



VA Research Currents

Antibiotic fails to show long-term benefit in Gulf War illnesses trial

The antibiotic doxycycline did little better than placebo over 12 months in a study of nearly 500 veterans with Gulf War illnesses, report VA researchers and colleagues in the July 20 *Annals of Internal Medicine*.

The trial, conducted at 26 VA medical centers and two Department of Defense sites, was prompted by the theory that Gulf War veterans' illnesses (GWVIs) may be caused by mycoplasma, a type of bacteria that has been studied as a possible cause of chronic fatigue syndrome and fibromyalgia. The effort, funded with \$7.8 million from VA and \$5.2 million in drugs and placebos from Pfizer, was the largest clinical trial yet to test whether antibiotics could ease Gulf War veterans' health problems.

The symptoms of GWVIs resemble those of chronic fatigue syndrome:

fatigue, pain, respiratory problems, depression, poor concentration, memory loss. Studies have confirmed that service men and women deployed to the Persian Gulf in 1990 and 1991 are at higher risk for the condition, but researchers are still exploring possible causes. Most theories center on infections, exposure to environmental toxins, or stress reactions.

No treatment has emerged as highly effective, though a VA-DoD trial published last year in the *Journal of the American Medical Association* did find some benefits for exercise and cognitive behavioral therapy.

In the new trial, researchers enrolled 491 veterans who had symptoms of GWVIs and whose blood tested positive for mycoplasma DNA. Half the participants received doxycycline, the other half placebo. While the

antibiotic group showed greater improvements in physical health after three months, the differences evened out after six months. After a year, only about one in five veterans had improved significantly in their physical functioning, regardless of which group they were in. Those receiving the antibiotic, as expected, experienced higher rates of side effects such as stomach upset and sensitivity to light.

The researchers also saw no difference in pain, fatigue, cognitive function or mental health between the two groups.

The investigators say they don't know whether participants in the study had active mycoplasma infection. The presence of mycoplasma DNA in the blood merely indicates past exposure to the pathogen. Interestingly, almost all

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VA, UCLA scientists pinpoint role of brain chemicals in sleep

Neurobiologist Jerome M. Siegel, PhD, and colleagues at the VA Greater Los Angeles Healthcare System and UCLA showed for the first time how three brain chemicals—serotonin, norepinephrine and histamine—play distinct roles in regulating sleep. According to their study, published recently in *Neuron*, serotonin and norepinephrine affect muscle tone, keeping the body still at night, while histamine controls wakefulness.

The researchers discovered this by studying Doberman pinschers with narcolepsy, a sleep disorder. Narcolepsy is marked by a puzzling phenomenon called cataplexy, in which the body goes limp, as if asleep, while the brain stays fully alert. Using implanted electrodes to monitor the dogs'

brain activity, the researchers noted that during cataplexy, neurons with histamine remained active, while those containing serotonin and norepinephrine fell silent.

"Our findings greatly improve our understanding of the brain activity responsible for maintaining consciousness and muscle tone while awake," said Siegel. He added that the results may help guide the development of new drugs to induce sleep or maintain alertness.

In 2000, Siegel's team published its findings that narcoleptics had 95 percent fewer hypocretin (orexin) nerve cells in their brains than those without the illness. The study was the first to show a possible biological cause of narcolepsy. ■

Recent publications and presentations

The following is a sampling of recent publications and presentations by VA researchers. Due to space constraints, only VA-affiliated authors are listed. Send notifications of upcoming or recent publications and presentations to VA R&D Communications at researchinfo@vard.org.

“Aged Obese Rates Exhibit Robust Responses to Melanocortin Agonist and Antagonist Despite Leptin Resistance.” Yi Zhang, PhD; Nihal Tumer, MS, PhD; Philip J. Scarpace, PhD. **Gainesville**. 86th Endocrine Society Meeting, New Orleans, June 2004.

“Alcohol Dependence, Other Psychiatric Disorders, and Health-Related Quality of Life: A Replication Study in a Large Random Sample of Enrollees in the Veterans Health Administration.” David Kalman, PhD; Donald R. Miller, ScD; Avron Spiro III, PhD; Xinhua S. Ren, PhD; Lewis E. Kazis, ScD. **Bedford**. *American Journal of Drug and Alcohol Abuse*, May 2004.

“Cardiology Management Improves Secondary Prevention Measures Among Patients with Coronary Artery Disease.” P. Michael Ho, MD; Anne E.

Sales, PhD; Karl E. Hammermeister, MD; John S. Rumsfeld, MD, PhD. **Denver** and **Seattle**.

“Cervical Cancer Screening Among Women without a Cervix.” Brenda E. Sirovich, MD, MS; H. Gilbert Welch, MD, MPH. **White River Junction**. *Journal of the American Medical Association*, June 23, 2004.

