



VA Research Currents

Brain scans show how placebo eases pain

Two related studies at the Ann Arbor VA Medical Center and other sites have produced the strongest evidence yet that placebo—or the mere expectation of relief, with no real treatment—causes physical changes in how the brain responds to pain. The findings appeared in the Feb. 20 issue of *Science*.

In trials at VA, the University of Michigan and Princeton University, researchers used functional magnetic resonance imaging (fMRI) to map changes in blood flow in the brains of volunteers. The volunteers were subjected to harmless but occasionally painful electric shocks or heat. When they believed an anti-pain cream had been applied to their arm, they rated the pain as less intense—and the pain circuits in their brain showed less activity.

Doctors have long recognized the power of placebo to make patients feel better. But scientists are unsure why it works, and whether nerve pathways are actually affected. The new studies provided the first scans documenting the changes induced by placebo in the brain’s pain pathways.

“We’ve shown what the old family doctor knew very well—that his interaction with the patient made a great difference in the effectiveness of whatever treatment he was giving,” said team member Kenneth L. Casey, MD, who has studied pain for three decades. Casey is a neurology consultant for VA and a professor at the University of Michigan. Lead author was Tor D. Wager, MD, a graduate student at the University of Michigan when the research was conducted.

Researchers have performed brain experiments with fMRI since the early 1990s. It uses the technology of MRI—radio waves and a strong magnetic field—to show regions of the brain where blood vessels are widening and extra oxygen is

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Growth of HSR meeting seen as tribute to Demakis

Speaking at the recent national meeting of VA’s Health Services Research and Development (HSR&D) service, John Demakis, MD, recalled his first HSR&D meeting 22 years ago. There were 30 attendees.

At this year’s meeting, March 9 – 11 in Washington, DC, some 563 registrants packed a ballroom at the Marriott Wardman Park Hotel and together took in more than 150 papers, posters, workshops and panel discussions.

“This meeting is very much a tribute to all [that John Demakis] has accomplished over the years,” said Dan Berlowitz, MD, MPH, associate director of VA’s Center for Health Quality, Outcomes and Economic Research, which hosted the meeting.

Demakis, who has served with VA 32 years and directed HSR&D since

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Gauging provider attitudes toward VA’s Clinical Practice Guidelines

VA needs to more effectively market its Clinical Practice Guidelines (CPGs) to its physicians, nurses and other clinicians, according to a survey reported in the February issue of *Federal Practitioner*. The survey of providers, conducted in 1999, found that only about 60 to 70 percent of the 1,415 respondents were aware of the guidelines. Only half had read the CPG on diabetes, for example. And only half of physicians felt the guidelines were applicable to their patients.

The survey was conducted by the Implementation and Education Subcommittee of VA’s National Clinical Practice

Guideline Council. The report was authored by Michael Davies, MD, chief of staff at the VA Black Hills Health Care System; Jacqueline Pugh, MD, director of VA’s San Antonio-based Veterans Evidence-Based Research, Dissemination and Implementation Center; and William Spears, PhD, a management and policy expert at the University of Texas Health Science Center.

On the positive side, about 8 of 10 providers who read the CPGs, especially non-physicians, found them helpful.

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Study confirms testosterone–depression link

A two-year study of 278 older men at a VA hospital showed that men with low testosterone are four times more likely to be depressed. The study, in the February *Archives of General Psychiatry*, is one of the most definitive studies to date on a topic that for decades has produced mixed research findings.

Researchers at the VA Puget Sound Health Care System and the University of Washington studied the medical records of men who had their testosterone levels checked at least once before and once during the period from January 1998 through December 1999. The tests were ordered for sexual problems or a variety of other medical reasons. None of the men, ranging in age from 52 to 72, had a history of depression.

The researchers found that men with consistently low levels of total testosterone—200 nanograms per deciliter (ng/dL) or less—were four times more likely to receive a diagnosis of depression during the two-year follow-up. The average testosterone level in the normal-testosterone group was 520 ng/dL.

“If future studies confirm this finding, it could have important implications for treating depression in older men,” said study leader Molly M.

Shores, MD. She said the findings could have other important implications as well because depression is linked with increased mortality, decreased quality of life and increased complications from medical illness.

