Can diabetes drug stall Alzheimer’s disease?

Researchers led by Suzanne Craft, PhD, of the VA Puget Sound Healthcare System and the University of Washington, are gearing up to test whether rosiglitazone, a diabetes drug that boosts insulin sensitivity, can slow the onset of Alzheimer’s disease.

People with diabetes can’t properly use—or don’t make enough of—inulin, the main hormone that breaks down the sugar from food. As a result, too much sugar, or glucose, remains in the bloodstream. Drugs such as rosiglitazone improve patients’ response to insulin and help normalize glucose metabolism.

The new trial, funded mainly by the National Institute on Aging (NIA), will involve up to 150 volunteers with mild cognitive impairment. It follows more than a decade of work by Craft’s group pursuing the link between memory loss and insulin resistance.

The brain relies on glucose for cognitive function, and Craft’s early studies exploring glucose therapy for Alzheimer’s patients revealed problems with how they used the nutrient. The culprit, it turned out, was impaired insulin action.

“When we administered glucose to these patients, their insulin levels went abnormally high and persisted in an elevated state for a very long time,” said Craft, who is director of the Memory Disorder Clinic and associate director of the Geriatric Research, Education and Clinical Center at the Puget Sound VA.

High blood-glucose levels linked to ICU mortality

A study of 216,000 critically ill patients conducted by the Cincinnati-based VA Inpatient Evaluation Center showed that hyperglycemia, or high blood glucose levels, is associated with overall increased death rates among patients in VA intensive care units. The findings were presented on June 12 at the 66th Annual Scientific Sessions of the American Diabetes Association in Washington, DC.

In the study, led by VA endocrinologist Mercedes Falciglia, MD, hyperglycemia was found to be an independent predictor of mortality starting at one milligram

FDA approves VA-tested shingles vaccine

The U.S. Food and Drug Administration has approved the vaccine Zostavax for the prevention of shingles, a painful nerve and skin infection. The vaccine, made by Merck, had been studied by a research team led by Michael Oxman, MD, of the San Diego VA Healthcare System, in one of the largest adult vaccine trials ever. Findings from the trial appeared last year in the New England Journal of Medicine.

Shingles, also known as herpes zoster, is caused by a re-awakening of dormant chickenpox virus in the body. It is marked

Update from the CRADO...

Notifying ORD about upcoming articles is vital

By Joel Kupersmith, MD, chief research and development officer

In today’s digital age, news travels with incredible speed. Once a story breaks, it is available to information consumers around the world within minutes.

What does this mean for health researchers? For those studies that are of interest to the general public and are “picked up” by a reporter, the findings can be disseminated instantly to a global audience. This applies whether the study is originally reported on by a local, national or international media outlet. Rather than being read only by a relatively narrow audience of your professional peers, your work is communicated in lay terms to tens of thousands, or even millions. While this process can sometimes have negative outcomes for individual researchers or their organizations, especially when the subject matter is controversial.
‘Beetle Bailey’ cartoons enlisted for stroke-prevention outreach

Cartoonist Mort Walker, a World War II veteran and creator of the Beetle Bailey comic strip, donated custom cartoons for the VA Stroke Quality Enhancement Research Initiative (QUERI) Center to use as part of an education and prevention project launched last month to coincide with National Stroke Awareness Month.

Colorful posters featuring Walker’s cartoons were displayed during May in waiting areas of selected VA sites in North/Central Florida and Indianapolis. The posters showed the Beetle Bailey character “Sarge” demonstrating behaviors considered high-risk for stroke—for example, eating unhealthy foods and remaining sedentary—as well as some positive behaviors, such as eating fruit and walking. Each poster contained a “Take One” pocket with cards telling veterans how to request a packet of information on stroke prevention via mail, telephone or the Internet.

As part of “Disseminating Stroke Prevention Materials to Veterans: The Development of a Direct-to-Consumer Implementation Strategy,” lead investigator Rebecca Beyth, MD, MSc, and her team will conduct follow-up surveys with veterans to determine if they found the information beneficial and whether or not it influenced their health behavior.

