



# VA Research Currents

Update from the Office of Research and Development...

## Financial conflicts of interest: Take the high road

By Joel Kupersmith, MD, chief R&D officer

**N**umerous articles, reports, commentaries, government rules, and ethics conferences have addressed how and why scientific researchers need to avoid financial conflicts of interest. Recent problems at the National Institutes of Health (NIH) prompted the issuance of strict rules that were later rescinded and revised, with the issuance of changes effective Aug. 31, 2005. The issue is important and not without controversy.

The June 9, 2005, issue of *Nature* featured a 2002 survey, funded by the federal Office of Research Integrity and NIH and conducted by a team at the University of Minnesota and HealthPartners Research Foundation, that found that a third of American biomedical scientists—all NIH-funded—had engaged in one or more questionable research practices in the previous three years.

Lead author Brian C. Martinson and colleagues wrote: “Our findings reveal a range of questionable practices that are striking in their breadth and prevalence. ... With as many as 33 percent of our survey respondents admitting to one or more of the top-ten behaviors, the scientific community can no longer remain complacent about such misbehavior.”

As VA investigators, we can and must serve as a model for the nation. We need to proactively avoid problems that other government agencies and the

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## VA-Yale team finds molecular basis for ‘phantom pain’

Many amputees and patients with spinal cord injury experience the sensation of excruciating pain in a limb that is no longer there, or that has lost all perception. Now, a team at Yale School of Medicine and VA’s Center of Excellence on Restoration of Function in Spinal Cord Injury and Multiple Sclerosis has identified a molecular basis for this so-called “phantom pain.”

Reporting in the October issue of *Brain*, the researchers say the problem is due to hypersensitive neurons in the brain’s thalamic region.

Experiments in a rat model of spinal cord injury showed that these neurons contain abnormally high levels of a particular type of sodium channel, Nav1.3. Sodium channels are specialized proteins in the membrane of brain cells that regulate the flow of sodium ions into the cell. They serve as a “battery” to allow electrical impulses to travel between neurons.

When the researchers designed molecules to suppress Nav1.3 and injected them into the spinal fluid of the

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## Large study links statins, bone health

A team that compared the medical charts of more than 91,000 VA patients found that those on statins were 36 percent less likely to break a bone than those not on the cholesterol-lowering drugs. The study, one of the largest to-date to evaluate whether statins help prevent fractures, appeared in the Sept. 26 *Archives of Internal Medicine*.

While the researchers say their study doesn’t show cause and effect, the findings will likely fuel the debate over whether the much-touted drugs—taken by more than 12 million Americans—really do strengthen bones.

“This finding is particularly important because millions of people suffer from fractures that potentially could be prevented, to some extent, by a therapy that’s so commonly used,” said lead author Richard E. Scranton, MD, of VA’s Boston-based Massachusetts Veterans Epidemiology Research Information Center (MAVERIC), Brigham and Women’s Hospital, and Harvard Medical School.

Statins, which include popular brand-name drugs such as Lipitor and Zocor, are designed to lower cholesterol by blocking an enzyme that enables natural production of cholesterol in the liver. When the liver is low in cholesterol, it takes in

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## Career milestones

**Thomas Rando, MD, PhD**, chief of neurology and director of the Geriatric Research, Education and Clinical Center at the Palo Alto VA, is among 13 recipients nationwide of the 2005 NIH Director's Pioneer Award. The award, which includes \$500,000 in direct costs per year for five years, is designed to support "creative scientists who take innovative approaches to major challenges in biomedical research." Rando's research draws on the fields of stem cell biology, aging biology and bioengineering to understand the molecular basis for the age-related decline in the body's ability to repair its tissues.

**Jennifer Moye, PhD**, a psychologist and director of the Geriatric Mental Health Clinic at the VA Boston Healthcare System, received one of 55 Scholars in Medicine fellowships awarded this year by Harvard Medical School, where she is an assistant professor of psychiatry. The fellowships were established in 1995 to celebrate a half-century of the admission of women to Harvard Medical School, and to mark their contributions to the school. Moye's research centers on helping doctors evaluate patients' competence to make their own healthcare decisions.

**Anjan Kowluru, PhD**, a research career scientist at the Detroit VA, won an Outstanding Research Recognition Award from Wayne State University, where he is a professor of pharmaceutical sciences. Kowluru, a diabetes researcher, studies signal transduction mechanisms affecting insulin secretion in pancreatic beta cells.

**Tai-June Yoo, MD, PhD**, chief of the allergy-clinical immunology section at the Memphis VA, was named the 2005 Il-Chun Award laureate by the Korean Society of Molecular and Cellular Biology. Yoo received the award, named for a pioneering Korean scientist, at the society's annual meeting this month in Seoul. A naturalized U.S. citizen, Yoo was decorated for his service with the U.S. Army Medical Corps in Vietnam, and retired from the military as a full colonel. His lab at the Memphis VA focuses on various topics in immunology, allergies and otolaryngology.