“Control of Proteolysis: Hormones, Nutrients, and the Changing Role of the Proteasome.” Frederick G. Hamel, PhD; Janet Fawcett, PhD; Robert G. Bennett, PhD; William C. Duckworth, MD. **Omaha** and **Phoenix**. *Current Opinion in Clinical Nutrition and Metabolic Care*, May 2004.

“Cytoarchitecture and Cortical Connections of the Posterior Cingulate and Adjacent Somatosensory Fields in the Rhesus Monkey.” Patsy B. Cipolloni, MD. **Bedford**. *Journal of Comparative Neurology*, Jan. 26, 2004.

“Ethnic Differences in Satisfaction and Quality of Life in Veterans with Ischemic Heart Disease.” Andrea Ohldin, MD, MS, MSHA; Bessie Young, MD, MPH; Ann Derleth, MSPH; Mary McDonell, MS; Paula Diehr, PhD; Catarina Kiefe, PhD, MD; Stephan Fihn, MD, MPH. **Birmingham** and **Seattle**. *Journal of the National Medical Association*, June 2004.

“Pituitary-Thyroid State Correlates with Central Dopaminergic and Serotonergic Activity in Health Humans.” Bernadette B. D’Souza, MD; T.D. Geraciotti Jr., MD. **Cincinnati**. *Neuropsychobiology* 2004.

“Primary Care Practice and Facility Quality Orientation: Influence on Breast and Cervical Cancer Screening Rates.” Caroline Lubick Goldzweig, MD, MSHS; Donna L. Washington, MD, MPH; Andrew B. Lanto, MA;

Elizabeth M. Yano, PhD. **Los Angeles**. *American Journal of Managed Care*, April 2004.

“Prospective Analysis of Incidence and Risk Factors of Dysphagia in Spine Surgery Patients: Comparison of Anterior Cervical, Posterior Cervical and Lumbar Procedures.” Carol A. Smith-Hammond, PhD; Kent C. New, MD, PhD; David J. Curtis, MD; Candice H. Scharver, MA; Dennis A. Turner, MD, MA. **Durham**. *Spine*, July 1, 2004.

“Racial Disparity in Knee Arthroplasty Utilization.” Said Ibrahim, MD, MPH. **Philadelphia**. Third International Congress of the International Society for Equity in Health, Durban, S. Africa, June 2004.

“Stimulation of Beta-Amyloid Precursor Protein Alpha-Processing by Phorbol Ester Involves Calcium and Calpain Activation.” Hugo L. Fernandez, PhD; Ming Chen, PhD. **Bay Pines**. *Biochemical and Biophysical Research Communications*, April 2, 2004.

“Ten-Year Patterns of Alcohol Consumption and Drinking Problems Among Older Women and Men.” Rudolf H. Moos, PhD; Kathleen Schutte, PhD; Penny Brennan, PhD, Bernice S. Moos. **Palo Alto**. *Addiction*, July 2004.

“Thyroid Hormone Causes Mitogen-Activated Protein Kinase-Dependent Phosphorylation of the Nuclear Estrogen Receptor.” Hung-Yun Lin, PhD; Paul J. Davis, MD. **Albany**. *Endocrinology*, July 2004.

“Use of Psychiatric and Medical Health Care by Veterans with Severe Mental Illness.” Hayden B. Bosworth, PhD; Patrick S. Calhoun, PhD; Karen M. Stechuchak, MS; Marian I. Butterfield, MD, MPH. **Durham**. *Psychiatric Services*, June 2004. ■

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Depression linked to excess neurons in brain

VA researchers and colleagues have discovered a link between major depression and an increased number of nerve cells in the thalamus, part of the brain.

A team at the Central Texas Veterans Health Care System, University of Texas Southwestern Medical Center and Texas A&M University System Health Science Center compared postmortem brains from patients who had been diagnosed with major depression against brains from normal subjects and those with schizophrenia and bipolar disorder. The brains from patients with major depression had about 30-percent more nerve cells in regions of the thalamus involved with emotional regulation. In addition, these regions appeared larger in the patients with major depression. A history of antidepressant use during the patient's lifetime did not appear to affect the neuron levels.

The research, reported in the July *American Journal of Psychiatry*, may be the first to link a psychiatric disorder with an increased number of neurons in the brain. Earlier studies have associated psychiatric conditions such as schizophrenia and bipolar disorder with decreased, not increased, levels of neurons, said lead investigator Keith A. Young, PhD.