About 22 percent of the low-testosterone men in Shores’ study received a diagnosis of depression in 1998 or 1999, versus only 7 percent in the normal-testosterone group. After the researchers adjusted for factors other than testosterone that may have accounted for mood differences between the groups, the low-hormone group showed a fourfold depression risk. ■

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being delivered. These are signs of activity in the brain. By taking fMRI images as patients perform different tasks, researchers learn which areas of the brain control which functions.

The Michigan and Princeton pain studies, each involving about two dozen volunteers, show the prefrontal cortex as the area of the brain active in the placebo response. Scientists have developed intriguing models of how this area of the brain guides thought and action based on internal goals and expectations. In support of those theories, the new research by Casey and Wager’s group provides the first images of how the prefrontal cortex is activated by the expectation of pain relief, and how this in turn triggers a reduction of activity in pain-sensing areas of the brain: the thalamus, somatosensory cortex, and other parts of the cerebral cortex.

According to Casey, this clearer knowledge of the brain’s pain pathways may lead to new therapies for those with chronic or acute pain. “One could

O’Leary to lead Lab Service

Timothy O’Leary, MD, PhD, has been named director of VA’s Biomedical Laboratory Research and Development Service (BLR&D). O’Leary, who holds a doctorate in physical chemistry from Stanford University and a medical degree from the University of Michigan, had chaired the department of cellular pathology at the Armed Forces Institute of Pathology since 1987.

BLR&D is a new service created through a reorganization of the former Medical Research Service. O’Leary will oversee all VA research that explores basic biological or physiological principles in humans or animals but does not involve intact human beings. The service includes research on animal models and investigations of tissues, blood or other biologic specimens from humans.

O’Leary’s own research interests include molecular changes in gastric tumors, ultrasensitive detection of biological toxins, and mechanisms of formaldehyde fixation. He is credited with expanding the capacity of the

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imagine compounds that would activate these control systems specifically,” he said.

Casey also said the research sheds new light on the tangible benefits of the placebo effect in medicine. “If you’re providing a treatment to a patient, it’s important that you realistically provide them with the expectation that it would work, so you enhance the effect. If you gave them a drug or any kind of treatment with the attitude, either explicit or implicit, that this might not be effective, it would be much less likely to be effective.” ■

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1998, is retiring this spring. He accepted the VA Exemplary Service Award from Under Secretary for Health Robert H. Roswell, MD and was “roasted” by colleagues at a dinner on March 9.

Citing examples of HSR impact

In his “state of the service” talk, Demakis shared statistics to show the growth of HSR&D from 1998 to today—for example, an increase in annual funding from \$33 to \$60 million, and an increase in proposal submissions from 30 to 100 per review cycle. He cited the addition of four centers of excellence during the six-year period, bringing the total to 13, and said HSR is preparing to fund another one or two in the near future.

Demakis also referred to the establishment of Research Enhancement Award Programs (REAPs) for HSR&D, and, more recently, Targeted

Research Enhancement Programs (TREPs). He cited a twofold increase in career development awardees since 1998, bringing the current total to 67. “To me, this is the future of our science,” said Demakis.

Demakis also spoke of improvements in VA clinical care that he said are a direct result of health services research. He cited VA’s National Surgical Quality Improvement Program, started in 1991, as a successful effort that has lowered surgical mortality from 3 to 2 percent and the rate of surgical complications from 17 to 9 percent. And he credited the Quality Enhancement Research Initiative (QUERI) for Spinal Cord Injury (SCI) with helping to double the rate of influenza vaccination rates among SCI patients in VA.

‘Translating intellectual curiosity into better health care’

In her remarks, Mindy Aisen, MD, deputy chief research and development

officer (CRADO), referred to health services research as “the glue that holds research together.”

Jonathan Perlin, MD, PhD, acting CRADO, said VA is a major driving force in American health care and “the world’s largest and most coherent platform for health services research and clinical research.” He said health services researchers, taking advantage of VA’s extensive electronic health-records system, have a critical role to play in driving VA from interventional, to preventive, to evidence-based “prospective medicine.”

