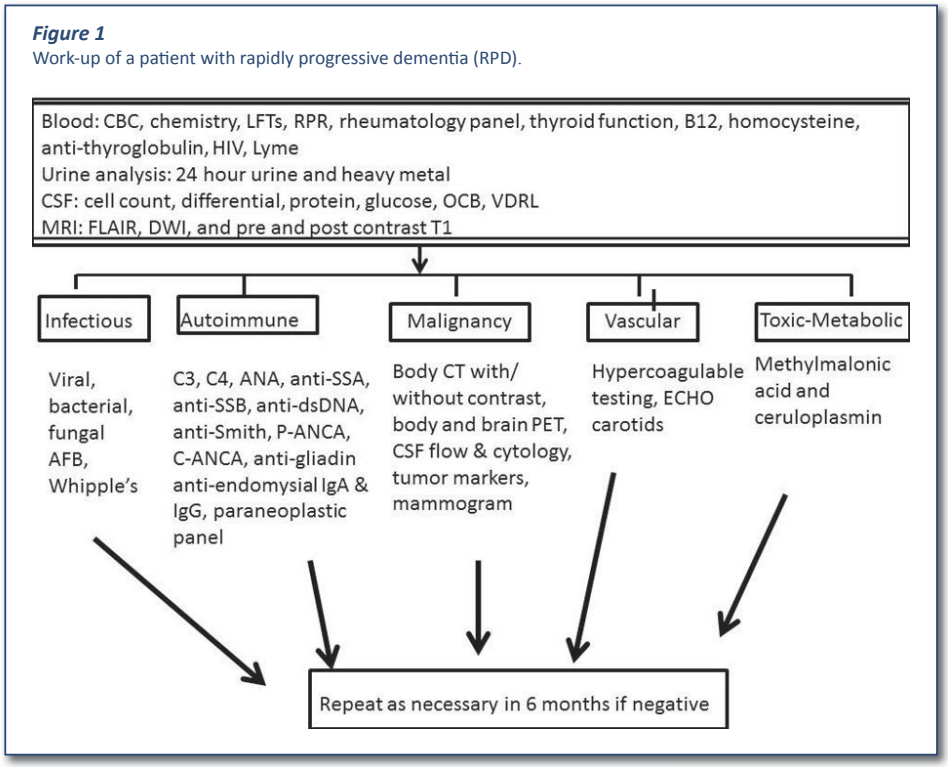


Table 1. Paraneoplastic disorder etiologies

Clinical presentation	Most Frequent Tumors	Associated Antibodies
Limbic encephalitis and Encephalopathy	Small cell lung cancer, testicular cancer, thymoma, teratoma	**Anti-Hu (ANNA-1)**, anti-Yo (PCA-1), anti-Ri (ANNA-2), ANNA-3, anti-Ma1, anti-Ma2, anti-amphiphysin, anti-CRMP5, anti-NMDA (and other neuropil antibodies), anti-VGKC, nicotinic ganglionic AChR autoantibody
Cerebellar degeneration	Breast cancer, ovarian cancer, small cell lung cancer, Hodgkin disease	Anti-Yo (PCA-1), anti-Hu (ANNA-1), anti-Ri (ANNA-2), anti mGluR1, anti-VGCC, anti-Ma1, anti-CRMP5(CV2)
Opsoclonus-myoclonus	Neuroblastoma, small cell lung cancer, breast	Anti-Ri (ANNA-2), anti-Yo (PCA-1), anti-Hu (ANNA-1), anti-Ma1, anti-Ma2,anti-amphiphysin, anti-CRMP5(CV2)
Stiff-person syndrome/PERM	Breast cancer, small cell lung cancer, Hodgkin disease	Anti-amphipysin, anti-GAD, anti-glycine, anti-Ri (ANNA-2)
Motor neuron disease	Lymphoproliferative disorders, small cell lung cancer, breast cancer, ovarian cancer	Anti-Hu (ANNA-1), anti-Yo(PCA-1), anti-SGPS, anti-gangliosides GM1, GM2, GD1a and GD1b
Peripheral neuropathy	Small cell lung cancer, thymoma, lymphoproliferative disorders	Anti-Hu (ANNA-1), anti-CRMP5(CV2), anti-SGPS, anti-gangliosides GM1, GM2, GD1a and GD1b
Neuromyotonia	Thymoma, Hodgkin disease, small cell lung cancer	Anti-VGKC, anti-Hu (ANNA-1)
Lambert-Eaton syndrome	Small cell lung cancer	Anti-P/Q VGCC

CRMP = collapsin response mediator protein; NR, NMDA= *N*-methyl-D-aspartate; ANNA= antineuronal nuclear antibody; PCA= purkinje cell autoantibody; VGCC= voltage-gated calcium channels; GAD= glutamic acid decarboxylase; TULP1= tubby-like protein 1; PTB= polypyrimidine-tract binding; MAG= myelin-associated glycoprotein; SGPS= sulfated glucuronic acid paragloboside; VGKC= voltage-gated potassium channels; PERM = progressive encephalomyelitis with rigidity and myoclonus; AChR = acetylcholine receptor

Modified from Toothaker and Rubins, Neurologist, 2009.

This review will focus on disorders of the CNS. Antibodies that are more likely to be associated with an underlying malignancy relative to others are presented in Table 1.

Antibody testing often involves analysis of panels of antibodies and any positive result needs to be interpreted within the appropriate clinical context as it may not always be of clinical significance. How to interpret a "positive" result and how the presence of an antibody will be incorporated into the patient's care are important questions to consider before sending these tests as false positive results are not uncommon.[5] The diagnosis of many of the autoimmune etiologies of RPD can be made using a combination of blood tests (See Figure 1), systemic imaging studies to screen for malignancy (including body computerized tomography (CT) and whole body positron emission tomography (PET)), cerebrospinal fluid analysis including glucose, protein, cell count, flow cytometry and cytology, pertinent microbiologic studies and polymerase chain reaction studies (PCRs) for specific viruses, an immunology profile (evaluation for oligoclonal bands and quantitative IgG relative to serum) and biomarkers for neurodegeneration including quantitation of the 14-3-3 antigen and total tau levels, and neuroimaging using magnetic resonance imaging (MRI) to evaluate for abnormalities characteristic of infectious, autoimmune or neurodegenerative etiologies.[3] In some instances, repeat evaluations may be required every six months to detect malignancies that are suspected but not yet confirmed. It is

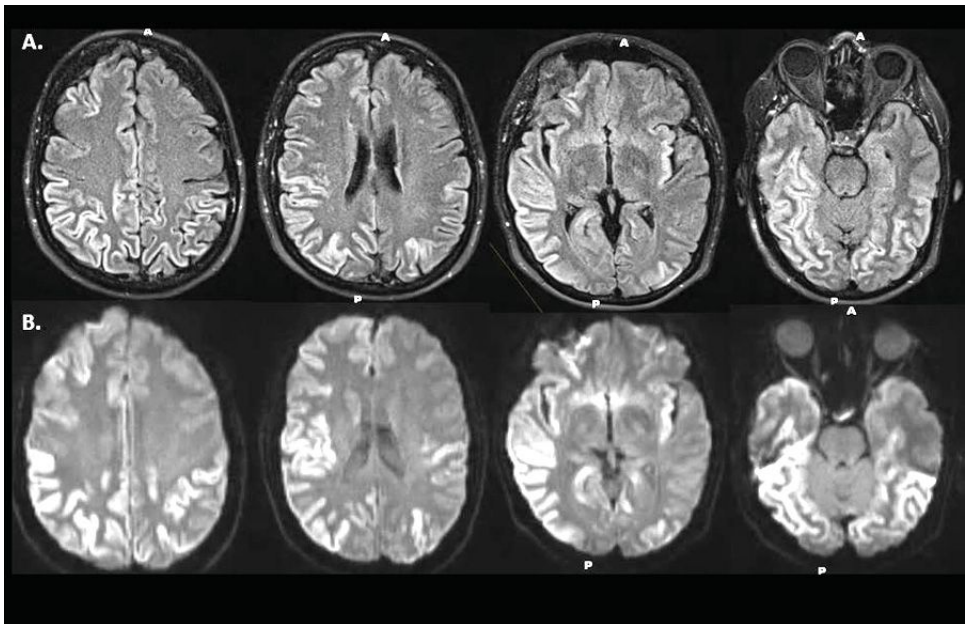
not uncommon for the paraneoplastic syndrome to predate the detection of an underlying malignancy by months to years.[6]

Treatment for autoimmune dementias varies based on the underlying etiology, the patient's medical comorbidities and the presence or absence of a possible underlying malignancy.[2] Treatment regimens include oral or intravenous steroids, intravenous immunoglobulin, plasma exchange, or other immunomodulatory agents (e.g. rituximab, cyclophosphamide, azathioprine, mycophenylate mofitil, or methotrexate).[5,7] For paraneoplastic disorders, the main priority is to identify and treat the possible underlying malignancy. While some paraneoplastic syndromes may initially respond to immunomodulatory therapies, for the vast majority this response will not persist unless definitive cancer treatment is pursued. With few exceptions, anti-neural antibodies directed against cell surface antigens are often responsive to immunomodulatory therapies, while those directed against intracellular antigens are unlikely to respond to treatment. Examples include antibodies (Ab) directed against the voltage-gated potassium channel complex (VGKC), a cell surface antigen.