Young added: "This represents a change in the way we think about major depression, which has been considered by most scientists and physicians to be related to neurochemical imbalances, rather than being caused by abnormal brain development and structure." ■

Diabetes drug may help stall Alzheimer's

Researchers at the VA Puget Sound Health Care System found that the drug rosiglitazone, used to improve insulin sensitivity, may help slow the progression of Alzheimer's disease.

G. Stennis Watson, PhD, and Suzanne Craft, PhD, presented data from a 24-week pilot study at the 9th International Conference on Alzheimer's Disease and Related Disorders, held earlier this month in Philadelphia. The study included 30 older adults with mild Alzheimer's disease or another form of mild cognitive impairment. Twenty participants received rosiglitazone and 10 received placebo. Those who took rosiglitazone did not decline in their performance on

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Demakis, driving force behind 'QUERI,' retires as HSR&D director

John G. Demakis, MD, retired as director of VA's Health Services Research and Development Service (HSR&D) on July 2. Demakis served 32 years with VA. During his six-year tenure as HSR&D director, that service's research budget more than doubled and its career development awards nearly doubled.

Demakis added several new HSR&D centers of excellence, including three newly funded centers: one for management research, and two that will focus on implementation research. He also added resource centers to support VA researchers in specialized areas such as informatics, measurement, information dissemination, and economics research.

Demakis was instrumental in the growth of VA's Quality Enhancement Research Initiative (QUERI), which

today is highly regarded as a national model for translation and implementation research. QUERI uses a six-step process that emphasizes documenting best practices, developing strategies for

implementation, evaluating results, and disseminating findings and recommendations.

Shirley Meehan, PhD, has been named acting director of HSR&D.

Special journal issue on VA informatics

A special issue of the *Journal of the American Medical Informatics Association (JAMIA)*, electronically published in June with print publication in September, features six articles on VA's Quality Enhancement Research Initiative (QUERI). The QUERI program, now in its sixth year, is a large-scale, multidisciplinary quality improvement initiative designed to translate and implement evidence-based research into practice. QUERI targets nine diseases or conditions that are prevalent among veterans, and its investigators rely on VA's vast data resources to carry out their research.

This special issue of JAMIA highlights the role of information systems in the QUERI process. The issue includes overviews of QUERI and VA information systems, as well as articles that target specific data-related projects. To access these articles, visit the JAMIA web site at <http://www.jamia.org/preprints.shtml>.

Career milestones

Gohar Azhar, MD, received the 2004 Merck New Investigator Award from the American Geriatrics Society for her studies on the aging heart. Azhar is a fellow in the Advanced Geriatric Special Fellowship Program at the Geriatric Research, Education and Clinical Center at the Central Arkansas Veterans Healthcare System.

Cayla R. Teal, PhD, a post-doctoral fellow with VA's Houston Center for Quality of Care and Utilization Studies, was named a Kellogg Scholar in Health Disparities by the Center for the Advancement of Health and the W.K. Kellogg Foundation. The award comes with \$52,000 per year for up to two years.

Rory Cooper, PhD, director of VA's Center of Excellence for Wheelchair and Related Technologies, received the American Paraplegia Society's 2004 Excellence Award for demonstrating leadership and expertise in the field of spinal cord injury health care, research and education.

R. John Leigh, MD, a neurologist with the Louis Stokes Cleveland VAMC, was elected to the Johns Hopkins Society of Scholars, recognizing sustained scholarly activity. Leigh's textbook on the neurology of eye movements is highly regarded, and he has published more than 200 peer-reviewed manuscripts. His research focuses on eye-movement disorders in patients with neurological diseases.

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memory and attention tests, whereas those who took the placebo declined at a rate typical for Alzheimer's.

The researchers said rosiglitazone may have beneficial effects on brain insulin levels, beta amyloid levels, and inflammation, all of which have been linked to Alzheimer's disease.

In prior studies, researchers have found that diabetes increases the risk of Alzheimer's by 65 percent. This finding has been supported by animal studies showing that a protein called insulin-degrading enzyme is involved with both diabetes and dementia. ■

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study participants had cleared the germ from their blood by the study's conclusion, regardless of whether they took the antibiotic or not. The researchers believe the level of infection may have influenced whether doxycycline was effective.

"Antibiotics are clearly effective for true mycoplasma infections," said study co-author Lisa L. Dever, MD, an infectious-diseases specialist at the East Orange, N.J., VA Medical Center. "For example, we know that in cases of mycoplasma pneumonia, doxycycline shortens the duration of people's illness."

Mycoplasma are tiny bacteria that live in the mouth, urinary tract and other areas of the body. They reproduce on their own, without a host cell.

The pathogens do not have a cell wall, like most bacteria, and their metabolism periodically slows down. These factors may enable mycoplasma to evade the knock-out punch of conventional antibiotics. ■

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