Prospective medicine is the term used by Duke University’s Ralph Snyderman, MD, chair of the Association of American Medical Colleges, in advocating health care that is proactive, predictive and customized for the individual.

In his welcoming remarks, Under Secretary Roswell said HSR&D is integral to VA as an academic health care system.

“What makes our health care system special is not that we provide a service, but that we have the opportunity to do so in an intellectual environment,” said Roswell. “It’s VA research that allows us to express our intellectual curiosity. And it’s health services research that allows our intellectual curiosity to be translated into better health care, and allows each and every one of us to better serve our nation’s veterans.”

Also among the conference highlights was a keynote talk by Lisa Iezzoni, MD, MSc, of Harvard Medical School and Beth Israel Deaconess Medical Center. Iezzoni spoke on quality of care for patients with disabilities. She focused on variations in the definition of “disability” and what this means for health services researchers. ■

Under Secretary’s Award to Ashton of Houston

Carol M. Ashton, MD, MPH, director of VA’s Houston Center for Quality of Care and Utilization Studies and chief of health services research at Baylor College of Medicine, received the 2004 Under Secretary’s Award for Outstanding Achievement in Health Services Research. Ashton is noted for her pioneering use of administrative databases to study quality of care. She has played a key role in numerous studies benchmarking VA care against the private sector, and examining racial and ethnic disparities in care.

Two recent examples of her work:

- Ashton led a major study published in the *Oct. 2003 New England Journal of Medicine* that showed that survival rates among veterans with serious chronic illnesses remained steady in the mid-1990s despite VA’s shift at that time from hospital-based system to one emphasizing more efficient outpatient and primary care. The study also showed that these veterans did not increase their use of non-VA hospital care to compensate for the cutbacks in VA hospital care.

- Ashton was senior author on a study published in *Medical Care* in Sept. 2002 that documented that the process of inpatient care in VA is generally similar for patients regardless of race.

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The survey focused on the CPGs for chronic lung disease, ischemic heart disease, depression and diabetes, all of which had been in use at least 18 months at the time of the survey.

VA began mandating the use of CPGs in 1996 to standardize care in line with best practices. External reviews of the CPGs have validated their effectiveness in improving care for several diseases, and in cardiac care VA now outperforms private hospitals in providing patients with beta blockers and other drugs shown in trials to be beneficial.

However physicians' acceptance of CPGs, while possibly on an upward trend, is still not very widespread: The survey found that only 57 percent of physicians felt the CPGs were "valid." Lack of time was cited as the biggest barrier to using CPGs in daily practice. Many providers felt the CPGs—bulky documents of 50 to 100 pages—were inconvenient or awkward to access during a patient visit. A small number of respondents expressed opposition to "cookbook medicine."

In response, the study authors suggest that VA consider "direct marketing" of the CPGs—"putting the CPGs in the hands of those who will use them." VA, says the report, "needs to attend to some basic principles of marketing and learning in the context of the CPGs."

Based on the responses, the authors recommend making the CPGs available in a variety of formats, such as pocket cards or brief summaries. Electronic versions were highly favored by respondents.

Significantly, the survey shows that an increasing number of providers desire feedback on their compliance with CPGs. According to the authors, this demonstrates "an important shift in culture from such feedback being perceived as punitive to it being perceived as useful for improving patient care. The challenge for our system is to create procedures that generate such feedback easily, inexpensively and accurately." ■

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Armed Forces Pathology Institute to include molecular genetics and tissue magnetic resonance microscopy.

O'Leary is certified in anatomic pathology by the American Board of Pathology and in molecular genetic pathology by the American Board of Pathology and the American Board of Medical Genetics. He has authored or co-authored more than 130 scientific papers since 1973 and written numerous book chapters. He edited the 2002 text *Advanced Diagnostic Methods in Pathology: Principles, Practice and Protocols*.

In addition, O'Leary is a reserve member of the Public Health Service Commissioned Corps, which recalled him to active duty for four months in 2003.

"We're very pleased to have Dr. O'Leary with us," said Jonathan Perlin, MD, PhD, acting chief research and development officer. "He's an accomplished scientist, and his experience and achievements will serve us well as we chart the course of the new Biomedical Laboratory Research and Development Service." ■

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