In fact, the majority of patients with anti-VGKC syndromes do not have an underlying cancer and these patients usually respond very well to immunomodulatory therapies. In contrast, syndromes associated with antibodies against neuronal nuclear antigen 1 (ANNA-1, also known as Hu) are almost always associated with an underlying malignancy and do not respond to treatment unless the underlying cancer is identified and treated.[2] Prognosis for paraneoplastic dementias varies and is primarily based on the underlying cancer. For non-paraneoplastic dementias and other autoimmune dementias, the prognosis is often quite good if recognized early. In fact, as the name suggests, steroid-responsive encephalopathy with autoimmune thyroiditis (SREAT, also known as Hashimoto's encephalopathy) is defined by its marked improvement after administering steroids.

Figure 2

Characteristic magnetic resonance imaging (MRI) findings of a patient with Creutzfeldt-Jakob disease (CJD). Striking diffusion restriction is present in the cortical ribbon on multiple axial slices using (a) fluid level attenuated inversion recovery (FLAIR) and (b) diffusion weight imaging (DWI).



Creutzfeldt-Jakob Disease

In contrast to autoimmune etiologies, Creutzfeldt-Jakob Disease (CJD) is a fatal RPD without known treatment.[8] Most CJD cases are sporadic (sCJD) (85%) in nature but familial (15%) and acquired (≤ 1%) forms exist. The pathogenesis of sCJD remains poorly characterized but is believed to be due to a conformational change in the normal prion protein (PrP to an abnormal form (PrP^{Sc}) that is resistant to degradation. The term "prion" was initially coined by Stanley Prusiner in 1982 to describe proteinaceous infectious particles. Prusiner hypothesized once the abnormal PrP^{Sc} (for PrP scrapie, a spongiform encephalopathy in sheep) is formed, it acts as a template that subsequently converts normal surrounding PrP to PrP^{Sc}. This leads to an exponential growth in PrP^{Sc} and subsequent widespread propagation of neuronal degeneration.[9] Of note, there is growing evidence that prion-like mechanisms play a role in not only CJD but other, more common, neurodegenerative disorders such as Alzheimer disease, amyotrophic lateral sclerosis, and Parkinson disease.[10]

Table 2A: University of California San Francisco Criteria for Probable CJD

Clinical Symptoms
Rapid cognitive decline with any two of:
Myoclonus
Pyramidal/extrapyramidal
Visual
Cerebellar
Akinetic mutism
Other focal cortical signs
AND Diagnostic Testing
Typical MRI changes on FLAIR and DWI
EEG findings of periodic sharp and wave complexes
AND No other condition to explain observed clinical findings

Modified from Geschwind, Continuum, 2010

Table 2B: Clinical signs seen in CJD

	Presenting	During*
Cognitive	40%	100%
Cerebellar	22%	70%
Constitutional	21%	N/A
Behavioral	20%	N/A
Sensory	9%	N/A
Motor (non-cerebellar)	9%	62%
Visual	7%	N/A

*Myoclonus = 80%

Modified from Geschwind, Continuum, 2010

The resistance of prions to typical sterilization procedures makes exposure to affected brain tissues (particularly dura mater grafts and human growth hormone preparations) a major public health issue, perhaps best exemplified by the marked increase in iatrogenic CJD in Japan, France, the United Kingdom and the United States that started in 1974 and peaked around the year 2000.[11] Fortunately, with increased awareness the number of iatrogenic CJD cases (~ 450 in total worldwide) has dramatically decreased since 2000, a public health feat that would not have been possible without the work of physicians to recognize this rare form of dementia. While definitive diagnosis of CJD often requires tissue confirmation, brain biopsy of a patient with suspected CJD is often precluded by for both financial and safety reasons. Many institutions choose to dispose of all instruments used during a biopsy surgery of a suspected CJD patient, a cost prohibitive practice in most circumstances. While strict precautions are used, the theoretical risk of iatrogenic transmission from surgical patients to health care personnel due to direct contact with contaminated tissue are also taken into consideration when considering a biopsy.[11] Accordingly, more recent criteria for the diagnosis of CJD include less invasive methods.

Currently, the incidence (the number of new cases) of CJD in the United States is estimated to be 1-1.5 per million per year. Rates have not changed over the past two decades despite increased public awareness and a substantial increase in the number of referrals to the National Prion Disease Surveillance Center (NPDSC).[12] The typical age of onset of sCJD is 55-75 years of age (median = 68 years old) with males and females equally affected. The median duration of survival is approximately 4.5 months from time of onset of symptoms to death with around 90% of patients living less than one year.[9] We provide more recent guidelines developed at the University of California San Francisco (See Table 2A). It is important to note that cognitive changes may not be the initial presenting symptom but may occur somewhat later in the course. Other common initial signs and symptoms are listed in Table 2B.[13] Noninvasive diagnostic tests outlined in the guidelines may help differentiate CJD from other more treatable RPD disorders. Currently the work-up of possible CJD at our institution includes a structural MRI, electroencephalogram (EEG), and cerebrospinal fluid (CSF) and serum analyses (See Figure 1).

Brain MRI has had the greatest impact on improving the accuracy of an antemortem diagnosis of CJD. Characteristic changes on fluid level attenuated inversion recovery (FLAIR) images and diffusion weight imaging (DWI) are extremely helpful for diagnosing CJD. We present characteristic MRI findings from a patient at initial presentation of symptoms (Figure 2). MRI alone has a sensitivity and specificity of 70-95% and 80-100%, respectively.[11,13,14]

Cerebrospinal fluid analysis can also assist in the diagnosis. In particular, CSF should be evaluated for elevated levels of 14-3-3 (a non-specific marker

Table 3. CSF 14-3-3 and tau values for RPD patients evaluated at our institution

	sCJD (n=24)	RPD (n=15)	Sensitivity	Specificity	Odds Ratio (Confidence Interval)
CSF 14-3-3 "+" (%)	68	68	68	71	5.4 (1.2 – 23)
CSF Tau "+" (%)	86	86	86	86	38 (6 – 262)
Mean CSF Tau (pg/ml)	4651	4651	NA	NA	NA
Tau Range (pg/ml)	440 – 16,131	440 – 16,131	NA	NA	**NA**

NA= not applicable

Modified from Wang et al., J Neurol, 2013

of neuronal death) and tau (a non-specific marker of neuronal degeneration). In particular, we have observed a marked elevation in tau in CJD patients (See Table 3). Differences exist concerning the sensitivity and specificity of each of these CSF measures for the diagnosis of CJD. Finally, EEG assessment for periodic sharp and wave complexes may also assist in the diagnosis of CJD.[14] However, the accuracy of this measurement may vary on when in the time course of the disease it is performed. At best (even at specialty centers like ours) the sensitivity and specificity of each of these tests is approximately 90%.[11,13] From our own previous experience with confirmed CJD patients we have seen significant improvement in the diagnosis using a combination of these tests.

Recent advances in using real-time quaking induced conversion (RT-QUIC) testing of CSF may allow for reliable antemortem diagnosis. Researchers have more recently demonstrated that RT-QUIC was capable of detecting femtogram amounts of PrP^{SC} present in CSF of patients with CJD. While this method has great promise it has not been used in large clinical settings.[15] Overall, diagnosis of CJD continues to remain very difficult and can be missed. Often the diagnosis of CJD is made at a tertiary referral center such as ours only after an extensive evaluation has been performed.

Unfortunately, no disease modifying therapies exist for CJD. To date, there have been two clinical trials, both of which failed to show any significant benefit with respect to cognitive function or survival in sCJD patients. The PRION-1 study[16,17] was a partially randomized, patient-preference clinical trial using the antimalarial drug quinacrine, a drug selected based on in vitro evidence of prion elimination from a cell culture prion model. An earlier study using flupirtine maleate, a non-opiod analgesic, failed to show any improvements in cognitive function or survival in CJD patients receiving this medication.[18] Currently there are no clinical trials for sCJD planned. However, ongoing interest in developing novel therapies for this rare disorder exists and treatments may also be relevant for more common neurodegenerative disorders.

While efficacious therapies do not exist for CJD, the role of the clinician remains extremely important in not only identifying possible treatable mimics of CJD but also providing supportive care to not only patients with sCJD but their families. The importance of identifying treatable mimics of CJD has been well illustrated by a large study by Chitravas and colleagues who demonstrated that from 2006 through 2009 the NPDSC received 1106 tissue specimens for diagnostic confirmation of CJD suspected on clinical grounds.[19] Three hundred and fifty two (32%) of these specimens showed evidence of an alternative diagnosis and 71 out of these 352 (7% of the total cohort) specimens showed treatable disorders that had gone undiagnosed. The treatable disorders included immune mediated (n=26), neoplastic (n=25), infectious (n=14), metabolic/toxic (n=6).

