

VA-NIH trial backs brain stimulation for some Parkinson's patients

George Schmid, a 62-year-old Army veteran living in southern New Jersey, decided two years ago with his VA doctor that it was time to try a new treatment for his Parkinson's disease. His left side would often stiffen up, and the drugs he took to tame the symptoms were wearing off faster and faster. Bumping up the dose further would likely result in unwanted side effects, such as flailing of the arms or legs.

Schmid had surgery at the Parkinson's Disease Research, Education and Clinical Center at the Philadelphia VA. Doctors used brain imaging to pinpoint the areas on either side of the brain where they would drill small holes and implant two electrodes. Then they ran thin wires under

the skin to a pacemaker-like device, about the size of a stopwatch, placed under the skin near the collarbone. Electrical stimulation from the battery-operated device would jam the brain signals causing the symptoms.

Today, Schmid says the treatment—called deep brain stimulation, or DBS—has worked well for him. His symptoms are under control, without higher doses of drugs.

Schmid was one of 255 patients who took part in a six-year clinical trial conducted by VA and the National Institutes of Health (NIH). The results appeared in the Jan. 7 *Journal of the American Medical Association*. The main

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Coping with Parkinson's—George Schmid, a patient at the Philadelphia VA, had two brain electrodes and a pacemaker-like device implanted in 2006 to treat his Parkinson's disease.

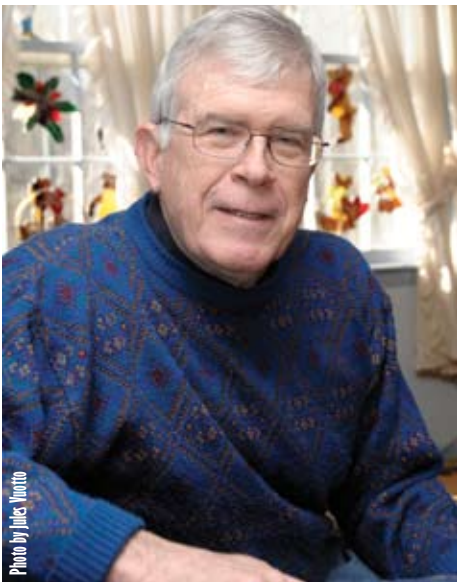
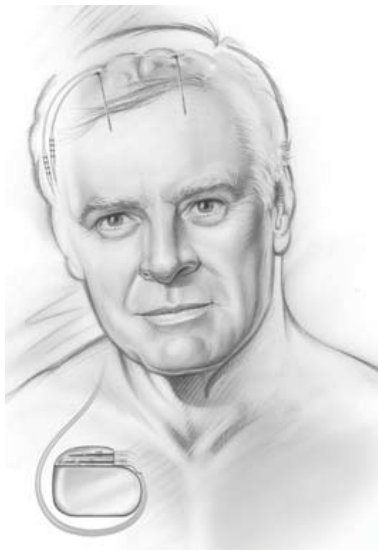


Photo by Jules Vintito



Courtesy of Medtronic

'Local Accountability for Research' meeting urges proactive approach

In what was probably the largest-ever meeting in the 60-year history of VA Research, more than 600 key staff representing all 116 VA facilities that conduct research convened in Baltimore on Jan. 13 and 14 for the 2009 ORD [Office of Research and Development] Local Accountability for Research meeting.

The goal of the meeting was to identify ways to improve local research programs, said Lynn Cates, MD, assistant chief research and development officer and director of VA's Program for Research Integrity Development and Education (PRIDE), which coordinated the event.

"The meeting focused on defining research-related responsibilities; distinguishing the respective research-related responsibilities of the VISN [Veterans Integrated Service Network] director, medical center director, chief of staff, associate chief of staff for research, administrative officer for research, and research compliance officer; and designing a plan for an ongoing local program to heighten awareness of research issues and responsibilities and to instill a culture of responsibility for research throughout the facility," said Cates.

Beyond those specific issues, the event gave attendees an opportunity to learn more about virtually every aspect of managing research, from understanding

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DBS (from page 1)

finding: DBS is riskier than drug therapy but may hold significant benefits for those with Parkinson's disease who no longer respond well to medication alone.