The QUERI Center approached Walker at the suggestion of their dissemination specialist, Kristen Wing, who recalled that he had been active in other veteran-related projects.

“He was very enthusiastic about our project,” said Beyth. “He quickly drafted some sketches for the team to review, made some minor modifications per our request, and then finalized the cartoons. He generously donated the cartoons and authorized the VA Stroke QUERI Center to use them in any way we saw fit to promote stroke prevention. He is genuinely committed to doing what he can to help veterans.”

The poster campaign was part of a larger Stroke QUERI outreach effort to veterans and VA staff through emails, website articles, and other means. The stroke-information packet itself was based on existing VA patient-education materials and supplemented with literature from VA’s MOVE! (Managing Overweight/Obesity for Veterans Everywhere) program, the American Stroke Association, the National Stroke Association, and the Partnership for Clear Communication. Said Wing, “The strategy of Stroke QUERI is truly non-traditional in that we utilize low-cost or no-cost communication channels and resources that already exist within VA.”

The Stroke QUERI is one of a 10 such programs funded by VA’s Health Services Research and Development Service, each one focused on a health condition prevalent among veterans. The programs aim to help translate research finding into improved healthcare delivery and patient care.

For more information on the Stroke QUERI, visit www.va.gov/stroke-queri.

NCRAR to open new clinical research center

The National Center for Rehabilitative Auditory Research (NCRAR), based at the Portland VA Medical Center, will open a new clinical research facility on June 27. The 21,000-square-foot facility will house nine sound booths, an anechoic—or echo-free—chamber, and office space for research audiologists and other staff. The newly constructed center will also contain patient-education space, a conference room, and a library.

Founded in 1997, the NCRAR is the only VA center dedicated to helping veterans with hearing impairment and tinnitus. It conducts research, trains new scientists, and disseminates information to clinicians, veterans and the general public.
Can diabetes drug stall Alzheimer’s disease? (cont. from pg. 1)

Further research over the past decade, including epidemiologic findings of a higher risk for Alzheimer’s among diabetic patients, has supported the notion that insulin problems may contribute to memory loss. A pilot study published by Craft’s group last year found that rosiglitazone improved recall in 30 patients with mild Alzheimer’s or cognitive impairment. The drug also favorably affected blood levels of beta-amyloid, the protein that makes up the sticky brain plaques seen in Alzheimer’s disease.

Positive findings also emerged from a larger, international trial sponsored by drugmaker GlaxoSmithKline. The company, which is supporting a small part of Craft’s upcoming study, is launching a set of its own trials this summer to further test the benefits of rosiglitazone for Alzheimer’s patients. Craft’s clinic will take part in those efforts, but she is especially excited about her NIA-funded trial because of its focus on early-stage memory loss.

“This is a very critical group of people in which to identify effective interventions,” she said. “Mild cognitive impairment has been shown to be a preclinical stage of Alzheimer’s disease, where patients have significant memory impairment, but are not yet functionally impaired. The idea is to try to keep them at a functional stage where they are still able to live independently.”

Study to include MRI of brain structure

In Craft’s study, patients will receive either the medication or placebo for 18 months. They’ll take tests of thinking and memory before, during and after the treatment phase. Craft’s team will also use MRI to track whether rosiglitazone helps preserve the brain’s medial temporal lobe, which supports memory.

The researchers plan to enroll equal numbers of volunteers with and without a genetic risk factor called APOE-e4, which has been shown to modulate the response of dementia patients to insulin-based treatments. A GlaxoSmithKline trial with 511 Alzheimer’s patients, published earlier this year in Pharmacogenomics, found that only those without the risk factor responded positively to rosiglitazone. Craft’s earlier research has yielded similar findings, although she noted: “We can’t predict with certainty [who will respond and who won’t], as we are using a higher dose of rosiglitazone than in our past study, and a longer treatment period. There is certainly a possibility that APOE-e4 carriers will respond.”

Her study will exclude patients with diabetes, but not those with pre-diabetic glucose intolerance. “This condition occurs in a large number of older adults and Alzheimer’s disease patients in general, and may very well be a marker of treatment response,” she explained.