**Avinash G. Patwardhan, PhD**, director of the Musculoskeletal Biomechanics Laboratory at the Hines VA, led an international team of researchers that won the 2005 "Best Paper" award from the North American Spine Society. The winning paper described the group's use of state-of-the-art technology developed at the Hines lab to document the motion patterns of artificial discs implanted in the lumbar spine of human cadavers.

**Kelli D. Allen, PhD**, of HSR&D's Center for Excellence in Primary Care at the Durham VA Medical Center, received the 2004 "Best Paper of the Year" award from *The Journal of Pain and Palliative Care Pharmacotherapy*. VA coauthors of the paper, titled "Patterns of Opioid Analgesic Prescription among Patients with Osteoarthritis," were Hayden Bosworth, PhD, and Tara Dudley, M.Stat. ■

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more of the waxy, artery-clogging substance from the bloodstream, thus lowering heart risk. But several studies in recent years have suggested further health benefits for the drugs, possibly due to their antioxidant and anti-inflammatory properties. The exact mechanism by which statins may help bones is unclear, but several theories exist. Some researchers believe, for example, that the drugs promote the growth of new bone by improving the function of small blood vessels.

Scranton's team analyzed the records of 91,052 patients—mostly men—who received care at the New England Veterans Healthcare System between January 1998 and June 2001. More than 28,000 of the patients had prescriptions for statins, while more than 2,000 others were on non-statin cholesterol-lowering drugs. After the researchers adjusted for differences in patients' age, sex, race, weight and general health, they found that the statin group had a 36-percent lower risk of bone fractures when compared with those on no lipid-lowering therapy. The statin group had a slightly smaller, but still significant, edge—32 percent—over those on cholesterol-lowering drugs other than statins.

According to Scranton, the comparison between the two groups on cholesterol-lowering drugs—statins versus non-statins—is key. Some proponents of statins assert that randomized trials have failed to show a bone benefit for the drugs because the studies compared two groups of patients with similarly high cholesterol levels. Higher cholesterol by itself—or as a marker for higher body weight—may be bone-protective, regardless of statin use. By showing that statin-users have fewer fractures even compared to non-statin users with similar choles-

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## Analysis suggests implantable defibrillators are worth the cost for some patients

**R**esearchers with VA, Stanford University and Duke University reported in the Oct. 6 *New England Journal of Medicine* that the implantable cardioverter defibrillator (ICD)—one of the most expensive medical devices available—is a relatively cost-effective way to help prevent sudden cardiac deaths for some high-risk patients.

Senior author Douglas K. Owens, MD, MS, a physician and health-services investigator at the VA Palo Alto Health Care System, and colleagues examined eight studies on the effectiveness of ICDs in various populations with cardiac disease. Six of the studies had found a survival advantage for patients who had received an ICD, compared to similar patients who had received only standard medical therapy.

According to the new analysis, the incremental cost of the ICD in those

six populations ranged from \$34,000 to \$70,200 per quality-adjusted life year (QALY), a statistical measure that takes into account quality of life as well as length of survival. By comparison, figures for other common therapies include: \$10,000 per QALY for beta blockers after heart attack; \$24,000 for stent therapy after heart attack; \$36,000 for automated external defibrillators; and \$50,000 to \$100,000 for kidney dialysis in end-stage renal disease. Treatments that cost \$50,000 or less per QALY are generally considered cost-effective.

ICDs are implanted in patients whose lower heart chambers beat too fast or quiver ineffectively and who are at risk of cardiac arrest. The device monitors the heart and sends an electrical shock if it detects dangerous rhythms, helping avoid sudden cardiac death. In the United States, some 416,000 defibrillators were implanted between 1990 and 2002.

Private and government healthcare payers have increasingly wanted to ensure that the devices are worth the hefty price tag. Medicare, which reimburses about \$28,000 for the device and the implantation procedure, estimates that as many as 500,000 patients could be eligible for an ICD.

Summarizing the findings, Owens said that for certain high-cardiac-risk populations in which a significant reduction in mortality has been demonstrated, ICDs are no more costly than other interventions often accepted as cost-effective. “In the appropriate patients, these devices provide value, despite their expense,” he said.

The study was funded by VA, the Agency for Healthcare Research and Quality, and the Blue Cross Blue Shield Technology Evaluation Center. Owens’ coauthors were Gillian Sanders, PhD, of Duke; and Mark Hlatky, MD, of Stanford. ■

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terol and weight profiles, the new study suggests statins themselves may be the crucial factor.