“DBS clearly offers hope for a large subset of patients with advanced Parkinson's disease who suffer from complications of longstanding medication therapy,” said lead author and study co-chair Frances Weaver, PhD, a researcher with the Center for Management of Complex Chronic Care at the Hines VA Hospital in Illinois.

Thousands of Americans have had DBS since it was introduced a few years ago, first for essential tremor and then for Parkinson's. Many patients report dramatic improvements. But questions remain about the procedure's benefits and risks, especially relative to drug therapy. And researchers are still exploring which target sites in the brain yield the best results.

The VA-NIH effort was only the second large-scale clinical trial in the world to compare DBS to “best medical therapy”—carefully managed medication plus speech, physical or occupational therapy as needed.

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The earlier trial, published by a German group in 2006, found DBS more effective than medical therapy for most, but not all, patients. The new VA-NIH trial was larger and included a wider age range—from 38 to 83.

The study took place at VA's national network of Parkinson's centers (www.parkinsons.va.gov) and six university hospitals. All the patients were no longer being helped adequately by drugs. They were randomly divided into two groups: 134 patients continued on medical therapy alone while the remaining 121 patients also received DBS. Most DBS patients had their medication reduced—or even stopped altogether—as symptoms improved.

Findings include more 'on time' for DBS patients

After six months, the study showed:

- Patients who received DBS gained an average of 4.6 hours per day of “on time,” compared with no gain for those on best medical therapy. “On time” refers to periods of good motor control and few or no involuntary movements of the face or limbs.
- 71 percent of DBS patients showed clinically significant gains in motor function, compared with only 32 percent of medical therapy patients.
- DBS patients showed significant improvements in several quality of life measures, compared with little change for the other patients, relative to baseline scores.
- Serious adverse side effects were nearly four times more common in the DBS group, but almost all the events in both groups were resolved by the six-month follow-up. The most common side effects from DBS were infections, falls, depression, gait and balance problems, and pain. Most of those who developed infections had their devices removed and later re-implanted and were thus able to continue DBS therapy.

About a quarter of those in the trial were over age 70.

Besides the higher likelihood of serious side effects with DBS, compared with drug therapy, the therapy has another drawback: It generally improves movement but does little to help other Parkinson's symptoms such as depression, declines in mental ability, gait and balance problems, and trouble with gastrointestinal, urinary or sexual function. Moreover, while not a major issue in this study, past research has linked DBS to the possibility of behavioral and psychiatric problems over time.

“The risks and outcomes of DBS should not be over- or under-stated,” said study coauthor and cochair Kenneth Follett, MD, PhD, a neurosurgeon at the Omaha VA and University of Nebraska. He said the best candidates for DBS are Parkinson's patients who have ongoing problems with movement despite medication or who suffer troubling side effects from the drugs, and who do not have significant cognitive problems or contraindications to surgery. He added that older age itself should not be a reason to rule out DBS. About a quarter of those in the VA-NIH trial were over age 70—a group usually excluded from DBS research or treatment.

The team is now studying which of two implantation sites may be more effective. Half the DBS patients in the VA-NIH trial had the electrodes implanted in the subthalamic nucleus, while the other half had the surgery in a part of the brain called the globus pallidus. The results from that analysis are expected later this year.

The trial was sponsored by VA's Cooperative Studies Program and the National Institute of Neurological Disorders and Stroke, part of NIH. Additional support came from Medtronic, which makes the DBS system used in the study. —

Easing spinal cord pain

By training, Eva Widerstrom-Noga, DDS, PhD, is a dentist—a discipline that deals with its share of pain. This background, together with a doctorate in pain physiology, led her to her role at the Miami VA: studying new ways to evaluate and treat pain in those with spinal cord injury.

VA cares for more than 25,000 veterans with spinal cord injuries (SCI) or disorders. Studies show that at least 7 in 10 of these patients have chronic pain. The pain can be constant and excruciating, says Widerstrom-Noga. She calls it “the most difficult pain problem of all.”

Widerstrom-Noga is also with the Miami Project to Cure Paralysis, a center of excellence at the University of Miami. Recently, she served as guest editor for an upcoming issue of VA’s *Journal of Rehabilitation Research and Development (JRRD)* that focuses on SCI pain. It will be available online this spring at www.rehab.research.va.gov.