The investigator pointed out that rosiglitazone is just one of several approaches her team is trying. “Anything that improves insulin resistance may help. We have studies going on with exercise, which is a very potent insulin sensitizer, and studies looking at administering insulin directly to the brain.

“It’s too early to tell which approach will work best,” she added. “It’s a very exciting time, but we are really still at the beginning of seeing what the full benefits will be, and who will benefit.”

CSP cited for impact on clinical practice

The National Institutes of Health (NIH) highlighted VA’s Cooperative Studies Program (CSP), along with 28 other leading clinical research networks, in a report presented at a two-part scientific meeting in Rockville, Md., on May 31 and June 1.

As part of NIH’s Roadmap initiative, the agency’s Inventory and Evaluation of Clinical Research Networks Best Practices Study identified 28 networks in the United States and one in the United Kingdom that excel in areas such as efficiency, training, effective use of information technology, and impact on clinical practice.
Recent publications and presentations

Below is a sampling of recent publications and presentations by VA investigators, based on notifications received by VA R&D Communications. (See reporting requirements at www.research.va.gov/resources/policies/pub_notice.cfm.) Every attempt is made to present a cross section of investigators, topics and medical centers. Due to space constraints, only VA-affiliated authors are listed.

“Alpha-1-Antitrypsin Uptake and Anti-Apoptotic Effect in Pulmonary Artery Endothelial Cells Is Down Regulated by Blockage of VEGF R2.” Edward R. Block, MD; Jawaharlal M. Patel, PhD; Michael A. Apicella, MD; William M. Nauseef, MD. Gainesville, American Medical Association, June 2006.

“Basis for the Failure of Francisella Tularensis Lipopolysaccharide to Prime Human Polymorphonuclear Leukocytes.” Jason H. Barker, MD; Jerrold Weiss, PhD; Michael A. Apicella, MD; William M. Nauseef, MD. Iowa City, Infection and Immunity, June 2006.


“Evaluating the Quality of Interaction between Medical Students and Nurses in a Large Teaching Hospital.” Richard M. Frankel, PhD. Indianapolis, BMC Medical Education, April 25, 2006 (online).

“Evaluation of Selected Laboratory Components of a Comprehensive Periodic Health Evaluation for Veterans with Spinal Cord Injury and Disorders.” Howard Choi, MD, MPH; Marjorie L. Oropilla, MD; Ervin E. Bernotus, MD; Maura A. Nee, MSN, RN, ANP; Elizabeth A. Tammaro, BSN, RN, CRRN; Sunil Sabharwal, MD. Boston, Archives of Physical Medical and Rehabilitation, May 2006.

“Factors Affecting Compliance with Diabetes Hypertension Guidelines,” Julie C. Lowery, MSHA, PhD; Sarah L. Krein, PhD. Ann Arbor, Academy Health annual research meeting, June 2006.


“Implementing Evidence-Based Practices to Reduce Catheter-Related Bloodstream Infections in the Intensive Care Unit.” Patricia Burns, MD; Delores Ellis, MSN; Marta L. Render, MD. Cincinnati, Kentucky Organization for Nurse Leaders meeting, May 2006.


“Medical Team Training in the VA.” Peter Mills, PhD, MS; Julia Neil, RN, MS, MPH; Edward J. Dunn, MD, MPH; William Weeks, MD, MBA. White River Junction.


“Office and Ambulatory Blood Pressure are Independently Associated with Albuminuria in Older Subjects with Type 2 Diabetes.” Andrew Moran, MD; Ruth S. Weinstock, MD, PhD. San Francisco, Syracuse, Hypertension, May 2006.

“Predictors of Untreated Remission from Late-life Drinking Problems.” Kathleen K. Schutte, PhD; Rudolf H. Moos, PhD; Penny L. Brennan, PhD. Palo Alto. Journal of Studies on Alcohol, May 2006.

“Racial Differences in Prevalence of Coronary Obstructions among Men with Positive Nuclear Imaging Studies.” Jeff Whittle, MD, MPH; Nancy R. Kressin, PhD; Michelle B. Orner, MPH; Mark Glickman, PhD; Laura A. Petersen, MD, MPH. Milwaukee, Bedford, Houston. Journal of the American College of Cardiology, May 16, 2006.