“We believe that additional studies should be performed to fully describe the potential role of statins in protecting bones,” said Scranton. “The need is too great to ignore this finding, particularly when we consider that one class of drugs could potentially reduce the suffering of two common conditions plaguing our society—heart attacks and bone fractures.”

Even if further study does confirm that statins directly benefit bones, physicians are unlikely to prescribe the drugs mainly for that purpose. The drugs may cause side effects, ranging from mild stomach upset to serious liver damage or muscle pain, so strategies such as mineral supplementation or weight-bearing exercise would likely be a better approach for most patients.

The study was funded by VA’s Cooperative Studies Program, the National Institutes of Health, and the Arthritis Foundation. Collaborating with Scranton were Melissa Young, MPH, and Elizabeth Lawler, MPH, of MAVERIC; Daniel Solomon, MD, MPH, of Brigham and Women’s Hospital and Harvard; David Gagnon, MD, PhD, of MAVERIC and the Boston University School of Public Health; and senior author Michael Gaziano, MD, of MAVERIC, Brigham and Women’s, and Harvard. ■

### PAIN (cont. from pg. 1)

injured rats, pain signals were reduced. “This study is the first to show that thalamic neurons contain abnormally high levels of Nav1.3 after injury to the spinal cord, and that suppressing the activity of Nav1.3 in these neurons can mitigate pain,” said senior author Stephen Waxman, MD. Waxman said the study must be validated in higher-order animals, and then in humans, but the findings represent an “important step forward.”

Waxman’s collaborators were Bryan C. Hains, PhD, and Carl Y. Saab, PhD, of Yale. The work was supported by VA, the United Spinal Association, the Paralyzed Veterans of America, and Pfizer.

**CONFLICTS** (cont. from pg. 1)

research community in general seem to have with increasing frequency. We must be absolutely determined to maintain the public's trust and safeguard the integrity and quality of the research we conduct on behalf of veterans and all Americans.

Revisions to VHA Handbook 1200.13, "Financial Conflicts of Interest," are currently under review. Writing rules and policy that are fair and effective is definitely a task easier said than done, and this process has taken longer than expected, but we are making progress. Until a new handbook is issued, I want to emphasize that other resources exist within VA that can provide valuable assistance.

For example, I recently issued a memo titled "Financial Conflicts of Interest in Research" ([www.va.gov/resdev/resources/policies/docs/COI-Memo-092305.pdf](http://www.va.gov/resdev/resources/policies/docs/COI-Memo-092305.pdf)) as a reminder for all VA researchers about their obligations under existing federal laws and regulations related to financial conflict of interest. These are the rules that we have operated under for some time,

and they provide useful general guidance on the subject.

Another helpful resource is VA's Office of General Counsel. I strongly encourage you to visit their website (<http://vawww.gc.va.gov/ethics>) and review the many relevant documents found there. For example, a booklet titled "Take the High Road" summarizes eight key standards of conduct that must be followed, including avoiding financial conflicts of interest.

To speak with a General Counsel staff member about a specific issue you're involved with, such as an offer to consult for an outside firm or an opportunity to receive royalty payments, call your Regional Counsel or the VACO OGC attorneys, who can answer questions about conflict of interest, at (202) 273-6334/6335.

It is much better to ask a question, so that you can avoid problems or perhaps restructure something to meet all ethical requirements, rather than face questions later. The old adage about "an ounce of prevention" is certainly true in this area. ■

**About that upcoming article...**

To notify R&D Communications of your upcoming scientific publications or presentations, in accordance with VHA Handbook 1200.19 (online at [www.va.gov/vhapublications](http://www.va.gov/vhapublications)), send email to "VHA Co 12 Publication/Presentation Notifications," as found in the Global Address List in VA's Outlook system. From outside the VA system, the address is "research.publications@va.gov." Include the article or abstract title, along with an electronic copy of the abstract, manuscript or poster; VA investigators' full names and degrees; and the journal or meeting title and date. Include a note if you feel the research is particularly newsworthy, controversial or sensitive.

**Special note for HSR&D**

**investigators:** In addition to the above procedure, HSR&D investigators should follow the HSR&D publication notification process described in VHA Handbook 1204.5a and on the HSR&D website at [www.hsr.d.research.va.gov/for\\_researchers/pub\\_notice.cfm](http://www.hsr.d.research.va.gov/for_researchers/pub_notice.cfm). Questions may be sent to [VHACOHSRD@va.gov](mailto:VHACOHSRD@va.gov). ■

Mark your calendar...

- ORD field conference call: Oct. 31, 1:30 pm EST (Dial 1-800-767-1750, access code 17323)
- VA Research Week: May 7 - 13, 2006

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