Patterson and colleagues have also noted a similar percent misdiagnosis in regards to cases that were initially identified with other dementias but were subsequently shown at autopsy to be sCJD.[20] To this end we concur with the approach of Dr. Michael

Websites to Assist in Evaluation of RPD Patients

- National Prion Center
  http://www.cjdsurveillance.com/
- CJD Foundation
  http://www.cjdfoundation.org/
- Washington University in Saint Louis
  http://neuro.wustl.edu/research/researchlabs/anceslaboratory/interests/
- University of California San Francisco
  http://74.50.49.198/cjd/medical

Geschwind who regards CJD as "the great mimicker of other diseases. It can look like anything (and vice versa)."[11] As emphasized above, a thorough, systematic approach is needed to evaluate an RPD patient in order to rule out possible treatable disorders. We encourage all clinicians, if unsure, to contact our center to ensure that these patients undergo the thorough testing necessary to make this diagnosis. All patients and their families should be encouraged to consider pathologic confirmation of suspected disease. In addition, we provide our contact information as well as the CJD Foundation information for families and patients, and the NPDSC for pathological evaluation at autopsy.

References

1. Williams MM, Storandt M, Roe CM, Morris JC. Progression of Alzheimer's disease as measured by Clinical Dementia Rating Sum of Boxes scores. Alzheimer's & Dementia : the Journal of the Alzheimer's Association. 2013;9(1 Suppl):S39-44.
2. Dalmau J, Rosenfeld MR. Update on paraneoplastic neurologic disorders. Community Oncology. 2010;7(5):219-224.
3. Rosenfeld MR, Dalmau JO. Paraneoplastic disorders of the CNS and autoimmune synaptic encephalitis. Continuum. 2012;18(2):366-383.
4. Rosenbloom MH, Smith S, Akdal G, Geschwind MD. Immunologically mediated dementias. Current Neurology and Neuroscience Reports. 2009;9(5):359-367.
5. Toothaker TB, Rubin M. Paraneoplastic neurological syndromes: a review. The Neurologist. 2009;15(1):21-33.
6. McKeon A, Lennon VA, Pittock SJ. Immunotherapy-responsive dementias and encephalopathies. Continuum. 2010;16(2 Dementia):80-101.
7. Rosenbloom MH, Atri A. The evaluation of rapidly progressive dementia. The Neurologist. 2011;17(2):67-74.
8. Parchi P, Giese A, Capellari S, et al. Classification of sporadic Creutzfeldt-Jakob disease based on molecular and phenotypic analysis of 300 subjects. Annals of Neurology. 1999;{Perry, 2011 #473}46(2):224-233.
9. Geschwind MD, Shu H, Haman A, Sejvar JJ, Miller BL. Rapidly progressive dementia. Annals of Neurology. 2008;64(1):97-108.
10. Polymenidou M, Cleveland DW. Prion-like spread of protein aggregates in neurodegeneration. The Journal of Experimental Medicine. 2012;209(5):889-893.
11. Geschwind MD. Rapidly progressive dementia: prion diseases and other rapid dementias. Continuum. 2010;16(2 Dementia):31-56.
12. Aguzzi A, Falsig J. Prion propagation, toxicity and degradation. Nature Neuroscience. 2012;15(7):936-939.
13. Wang LH, Bucelli RC, Patrick E, et al. Role of magnetic resonance imaging, cerebrospinal fluid, and electroencephalogram in diagnosis of sporadic Creutzfeldt-Jakob disease. Journal of Neurology. 2013;260(2):498-506.
14. Zerr I, Schulz-Schaeffer WJ, Giese A, et al. Current clinical diagnosis in Creutzfeldt-Jakob disease: identification of uncommon variants. Annals of Neurology. 2000;48(3):323-329.
15. Atarashi R, Satoh K, Sano K, et al. Ultrasensitive human prion detection in cerebrospinal fluid by real-time quaking-induced conversion. Nature Medicine. 2011;17(2):175-178.
16. Collinge J, Gorham M, Hudson F, et al. Safety and efficacy of quinacrine in human prion disease (PRION-1 study): a patient-preference trial. Lancet Neurology. 2009;8(4):334-344.
17. Geschwind MD. Clinical trials for prion disease: difficult challenges, but hope for the future. Lancet Neurology. 2009;8(4):304-306.
18. Otto M, Cepek L, Ratzka P, et al. Efficacy of flupirtine on cognitive function in patients with CJD: A double-blind study. Neurology. 9 2004;62(5):714-718.
19. Chitravas N, Jung RS, Kofskey DM, et al. Treatable neurological disorders misdiagnosed as Creutzfeldt-Jakob disease. Annals of Neurology. 2011;70(3):437-444.
20. Paterson RW, Torres-Chae CC, Kuo AL, et al. Differential Diagnosis of Jakob-Creutzfeldt Disease. Archives of Neurology. 2012:1-5.

Financial Disclosure

Supported by the National Institute of Mental Health (K23MH081786 to B.M.A.) and National Institute of Nursing Research (R01NR012907, R01NR012657, and R01NR014449 to B.M.A).

MM

A Case for Neuroprotection in Ophthalmology: Developments in Translational Research

by Andrew J. Payne, PhD, Simon Kaja, PhD, Nelson R. Sabates, MD & Peter Koulen, MD

Retinal neuroprotection is a rapidly advancing field, full of interesting challenges and therapeutic potential.



Top, from left: Andrew J. Payne, PhD, is a Research Scientist and Simon Kaja, PhD, is an Assistant Professor in the Department of Ophthalmology at the University of Missouri – Kansas City School of Medicine. Bottom, from left: Nelson R. Sabates, MD, MSMA member since 1983, is a Professor and Chairman, Department of Ophthalmology and Director of the Vision Research Center, and Peter Koulen, MD, is a Professor and the Felix and Carmen Sabates Missouri Endowed Chair in Vision Research, Department of Ophthalmology, and the Director of Basic Research at the Vision Research Center at the University of Missouri – Kansas City School of Medicine.
Contact: koulenp@umkc.edu

Abstract

Cellular aging occurs by the lifelong accumulation of oxidative damage leading to neuronal apoptosis, termed 'neurodegeneration', and the functional deficits of aging. Loss of visual function is one of the most important quality of life measures for older adults. We discuss recent clinical and laboratory advances in the neuroprotective treatment of the aging eye with particular emphasis on the three major ocular neurodegenerative conditions: glaucoma, age-related macular degeneration (AMD), and diabetic retinopathy (DR).

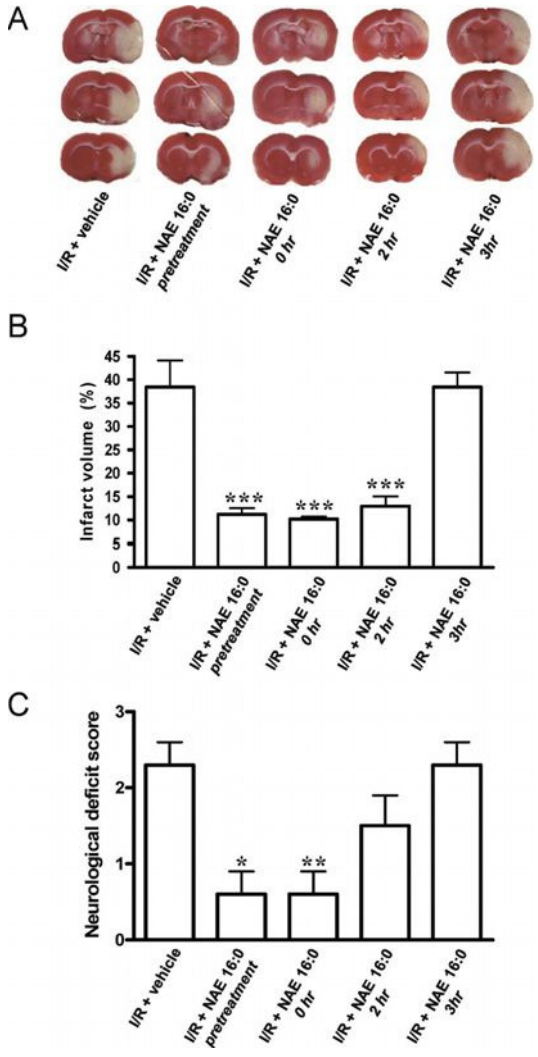
Introduction

Apoptosis, also known as programmed cell death, is a fundamental cellular signaling mechanism relevant to the proper function of a wide range of physiological processes from the single cell to the whole organism. As cells age, however, they accumulate damage from multiple sources, oxidative damage being the main focus of current aging research. A 'dysregulated' cell must either be destroyed or reverted to the healthy state in order to preserve the proper function of tissues and even the whole organism. The term 'neuroprotection', the protection of nerve cells from acute or chronic damage, should thus not be interpreted to mean solely the support of failing cells but should include the restoration of normal physiology. The goal of neuroprotection must be to prevent cell death by apoptosis or necrosis along with the correction of the physiology causing cellular pathology.