Tracing the ‘adventures’ of Gross, Oldendorf and other pioneers in VA research

The following is an excerpt from the introduction to “VA Research, 1925 – 1980,” a history compiled by Dr. Marguerite Hays, who directed VA’s Medical Research Service during the 1970s. The complete text is expected to be available in print or on CD by early next year.

Tracing the path of progress in VA medical research does not involve drawing a straight line. It requires, rather, sketching a jagged streak forward—the many high points marked by significant findings and the development of medical advances, the few downticks indicating an occasional disappointment—the trend always upward toward promise and hope for improved health care and a better quality of life.

The focus of this history is the innovation produced in this remarkable program; to cite just a few examples:

- The first decisive trials of effective treatments for tuberculosis;
- Demonstration of the lifesaving value of treating hypertension;
- Development of the concept of CT scanning;
- Discovery and development of radioimmunoassay, facilitating measurements of previously impossible precision;
- Cooperative studies proving the efficacy of psychoactive drugs in stabilizing psychiatric disorders;
- Demonstration of the relationship between smoking and lung cancer, leading to initial warnings in the Report of the Surgeon General; and
- Development of a practical, implantable cardiac pacemaker.

Although this research program produced more than enough accomplishments to completely occupy its text, this history also attempts to depict the pioneers who carved that path of progress. In large measure, the history of VA medical research is their story.

In several instances, personal comments are included from the men and women—investigators, managers and administrators—who brought VA research alive. Some of their accounts are truly fascinating, sounding more like adventure stories than what might appear in scientific journals. For example, Ludwig Gross, M.D., a war refugee who escaped Poland just ahead of the Nazis, came to America and became a U.S. Army doctor. After the war, he joined the clinical staff of the Bronx (NY) VA Hospital while still in uniform. Doing his research in an old bathroom after hours, he had to breed his own mice for his experiments, keeping them in cages in the trunk of his car. His early stages, so we know whom to treat, and when.” Weiner is principal investigator on a $60-million, five-year study to identify brain changes linked to Alzheimer’s disease, funded by the National Institute on Aging.

see CIND on pg. 7

Brain-imaging center dedicated in San Francisco

The San Francisco VA Medical Center marked the opening of its new Center for the Imaging of Neurodegenerative Diseases (CIND) on May 12 with a ribbon-cutting ceremony attended by officials from VA, the Department of Defense and other agencies, and a conference featuring international medical-imaging experts.

CIND will focus on early detection and monitoring of chronic and neurodegenerative brain conditions such as Alzheimer’s disease, posttraumatic stress disorder, Gulf War illness, Parkinson’s disease, epilepsy, and HIV dementia. Among other equipment, the center features a Bruker MedSpec MRI instrument, the only one of its kind in the VA system. At 4.0 Tesla—a measure of magnetic field strength—the device is several times more powerful than conventional MRIs, and allows for extremely detailed images of brain structures and activity.

“We conduct essential research,” said CIND director Michael Weiner, MD, who is also a professor of radiology, medicine, psychiatry, and neurology at the University of California, San Francisco. “Looking at Alzheimer’s alone, about five million Americans have it, and that number is only expected to grow. As new drugs are developed, it’s vital that we find ways to identify degenerative brain disease in its early stages, so we know whom to treat, and when.” Weiner is principal investigator on a $60-million, five-year study to identify brain changes linked to Alzheimer’s disease, funded by the National Institute on Aging.

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The rich history of VA research

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Notifying (cont. from pg. 1)

or sensitive, I think most of us would agree that it is, by and large, a positive force for research. Increased exposure can benefit us by building understanding of our work; attracting new funding; helping to recruit study participants; and reaching out to potential collaborators.

One way you can achieve these positive outcomes is to make sure you notify ORD—specifically, R&D Communications—about any upcoming scientific journal articles or meeting presentations.