VA Research Currents spoke with Widerstrom-Noga about SCI pain and her work in this area.

Q: What makes SCI pain so difficult to treat?

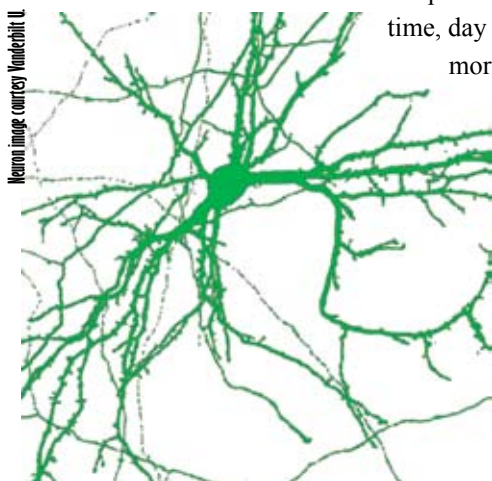
A: What many people don’t realize is that these patients are experiencing several types of pain at the same time. They have neuropathic (nerve) pain at or below the injury, and many, for example, have musculoskeletal pain in their shoulders from using a wheelchair all the time.

Q: How do SCI patients describe their pain?

A: People describe it in different ways, but one common word they use is “burning.” Some people say it feels like they’re sitting in a pot of boiling water all the time, day and night. That’s the more severe cases.

Q: How can patients feel pain where there is no nerve function and therefore no other sensation?

A: That’s a common question, and



Probing pain—Dr. Eva Widerstrom-Noga studies spinal cord pain at the Miami VA and the Miami Project to Cure Paralysis.

many patients themselves wonder about it. They may say, “How come I have pain when I can’t feel anything there?” Some say, “I’ve been told by my doctor that I can’t have pain because I’m spinal-cord injured.” I’ve had several patients who’ve come here and said that finally, someone is taking their pain seriously.

We tend to think about pain being generated in the periphery—which is true for those who don’t have nerve damage. But if you have damage to the spinal cord, the pain may be generated at different sites—in the spinal cord itself, for example, or in the part of the brain called the thalamus. We have a study where we’re looking at metabolic activity in the thalamus, which we know differs between SCI patients with and without pain. If we can detect conclusively what the differences are, we can target them for treatment.

Q: Are there any effective treatments for SCI pain?

A: Nothing is effective in all people, and treatments that seem to help other types of pain are generally not effective for SCI pain. Very few clinical trials have shown a conclusive positive effect for anything. It could be that the pains are so complicated—there are several types of pain going on at the same time, and they may interact in ways that change over time. The two most common medical treatments are anticonvulsants and antidepressants. [The antidepressants alter serotonin levels, which appears to modulate pain.] Opioids are sometimes used, but there tends to be a negative view of them, partly because one of the side effects can be

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Study sheds light on how brain recalls past events

—To pinpoint the role of different brain regions in memory, a team with VA and the University of California, San Diego, took brain images of study participants as they answered questions about news events that occurred over the past 30 years. The hippocampus—one of the first areas to show damage in Alzheimer’s disease—was most active when the volunteers recalled recent events, but gradually became less active as they recalled events that happened years ago. In the frontal, temporal and parietal cortices—regions located at the surface of the brain—activity increased as the events being recalled stretched deeper into the past. The findings offer key insights for scientists and may help guide the development of therapies or rehabilitation methods for people with brain injury or neurodegenerative disease. (*Journal of Neuroscience*, Jan. 28, 2009)



Identifying higher-risk periods for suicide

—A team with VA and the University of Michigan at Ann Arbor studied the records of nearly 888,000 veterans who were treated for depression between 1999 and 2004 to identify if there were periods of greater risk for suicide. The study found that patients were at very high risk for suicide for about a year after they were discharged from psychiatric inpatient