The retina is an ideal target for neuroprotection. Projected from the brain during development, the retina is exposed central nervous system (CNS) tissue that is more readily available for pharmacologic intervention than the remainder of the CNS. The regulated control of chemical access to the eye by the blood-retina barrier and the concomitant immune privilege allow interventions prohibitive elsewhere due to side effects.

Aging is theorized to occur by accumulative damage to the normal function of the cell by reactive oxygen species (ROS), such as free radicals and hydroxyl radicals,[1] often beginning as small synaptic changes but over time resulting in both synaptic and cellular dysfunction. The retina is a high oxygen demand tissue due to the large amount of energy required to drive visual signal transduction. Oxygen saturation and vascularization

Figure 1
NAE 16:0 is neuroprotective against ischemic tissue damage and improves neurological outcome following I/R.
(A) Representative TTC-stained sections of rat brain following 90 min. MCAO/24 h reperfusion (ischemia/reperfusion; I/R), treated with vehicle or NAE 16:0 at various time points. Viable tissue stains red, whereas damaged ischemic brain tissue appears unstained/white.
(B) Quantification of the volume of the ischemic lesion (infarct volume) revealed that NAE 16:0 was neuroprotective when administered from 30 min. before MCAO (pretreatment), up to two h after occlusion. Administration of NAE 16:0 at 3 h post-MCAO had no effect on the size of the ischemic lesion.
(C) I/R causes a moderate to severe neurological phenotype, as determined by the standardized neurological deficit score. NAE 16:0 reduced I/R-induced neurological deficits significantly (none to mild neurological phenotype) when administered before or at the time of occlusion. Data are shown as mean s.e.m. * p<0.05, ** p<0.01, *** p<0.001, compared with vehicle treated control group as determined using one-way ANOVA with Newman Keuls multiple comparison post-hoc test.



Reprinted from reference 9, Garg P, Duncan RS, Kaja S, Zabaneh A, Chapman KD, Koulen P. Lauroylethanolamide and linoleoylethanolamide improve functional outcome in a rodent model for stroke. Neurosci Lett. Apr 4 2011;492(3):134-138, with permission from Elsevier Ltd.; permission conveyed through Copyright Clearance Center, Inc. Further reproduction prohibited without permission.

decrease towards the inner retinal layers, but compensatory neovascularization in response to ischemia interferes with visual function and is a distinct marker of retinal disease.[2] The oxidative load created by normal visual signal transduction is counterbalanced by multiple antioxidant signaling systems, optimized and regulated to function in tandem. The cellular redox potential is actively maintained by antioxidant cascades that converge on the mitochondria. The mitochondrion is the primary metabolic organelle, responsible for producing ATP by the classical glucose pathway, but mitochondria also regulate intracellular pH, cytosolic calcium concentrations, and control cellular signaling resulting in apoptosis through specific enzyme and cellular messenger pathways.[3] The majority of intracellular ROS are generated as a byproduct of the mitochondrial respiratory chain through electron leakage from mitochondrial complex I and III leading to the production of superoxide ($O_2^{\cdot-}$).[4] Superoxide conversion to hydrogen peroxide (H_2O_2) is mediated by the scavenger enzymes superoxide dismutase (SOD), specifically the cytosolic Cu/Zn SOD1 and the mitochondrial matrix MnSOD2.[4] Hydrogen peroxide can react with reduced iron (Fe^{2+}) to form the hydroxyl radical ($^{\cdot}OH$), a potent ROS, that binds proteins, catalyzes the formation of lipid peroxyl radicals, and mutates DNA bases by a cyclization reaction.[4] Redox biochemistry and its clinical relevance have been recently reviewed by Valko and colleagues.[4]

Neuroprotective approaches have shown great promise in in vitro and in vivo studies. For instance, N-acylethanolamines (NAEs) are a class of signaling lipids endogenously expressed widely in the CNS[5], including the retina.[6] Several NAE species and NAE precursor molecules are up-regulated in response to chemical and traumatic insults, a cellular ability that decreases with age. This suggests a role in neuroprotection.[5,7]

NAEs such as NAE 20:4 (arachidonylethanolamine; AEA) bind cannabinoid receptors (CB1 and CB2), coining the term 'endocannabinoids'.[5] However, recent experimental evidence indicates that the neuroprotective effects of NAEs are not mediated via the cannabinoid receptor system.[7,8] Several NAEs (NAE 16:0, NAE 12:0, and NAE 18:2) have been shown to reduce stroke volume and improve behavioral outcomes in the rat middle cerebral artery occlusion stroke model (See Figures 1, 2).[7,9] Inhibitors for CB1 and TRPV1 receptors did not affect neuroprotection, while the cannabinoid uptake inhibitor AM404 blocked NAE-mediated neuroprotection.[7] Similar results were obtained from in vitro studies, which suggest that neuroprotection is mediated through an intracellular

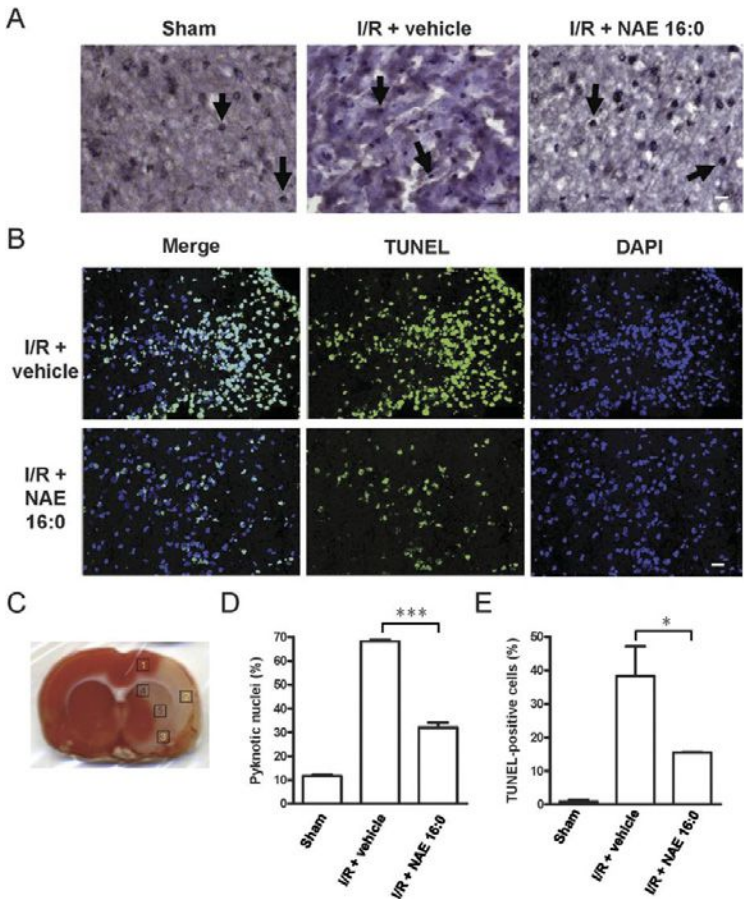


Figure 2
NAE 16:0 protects from I/R-induced apoptosis.
(A) Representative photomicrographs of hematoxilin/eosin (HE) staining within the ischemic area of the cortex in sham-operated and ischemic-reperfusion rats with or without NAE 16:0 treatment. Yellow arrows indicate pyknotic nuclei, indicative of cells undergoing apoptosis. Fewer pyknotic nuclei were observed following I/R in the presence of NAE 16:0. Scale bar: 100 µm.
(B) TUNEL labeling revealed a substantially reduced number of TUNEL-positive cells in the presence of NAE 16:0. In sham-operated animals, almost no TUNEL-positive cells were identified (data not shown). Scale bar: 50 µm.
(C) For quantification of pyknotic nuclei and TUNEL-positive cells, five areas in each section were analyzed. Areas are indicated here on a TTC-stained section of a vehicle-treated rat following I/R. Areas 1-3 are cortical and lie in the ischemic core and penumbral zone, whereas areas 4-5 represent subcortical areas mainly falling in the ischemic penumbral zone.
(D) Treatment with NAE 16:0 reduced the number of pyknotic nuclei following MCAO/reperfusion significantly by 53%, compared with vehicle-treated control.
(E) Similarly, the number of TUNEL-positive cells was 60% lower in NAE 16:0 treated brain sections, compared with vehicle control, indicating that NAE 16:0 treatment protects from induction of apoptosis and cell-death pathways. Data are presented as mean ± s.e.m. for each group. * $p<0.05$, *** $p<0.001$, using one-way ANOVA with Newman Keuls multiple comparison post-hoc test.