The current procedure is outlined on our website at www.research.va.gov. In the “Resources” column on the homepage, click on “Policies and Guidance,” and then on the “Publication Notification” link on the left side of the page. The Publication Notification page will give you the email address to which to send notifications (research.publications@va.gov), and outline the details that need to be included. HSR&D-funded investigators have an additional procedure to follow, as described on this Web page. R&D Communications is working with Information Technology to eventually transition to a Web-based system that we expect will be an efficient and powerful tool for both ORD and all our investigators and administrators in the field. More information on that project will be forthcoming later in the year.

With advance notice of upcoming publications, R&D Communications can take appropriate actions, such as preparing a background brief for VA or VHA leadership; coordinating publicity with the press office at your academic affiliate or outside funding agency; or preparing a VA news release.

It is also important to take advantage of other resources within VA. Have you met your local VA public affairs officer (PAO)? On numerous occasions in the past, PAOs have been instrumental in helping to spread the word about VA research. Besides the regular, required process of notifying ORD about any upcoming publications or presentations, you are advised to touch base with your VA PAO about any research findings—or new grants, for that matter—that you feel may be especially newsworthy. Your PAO can work with R&D Communications to decide on and implement a strategy for local or national publicity, if appropriate, and help coordinate publicity efforts with our academic affiliate.

On a different but related note, I am pleased to see the new enhanced and expanded format for this newsletter, which serves as an important link between ORD and the field. My hope is that through this and other communications vehicles, such as our website and monthly field conference calls, we can share information, knowledge and ideas that will foster our research and help us better serve veterans.

History (cont. from pg. 5)

work led to the proof of the viral cause of mammalian leukemia.

And, when Dr. William Oldendorf was working as a VA neurologist at the Los Angeles VA Hospital, he was looking for a way to avoid suffering by his patients who needed brain imaging, rather than doing painful pneumoencephalography. He reasoned that composite pictures of the brain area from X-ray images taken at many angles would serve the purpose. Using simple equipment—including an old model-railroad track—he personally built the prototype for CT scanning—which has since benefited millions of patients worldwide.

ICU (cont. from pg. 1)

per deciliter above normal glucose levels. The effect was highest in those without diagnosed diabetes and in those admitted with cardiovascular disorders. In some illnesses, however, such as chronic obstructive pulmonary disease and liver failure, there appeared to be no link between high glucose levels and mortality.

“These findings suggest that different disease states are variably affected by hyperglycemia,” said Falciglia.

Hyperglycemia has been shown in smaller trials to be associated with higher mortality in ICUs, but the outcomes of intervention trials with intensive insulin therapy have been mixed.

Said Falciglia, “Based on the outcome of this large study, we believe that the variable results of those studies may be due to the unique ways in which high blood glucose may or may not affect mortality in different types of diseases.” She added that these patterns “can be uniquely revealed through large and diverse databases such as those generated by the network of Veterans Affairs hospital ICUs.”

Shingles (cont. from pg. 1)

by a painful, blistering rash. It can affect anyone who had chickenpox as a youth, which is virtually all middle-aged and older Americans. Doctors in the United States treat about a million cases annually. Most cases clear up within a week, but some patients suffer anguish for years.

In the trial, which involved nearly 39,000 older adults, the vaccine reduced the incidence of the disease by 51 percent and dramatically lessened its severity in the cases that did occur. And the vaccine patients were only a third as likely to develop a complication known as post-herpetic neuralgia, a form of serious chronic nerve pain.
CIND (cont. from pg. 5)
and an alliance of federal, academic and private partners.

CIND has a staff of more than 60 physicians, physicists, computer scientists, radiologists, technicians, and support personnel. Interestingly, nearly a quarter-century ago, in the same building where his new center is located, Weiner established the first VA laboratory dedicated to nuclear magnetic resonance, the physical basis of MRI.

CSP (cont. from pg. 3)

The report said CSP is able to bring about change in clinical practice due mainly to its focused mission; rigorous scientific methods; and stable, comprehensive infrastructure. As part of the Veterans Health Administration, CSP has access to a large pool of study volunteers, and works closely with VA policymakers and clinicians to identify key research questions and translate findings into clinical practice as rapidly as possible. The report cited CSP as an example of “institutional completeness” because of these and other factors, such as pharmaceutical support and research expertise.