Reprinted from reference 9, Garg P, Duncan RS, Kaja S, Zabaneh A, Chapman KD, Koulen P. Lauroylethanolamide and linoleoylethanolamide improve functional outcome in a rodent model for stroke. Neurosci Lett. Apr 4 2011;492(3):134-138, with permission from Elsevier Ltd.; permission conveyed through Copyright Clearance Center, Inc. Further reproduction prohibited without permission.

mechanism, likely resulting in reduction of oxidative stress and glutamate excitotoxicity through the modulation of intracellular calcium homeostasis.[8,10] Of particular relevance, NAE 18:2 has potent neuroprotective effects against glutamate cytotoxicity in ex vivo retinal explants (See Figures 3, 4).[11]

Non-cannabinoid acting NAEs, such as NAE 16:0 and NAE 18:2, lack the acute and long-term chronic side-effects associated with cannabinoid use [6] and provide a safe alternative for neuroprotective approaches for disorders of the retina. Additional in vivo studies are warranted to establish the feasibility of therapeutic intervention strategies involving NAEs in glaucoma and other neurodegenerative disorders of the eye.

Oxidative damage causes a profound dysregulation of cellular physiology and contributes to the pathophysiology of neurodegenerative disorders such as glaucoma, diabetic retinopathy (DR), and age-related macular degeneration (AMD). The present review will discuss some recent advances in neuroprotective strategies developed to counter oxidative damage in these three major ophthalmic diseases.

Glaucoma

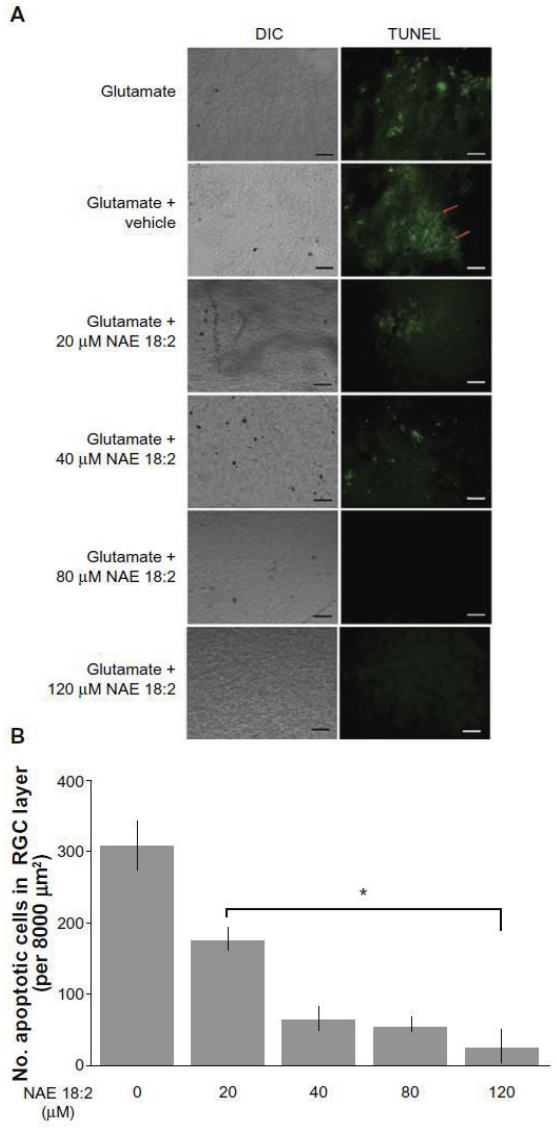
Glaucoma is a neuropathy of the aging eye primarily characterized by increased intraocular pressure (IOP) and eventual loss of visual function by destruction of the optic nerve and retinal ganglion cells (RGCs); the most common form is primary open angle glaucoma. [12] It should be noted that a significant minority of glaucoma patients present without increased IOP (i.e. normal tension glaucoma) and that glaucoma can also occur early in life or resulting from traumatic injury. However, IOP is the only clinically treatable modality and is the most predictive risk factor.[12] Debate exists over the causative role of IOP in disease progression, though the primary treatment endpoint for glaucoma remains the decrease of IOP by at least 25%

Figure 3
NAE 18:2 protects RGC layer neurons from glutamate excitotoxicity.
A) Exposure of retinas to 100 µM glutamate resulted in a dramatic increase in RGC layer neuron death (red arrows). Preincubation of retinas with NAE 18:2 for 6 hours prior to glutamate exposure resulted in a dose-dependent decrease in the number apoptotic, TUNEL-positive RGC layer neurons, with high physiological concentrations reducing the number of apoptotic RGCs.
B) Quantitative summary data for the NAE 18:2-mediated neuroprotection from glutamate toxicity as measured by TUNEL histochemistry.

Notes
* denotes $P < 0.05$ as determined by a one-way analysis of variance test. Scale bar: 50µm.

Abbreviations
DIC, differential interference contrast; NAE, *N*-acylethanolamide; RGC, retinal ganglion cell; TUNEL, terminal deoxynucleotidyl transferase-mediated dUTP (2′-deoxyuridine 5′-triphosphate) nick-end labeling – green fluorescence.

Republished with permission of Dove Medical Press Limited, from reference 11, Duncan RS, Xin H, Goad DL, Chapman KD, Koulen P. Protection of neurons in the retinal ganglion cell layer against excitotoxicity by the N-acylethanolamine, N-linoleoylethanolamine. Clin Ophthalmol. 2011;5:543-548; permission conveyed through Copyright Clearance Center, Inc. Further reproduction prohibited without permission.



from the patient's baseline untreated IOP.[13] The order of disease progression of glaucoma, whether the death of RGCs presage or result from the degeneration of the optic nerve is an interesting topic but beyond the scope of this review.[12]

The canonical treatment for the reduction of IOP in the most common form of glaucoma, primary open angle glaucoma,[13] remains the topical use of β receptor antagonists or prostaglandin analogues, first separately but in combination if IOP does not decrease within one year following the initiation of treatment.[14] Common alternate treatment modalities include carbonic anhydrase inhibitors or β2 adrenergic agonists.[13,14] Many different treatment paradigms have been tested in recent years in an effort to preserve visual function by sustaining the RGCs. Initially, the most promising drug in clinical trials was memantine, an N-methyl-D-aspartate (NMDA) channel antagonist with micromolar affinity. Memantine binds the open NMDA channel, blocking calcium entry to the cell or synapse, which should be neuroprotective in cases of glutamate excitotoxicity.[15] Indeed, memantine is neuroprotective in laboratory tests with rodents[16] but has failed to protect RGCs in primate studies.[17,18] Memantine has been shown to alter structural parameters of the eye and retina,[19] but these data are not not clearly linked to any measurable functional effects. Repeated, expensive phase III clinical trials failed to find an indication for memantine in neuroprotection of RGCs or the treatment of glaucoma.[20] A related compound, bis(7)-tacrine, has been discussed as a possible successor to memantine due to its improved efficacy in laboratory tests of RGC survival but it has yet to reach clinical trials.[21]

Recent studies have shown that the well-known surgical and dental dye, methylene blue, has a unique mechanism of neuroprotection. In this novel mechanism of neuroprotection, methylene blue accepts electrons from NADH early in the mitochondrial electron transport complex and shuttles the electrons past complex I and III to cytochrome C.[22] The methylene blue alternative pathway to the

electron transport chain reduced production of superoxide and free radicals in response to physiological oxidative stress induced by glutamate, ischemia, or electron transport complex specific inhibitors but not to direct chemical oxidation by hydrogen peroxide or glucose oxidase.[22,23] The electron scavenging ability of methylene blue was neuroprotective in cultured rat RGCs exposed to mitochondria electron transport complex inhibitors rotenone and staurosporine.[24] Methylene blue has yet to enter clinical trials for neuroprotection but its safety is known due to its past use as an antimalarial agent. Furthermore, its high bioavailability from oral dosage makes it a potentially powerful systemic neuroprotectant.[25]

Direct control of the calcium flux into the cell by use of L-type calcium channel blockers may be neuroprotective in the retina.[26] Though their clinical use is decreased due to systemic side effects, calcium channel blockers acting on the plasma membrane calcium channels decrease the cytosolic calcium concentration. Elevation of cytosolic calcium is causative of many neuronal pathologies and leads to cellular dysregulation, oxidative stress, and apoptosis.[27] In glaucoma, calcium channel blockers have an indication for the dilation of retinal blood vessels to increase fluid drainage and decrease IOP.[26] The β blocker nimodipine has been clinically demonstrated to have a positive effect on the visual field [28], increase contrast sensitivity[29], and prevent RGC loss by the inhibition of extracellular calcium influx. Ex vivo studies of calcium channel blockers demonstrated that nimodipine, iganidipine, and lomerizine were neuroprotective against hypoxic insult in cultured RGCs.[30] Previous clinical trials for calcium channel blockers in ophthalmology have rightfully focused their endpoints on the IOP and ocular blood flow, but clinical trials with neuroprotective endpoints, including relevant functional tests, for calcium channel antagonists would be required to correlate the promising laboratory data with clinical utility.