“This report highlights how VA’s research program is a unique national laboratory that can expeditiously transfer research discoveries into clinical practice to benefit our nation’s veterans and healthcare in general,” commented Secretary of Veterans Affairs James Nicholson.

CSP had its origins in the days after World War II, when it enrolled thousands of veterans with tuberculosis in studies to evaluate new and existing drugs. Since then, it has helped establish treatments and clinical practices for schizophrenia, hypertension, septic shock, shingles, and other conditions. For more details on the program visit www.csp.research.med.va.gov. The Best Practices report is available at www.clinicalresearchnetworks.org.

The ‘art’ of science

New MRI method highlights white matter in brain

The images on this page come from the lab of Martha Shenton, PhD, who studies schizophrenia at the VA Boston Healthcare System and Brigham and Women’s Hospital. The images are computerized visualizations of data from diffusion tensor imaging (DTI), a relatively new magnetic resonance imaging (MRI) technique.

DTI measures the movement of water molecules through the nerve fibers that make up the brain’s white matter. Since water moves along the length of the fibers but not across them, DTI allows for a finely detailed image of the fibers’ structure. And since water moves more freely in damaged white matter than in healthy tissue, DTI can detect white-matter abnormalities, which researchers suspect may play a role in many brain and nervous-system disorders and injuries.

Says Shenton, “Unlike conventional MR scans, where white matter appears uniform and homogenous, this new technology affords an opportunity to investigate and quantify abnormal white matter fiber tracts in the human brain.”

Clockwise, from top right: the human cortex (the red threadlike structures show the underlying neuronal fibers); anatomically separated bundles of axons; a small fragment of human white matter, with shapes describing brain water diffusion; and an isolated view of white-matter fiber tracts. Images courtesy of Hae-Jeong Park, PhD; Gordon Kindlemann, PhD; Lauren O’Donnell, PhD; and Marek Kubicki, MD, PhD.
CSR&D seeks to fund studies on diagnostic-treatment combinations

VA’s Clinical Science Research and Development Service is seeking Merit Review applications focused on assessing combinations of diagnostic tests with clinical treatments. Successful proposals are expected to result in novel clinical trial designs. Full details can be found in the Solicitations section of the ORD website at http://www.research.va.gov/funding/solicitations.

Career milestones

Susan L. Garber, MA, OTR, Houston, was elected to the Academy of Research of the American Occupational Therapy Foundation in recognition of her contributions to research in spinal cord injury and pressure ulcer prevention, treatment and education.

Robert W. McCarley, MD, received the American Academy of Sleep Medicine’s William Dement Award for 2006 for his basic research on how the brain controls behavior, especially that of sleep and wakefulness. McCarley is chair of Harvard Medical School’s department of psychiatry and associate director of mental health at the VA Boston Healthcare System.

Bernard Ng, MD, Houston, was cited for outstanding research published by a developing researcher in the Journal of Allergy and Clinical Immunology by the journal’s editors and the American Academy of Allergy, Asthma and Immunology. Ng’s article, titled “Increased Noncanonical Splicing of Autoantigen Transcripts Provides the Structural Basis for Expression of Untolerized Epitopes,” appeared in 2004 and has added to the understanding of the pathogenesis and management of allergic and immunologic disease.

David Casarett, MD, MA, an HSR&D Career Development Awardee, received the 2006 Outstanding Scientific Achievement for Clinical Investigation Award from the American Geriatric Society at its annual scientific meeting last month. Casarett is a core investigator with HSR&D’s Center for Health Equity Research and Promotion (CHERP) at the Philadelphia VA Medical Center. His research focuses on health equity, research ethics, medical decision-making, informed consent, and end-of-life care.

VA statisticians’ group

The VA Statisticians’ Association, formed in 2005, invites VA-affiliated statisticians to join. Email your contact information to Laura Rabuck, of the Northwest Center for Outcomes Research in Older Adults, at Laura.Rabuck@va.gov. More details are available on the VA HSR&D website at www.hsrd.research.va.gov/for_researchers/vasa.