Age-Related Macular Degeneration

Age-related macular degeneration AMD is a common, multifactorial eye disease caused by an interaction of lifetime accumulated retinal damage and potentially also by genetic factors. Diagnostic

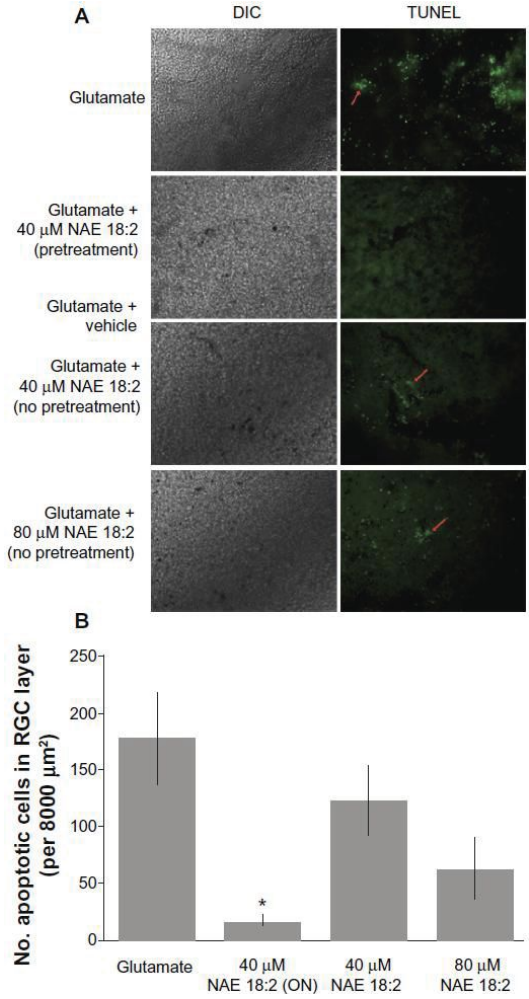
Figure 4
NAE 18:2 preincubation is required for protection of RGC layer neurons against glutamate excitotoxicity. NAE 18:2 preincubation is critical for its neuroprotective effect.

A) Retina explants were either pretreated for 24 hours (overnight, ON) with 40 μM NAE 18:2 prior to and during glutamate exposure or at the onset of glutamate exposure (no pretreatment). All glutamate exposures were for 24 hours and NAE 18:2 was present during the glutamate exposure period. Note the lack of protection without pretreatment (red arrows).
B) Quantitative summary data revealing the requirement for NAE 18:2 protection of RGC layer neurons against glutamate.

Notes
* denotes $P < 0.05$ as determined by a one-way analysis of variance test.
Scale bar: 50μm.

Abbreviations
DIC, differential interference contrast; NAE, N-acylethanolamide; RGC, retinal ganglion cell; TUNEL, terminal deoxynucleotidyl transferase-mediated dUTP (2′-deoxyuridine 5′-triphosphate) nick-end labeling – green fluorescence.

Republished with permission of Dove Medical Press Limited, from reference 11, Duncan RS, Xin H, Goad DL, Chapman KD, Koulen P. Protection of neurons in the retinal ganglion cell layer against excitotoxicity by the N-acylethanolamine, N-linoleoylethanolamine. Clin Ophthalmol. 2011;5:543-548; permission conveyed through Copyright Clearance Center, Inc. Further reproduction prohibited without permission.



guidelines for the 'dry' form of AMD require identification of intermediate to large deposits called drusen (>125 microns), autofluorescent lipofuscin granules, patchy loss of retinal pigment epithelium (RPE), and, in the aptly named 'wet' form of AMD, choroidal neovascularization.[31] AMD clinical pathology has been thoroughly described[32] and the genetic susceptibilities for AMD have recently been reviewed.[33] The progressive neovascularization in wet AMD, which is observed in about 15% of all AMD cases, usually responds well to treatment with inhibitors of vascular endothelial growth factor (VEGF).[31] Intravitreal injection of the corticosteroid triamcinolone acetonide has been proposed but conflicting reports on efficacy, and frequent reports of side effects with only marginal reduction of vision loss, decrease its clinical utility.[31,34]

Not surprisingly, since 'aging' is literally included in the name of the disease, cumulative lifetime oxidative stress is the presumptive mechanism of neurodegeneration. Completion of the Age-Related Eye Disease Study (AREDS) of dietary supplementation with antioxidants in AMD patients has yielded marginally positive results slowing disease progression after the intermediate stage, though longer trial endpoints (>5 years) will be needed to properly verify that claim.[31] Polyphenol compounds of certain green teas and their extracts are potentially neuroprotective in the photoreceptor outer segment and RPE if delivered in the proper dosages, namely about two cups of green tea per day.[35] Genetic knockdown of either cytosolic Cu/Zn SOD1[36] or mitochondrial MnSOD2[37] in mice increased markers of oxidative stress in the retina and recapitulated AMD phenotype with increased drusen, thickening of Bruch's membrane, and degeneration of the RPE and photoreceptor layers. Conversely, overexpression of MnSOD2 was neuroprotective against oxidative stress and decreased the AMD phenotype.[38] Recent studies have described a novel signaling cycle where generation of ROS by cytoplasmic NADPH oxidase triggers increased superoxide production in the mitochondria beyond the saturation point of MnSOD2.[39] Diffusion of superoxide to the cytosol activates NADPH oxidase to generate more ROS and promotes a vicious cycle of oxidative damage.[39] Relevant to both AMD and DR, increased activity of NADPH oxidase has been found to increase angiogenesis, vascular damage by leukocyte adhesion, and accumulation of advanced glycation end-products.[35]

Serotonin receptor 1A (5-HT1A) agonists have recently demonstrated neuroprotective properties in the retina although the mechanism is unclear. Topical treatment with the 5-HT1A agonists 8-OH DPAT and AL-8309 prevented damage to the photoreceptor layer and RPE when applied prior to hydrogen peroxide treatment in vitro[40] or phototoxic insult in vivo[41], respectively. Phototoxic damage proceeds from the singlet oxygen, superoxide, and hydrogen peroxide generated by blue light excitation of bisretinoids, compounds in lipofuscin granules of the photoreceptor outer segment.[42] The process of formation of lipofuscin granules is not clear but they seem to be photoreceptor outer segments incompletely digested by the RPE.[35,42] Serotonin agonists were also found to lessen the immune system aspect of drusen and lipofuscin deposition through a decrease in the recruitment of leukocytes, microglia, and certain proteins of the complement pathway.[43]

Diabetic Retinopathy

Diabetic Retinopathy (DR) is a common effect of diabetes with a 90% risk of onset within 25 years of diabetes diagnosis.[44] Neurodegeneration in DR is presaged by vascular degeneration in response to both the metabolic abnormalities and systemic high glucose concentration encountered in diabetes. Elevated blood glucose concentrations cause pericyte cell death, thickening of the capillary basement membrane, and accumulation of advanced glycation end-products.[44] Hard, yellow exudates accumulate from epithelia proliferation at the site of pericyte loss which leads to decreased blood flow and patches of ischemic damage in the microvascular circuit and surrounding neuronal cells. Ischemic lesions are the first clinically detectable symptom of non-proliferative DR.[44] The patient may advance to proliferative DR and more extensive damage caused by neovascularization, a compensatory response to the hypoxic conditions of non-proliferative DR.[44] During neovascularization, fragile new blood vessels connecting to the vitreous are stimulated to grow but fail to survive, causing scaring in the vitreous body and often leading to very poor vision or even blindness. Currently, the preferred treatment for DR is tight control of blood glucose but this often only delays retinal neurodegeneration.[45] Further treatments vary by severity and stage of DR progression but both laser photocoagulation and vitrectomy are invasive although both have decent outcomes.[45] Neovascularization can be slowed or blocked by inhibitors of VEGF.[45]

Dietary supplementation with antioxidants such as trolox, N-acetyl cysteine, and vitamins E and C has been suggested for DR but, as in AMD, the clinical trial outcomes are not overly encouraging due to similar experimental design concerns.[46] Green tea polyphenols such as (-)-epigallocatechin gallate are neuroprotective by

redox pathways in animal studies of the brain[47] and retina.[48] However, green tea extracts have been demonstrated to increase glucose crosslinking[49], a neurodegenerative effect of elevated blood glucose concentrations, therefore patients should be cautioned towards moderation in the use of green teas. Dietary supplementation with zeaxanthin, a photosensitive carotenoid concentrated in the retina, has shown some efficacy at preventing induction of VEGF and inhibition of the inflammatory immune response to DR.[50] Pharmacological neuroprotective treatments are possible in cases of DR but are retarded by patient non-compliance with glucose control, therefore the presumptive neuroprotective strategy would likely require prior and ongoing correction of blood glucose.

Conclusion

Retinal neuroprotection is a rapidly advancing field, full of interesting challenges and therapeutic potential. Neuroprotective treatment must first halt the apoptotic or necrotic death of post-mitotic cells and, in most cases, ideally arrest the advancement of disease. The second goal of a neuroprotective treatment is the reversion of pathologic cellular function to the healthy physiologic state. This second goal may be unattainable in some cases but often the inhibition of disease progression is contingent upon reversion to normal cellular function. Novel treatments targeting newly discovered neuroprotective pathways will enter clinical trials in the coming years and patients' lives will be improved by remission or correction of the pathologies of disease and aging. Neuroprotective strategies have been successful both in vitro and in vivo at halting or reversing damage to aged neurons. Clinical trials with dietary antioxidant supplementation have not produced an indication for neurodegenerative disease likely due to the choice of study endpoints or independent variables such as patient lifestyle and disease stage. Since retina pathologies tend to be multifactorial, neuroprotective treatments may be feasible as a component of treatment regimens that address multiple symptoms. For example, in glaucoma, where pharmacologic treatments exist to lower IOP, neuroprotective compounds that address the degeneration of the optic nerve or death of RGCs may aid in reversal of the multifactorial pathology.

Patients should be advised of the risk of pro-oxidative behaviors such as excessive exercise[51] or smoking.[35] The advancements discussed above will begin or have begun the translation to the clinic but some precautions can be widely advised to use antioxidant supplementation with polyphenols, readily available in green teas, or dietary restriction, such as tight blood glucose control and general caloric restriction. Antioxidant treatments for neuroprotection do involve some risk since many antioxidant compounds are capable of becoming pro-oxidants at high concentrations. Patients should be reminded of the carving in the lintel of the Delphic Temple of Apollo, μηδὲν ἄγαν - "Nothing excessively," that is still sage council.

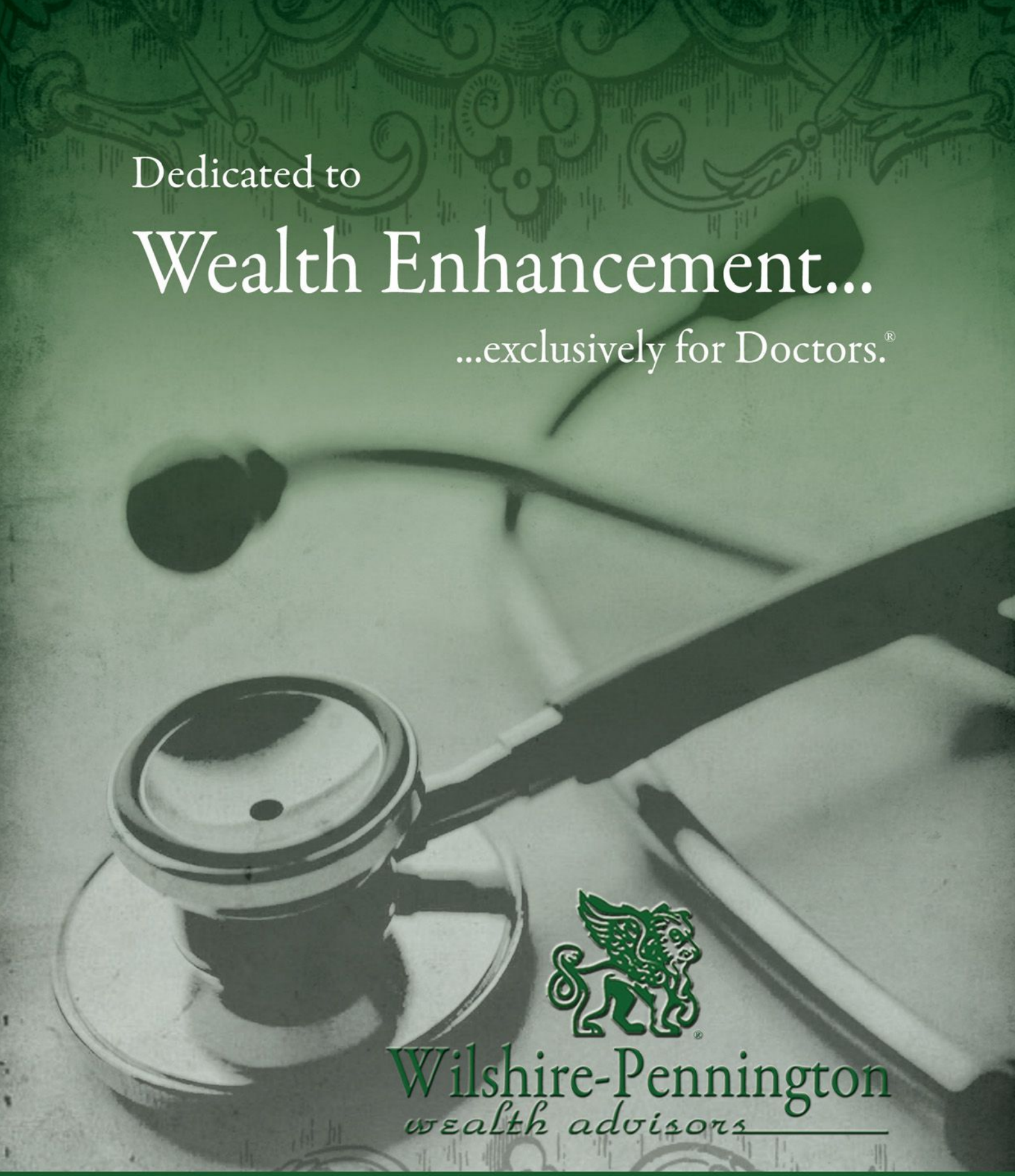
References

1. Harman D. Aging: a theory based on free radical and radiation chemistry. Journal of gerontology. Jul 1956;11(3):298-300.
2. Lange CA, Bainbridge JW. Oxygen sensing in retinal health and disease. Ophthalmologica. 2012;227(3):115-131.
3. Osborne NN, del Olmo-Aguado S. Maintenance of retinal ganglion cell mitochondrial functions as a neuroprotective strategy in glaucoma. Curr Opin Pharmacol. Feb 2013;13(1):16-22.
4. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol. 2007;39(1):44-84.
5. Fride E. Endocannabinoids in the central nervous system--an overview. Prostaglandins Leukot Essent Fatty Acids. Feb-Mar 2002;66(2-3):221-233.
6. Yazulla S. Endocannabinoids in the retina: from marijuana to neuroprotection. Prog Retin Eye Res. Sep 2008;27(5):501-526.
7. Garg P, Duncan RS, Kaja S, Koulen P. Intracellular mechanisms of N-acylethanolamine-mediated neuroprotection in a rat model of stroke. Neuroscience. Mar 10 2010;166(1):252-262.
8. Lombardi G, Miglio G, Varsaldi F, Minassi A, Appendino G. Oxyhomologation of the amide bond potentiates neuroprotective effects of the endolipid N-palmitoylethanolamine. J Pharmacol Exp Ther. Feb 2007;320(2):599-606.
9. Garg P, Duncan RS, Kaja S, Zabaneh A, Chapman KD, Koulen P. Lauroylethanolamide and linoleoylethanolamide improve functional outcome in a rodent model for stroke. Neurosci Lett. Apr 4 2011;492(3):134-138.
10. Duncan RS, Chapman KD, Koulen P. The neuroprotective properties of palmitoylethanolamine against oxidative stress in a neuronal cell line. Mol Neurodegener. 2009;4:50.
11. Duncan RS, Xin H, Goad DL, Chapman KD, Koulen P. Protection of neurons in the retinal ganglion cell layer against excitotoxicity by the N-acylethanolamine, N-linoleoylethanolamine. Clin Ophthalmol. 2011;5:543-548.
12. Calkins DJ. Critical pathogenic events underlying progression of neurodegeneration in glaucoma. Prog Retin Eye Res. Nov 2012;31(6):702-719.
13. American Academy of Ophthalmology Glaucoma Panel. Primary Open-Angle Glaucoma. Preferred Practice Pattern Guidelines San Francisco, CA: American Academy of Ophthalmology; 2010.
14. Boland MV, Ervin AM, Friedman DS, et al. Comparative effectiveness of treatments for open-angle glaucoma: a systematic review for the U.S. Preventive Services Task Force. Annals of internal medicine. Feb 19 2013;158(4):271-279.
15. Lipton SA. Failures and successes of NMDA receptor antagonists: molecular basis for the use of open-channel blockers like memantine in the treatment of acute and chronic neurologic insults. NeuroRx : the journal of the American Society for Experimental NeuroTherapeutics. Jan 2004;1(1):101-110.
16. Vorwerk CK, Lipton SA, Zurakowski D, Hyman BT, Sabel BA, Dreyer EB. Chronic low-dose glutamate is toxic to retinal ganglion cells. Toxicity blocked by memantine. Invest Ophthalmol Vis Sci. Jul 1996;37(8):1618-1624.
17. Hare W, WoldeMussie E, Lai R, et al. Efficacy and safety of memantine, an NMDA-type open-channel blocker, for reduction of retinal injury associated with experimental glaucoma in rat and monkey. Surv Ophthalmol. May 2001;45 Suppl 3:S284-289; discussion S295-286.
18. Hare WA, WoldeMussie E, Lai RK, et al. Efficacy and safety of memantine treatment for reduction of changes associated with experimental glaucoma

in monkey, I: Functional measures. Invest Ophthalmol Vis Sci. Aug 2004;45(8):2625-2639.
19. Hare WA, WoldeMussie E, Weinreb RN, et al. Efficacy and safety of memantine treatment for reduction of changes associated with experimental glaucoma in monkey, II: Structural measures. Invest Ophthalmol Vis Sci. Aug 2004;45(8):2640-2651.
20. Osborne NN. Recent clinical findings with memantine should not mean that the idea of neuroprotection in glaucoma is abandoned. Acta Ophthalmol. Jun 2009;87(4):450-454.
21. Fang JH, Wang XH, Xu ZR, Jiang FG. Neuroprotective effects of bis(7)-tacrine against glutamate-induced retinal ganglion cells damage. BMC neuroscience. 2010;11:31.
22. Wen Y, Li W, Poteet EC, et al. Alternative mitochondrial electron transfer as a novel strategy for neuroprotection. J Biol Chem. May 6 2011;286(18):16504-16515.
23. Poteet E, Winters A, Yan LJ, et al. Neuroprotective actions of methylene blue and its derivatives. PloS one. 2012;7(10):e48279.
24. Daudt DR, 3rd, Mueller B, Park YH, Wen Y, Yorio T. Methylene blue protects primary rat retinal ganglion cells from cellular senescence. Invest Ophthalmol Vis Sci. Jul 2012;53(8):4657-4667.
25. Walter-Sack I, Rengelshausen J, Oberwittler H, et al. High absolute bioavailability of methylene blue given as an aqueous oral formulation. European journal of clinical pharmacology. Feb 2009;65(2):179-189.
26. Araie M, Mayama C. Use of calcium channel blockers for glaucoma. Prog Retin Eye Res. Jan 2011;30(1):54-71.
27. Duncan RS, Goad DL, Grillo MA, Kaja S, Payne AJ, Koulen P. Control of intracellular calcium signaling as a neuroprotective strategy. Molecules. Mar 2010;15(3):1168-1195.
28. Piltz JR, Bose S, Lanchoney D. The effect of nimodipine, a centrally active calcium antagonist, on visual function and mascular blood flow in patients with normal-tension glaucoma and control subjects. J Glaucoma. Oct 1998;7(5):336-342.
29. Bose S, Piltz JR, Breton ME. Nimodipine, a centrally active calcium antagonist, exerts a beneficial effect on contrast sensitivity in patients with normal-tension glaucoma and in control subjects. Ophthalmology. Aug 1995;102(8):1236-1241.
30. Yamada H, Chen YN, Aihara M, Araie M. Neuroprotective effect of calcium channel blocker against retinal ganglion cell damage under hypoxia. Brain research. Feb 3 2006;1071(1):75-80.
31. American Academy of Ophthalmology Retina Panel. Age-Related Macular Degeneration. Preferred Practice Pattern Guidelines. San Francisco, CA: American Academy of Ophthalmology; 2008.
32. Ambati J, Ambati BK, Yoo SH, Ianchulev S, Adamis AP. Age-related macular degeneration: etiology, pathogenesis, and therapeutic strategies. Surv Ophthalmol. May-Jun 2003;48(3):257-293.
33. Ding X, Patel M, Chan CC. Molecular pathology of age-related macular degeneration. Prog Retin Eye Res. Jan 2009;28(1):1-18.
34. Maberley D, Canadian Retinal Trials G. Photodynamic therapy and intravitreal triamcinolone for neovascular age-related macular degeneration: a randomized clinical trial. Ophthalmology. Nov 2009;116(11):2149-2157 e2141.
35. Jarrett SG, Boulton ME. Consequences of oxidative stress in age-related macular degeneration. Mol Aspects Med. Aug 2012;33(4):399-417.
36. Imamura Y, Noda S, Hashizume K, et al. Drusen, choroidal neovascularization, and retinal pigment epithelium dysfunction in SOD1-deficient mice: a model of age-related macular degeneration. Proceedings of the National Academy of Sciences of the United States of America. Jul 25 2006;103(30):11282-11287.
37. Justilien V, Pang JJ, Renganathan K, et al. SOD2 knockdown mouse model of early AMD. Invest Ophthalmol Vis Sci. Oct 2007;48(10):4407-4420.
38. Kasahara E, Lin LR, Ho YS, Reddy VN. SOD2 protects against oxidation-induced apoptosis in mouse retinal pigment epithelium: implications for age-related macular degeneration. Invest Ophthalmol Vis Sci. Sep 2005;46(9):3426-3434.
39. Dikalova AE, Bikineyeva AT, Budzyn K, et al. Therapeutic targeting of mitochondrial superoxide in hypertension. Circulation research. Jul 9 2010;107(1):106-116.
40. Thampi P, Rao HV, Mitter SK, et al. The 5HT1a receptor agonist 8-Oh DPAT induces protection from lipofuscin accumulation and oxidative stress in the retinal pigment epithelium. PloS one. 2012;7(4):e34468.
41. Collier RJ, Patel Y, Martin EA, et al. Agonists at the serotonin receptor (5-HT(1A)) protect the retina from severe photo-oxidative stress. Invest Ophthalmol Vis Sci. Apr 2011;52(5):2118-2126.
42. Sparrow JR, Gregory-Roberts E, Yamamoto K, et al. The bisretinoids of retinal pigment epithelium. Prog Retin Eye Res. Mar 2012;31(2):121-135.
43. Collier RJ, Wang Y, Smith SS, et al. Complement deposition and microglial activation in the outer retina in light-induced retinopathy: inhibition by a 5-HT1A agonist. Invest Ophthalmol Vis Sci. 2011;52(11):8108-8116.
44. Madsen-Bouterse SA, Kowluru RA. Oxidative stress and diabetic retinopathy: pathophysiological mechanisms and treatment perspectives. Rev Endocr Metab Disord. Dec 2008;9(4):315-327.
45. American Academy of Ophthalmology Retina Panel. Diabetic Retinopathy. Preferred Practice Pattern Guidelines San Francisco, CA: American Academy of Ophthalmology; 2008.
46. Kowluru RA, Zhong Q. Beyond AREDS: is there a place for antioxidant therapy in the prevention/treatment of eye disease? Invest Ophthalmol Vis Sci. Nov 2011;52(12):8665-8671.
47. Choi YB, Kim YI, Lee KS, Kim BS, Kim DJ. Protective effect of epigallocatechin gallate on brain damage after transient middle cerebral artery occlusion in rats. Brain research. Sep 3 2004;1019(1-2):47-54.
48. Silva KC, Rosales MA, Hamassaki DE, et al. Green tea is neuroprotective in diabetic retinopathy. Invest Ophthalmol Vis Sci. 2013;54(2):1325-1336.
49. Mustata GT, Rosca M, Biemel KM, et al. Paradoxical effects of green tea (Camellia sinensis) and antioxidant vitamins in diabetic rats: improved retinopathy and renal mitochondrial defects but deterioration of collagen matrix glycoxidation and cross-linking. Diabetes. Feb 2005;54(2):517-526.
50. Kowluru RA, Menon B, Gierhart DL. Beneficial effect of zeaxanthin on retinal metabolic abnormalities in diabetic rats. Invest Ophthalmol Vis Sci. Apr 2008;49(4):1645-1651.
51. Camiletti-Moiron D, Aparicio VA, Aranda P, Radak Z. Does exercise reduce brain oxidative stress? A systematic review. Scandinavian journal of medicine & science in sports. Mar 15 2013

Acknowledgments

Research reported in this publication was supported in part by grants from the National Eye Institute (EY014227 and EY022774), the Institute on Aging (AG010485, AG022550 and AG027956), the National Center for Research Resources and National Institute of General Medical Sciences (RR022570 and RR027093) of the National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Additional support by the Felix and Carmen Sabates Missouri Endowed Chair in Vision Research, the Vision Research Foundation of Kansas City, and a Challenge Grant from Research to Prevent Blindness (PK) is gratefully acknowledged. The authors thank Margaret, Richard and Sara Koulen for generous support and encouragement. MM



(800)264-5815 • OFFICE:(405)751-8600 • FAX:(405)751-8898
3129 NW SIXTY THIRD STREET, OKLAHOMA CITY, OK 73116 • www.wilshire-pennington.com



You'll definitely want to call us in the morning

Patient Care Is ***Your*** Business.
Doctor Care Is ***Ours***.

MSMA Insurance has been caring for physicians and their professional liability needs for over 10 years. Let us care for you with a personalized quote:

866-676-2467 www.msma.biz

MSMA
Missouri State Medical Association
Insurance