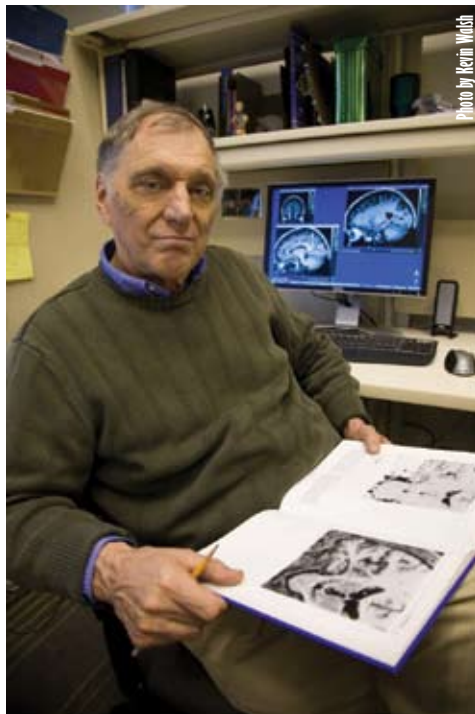


Photo by Kevin Walsh

New insights into memory

—Larry Squire, PhD, above, of VA and the University of California, San Diego, and colleague Christine Smith, PhD, used functional MRI to track brain activity related to memory. See item at left.

care and that patients were at higher risk for 12 weeks after starting antidepressants. Veterans aged 61 to 80 had the highest risk of any age group. VA has an aggressive suicide-prevention campaign, including a hotline at 800-273-TALK, but the researchers said the results may help focus the effort. (*Journal of Affective Disorders*, January 2009)

Alternative stress test

—Arm ergometers, like the one seen here being used by Navy veteran and VA employee James Black, could take the place of treadmills in cardiac stress tests for patients with lower-limb injuries or other disabilities, according to a study at the St. Louis VA. (*American Heart Journal*, January 2009)



Photo by Michael Moody

Effects on thinking skills similar between blast, non-blast brain injuries

—Researchers with the Tampa VA, the Defense and Veterans Brain Injury Center, and other VA and academic sites conducted neuropsychological tests with patients who had suffered brain injuries—some from blasts and some from other causes. The results from cognitive tests did not differ sharply between the two groups, although those who had experienced blasts were more likely to report symptoms of posttraumatic stress disorder. Researchers are increasingly exploring how the effects of blasts on the brain may differ from those of other types of injuries. (*Journal of the International Neuropsychological Society*, January 2009)



Genome study homes in on diabetes genes

—A team with VA and the University of Texas Health Sciences Center analyzed genetic information from 294 Mexican-American families with a high incidence of diabetes and determined that chromosome 12p is a likely site of genes associated with high triglycerides, which is part of the metabolic syndrome and linked to diabetes, obesity and heart disease. (*Diabetes*, January 2009)



Compounds seen as promising cancer-fighters

—A lab team led by Nobel laureate Dr. Andrew Schally at the Miami VA Medical Center found that a synthetic compound called JMR-132 acts as a strong antioxidant and stops the spread of human prostate cancer cells. The compound is one of several that Schally’s team has explored for their ability to stop tumors. They work as antagonists to a natural body chemical called growth hormone-releasing hormone (GHRH), which fuels tumors. (*Proceedings of the National Academy of Sciences*, online Dec. 15, 2008)

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the nuances of handbook policies and fiscal procedures to communicating about research to veterans and the public.

The event was the first time VA offered local accountability training through a national venue, rather than in smaller regional meetings. Though the overall gathering was large, much of the benefit for attendees came through small breakout sessions with peers from research programs facing similar challenges. Among the topics discussed in these groups was defining the exact roles of those involved in research.

“The reporting line is now much clearer to me—for example, how the new research compliance officer is going to interact with the ACOS [associate chief of staff] and the director, and what his or her responsibilities will be,” said Ram Sharma, PhD, MHSA, acting ACOS for research at the Kansas City (Mo.) VA Medical Center.

Another topic for the working groups was exploring ways to create and maintain the proper organizational culture regarding research. A note in the program suggested that this be “not just a ‘culture of compliance,’ but also pride in conducting quality research and awareness of ethical issues ... [that] should permeate the whole facility.”

Bradley Bender, MD, chief of staff at the Tampa VA, said that among his plans after the meeting was to help organize an event to make the community more aware of research at his and neighboring VA facilities. “Our VISN will have a Research Day, which we haven’t done before, to promote visibility.”

Networking with colleagues

“The working groups were the heart of the whole meeting,” said Cates. “They gave people an opportunity to meet with people with similar challenges throughout the country.”



Peer to peer—Working groups gave participants a chance to share ideas with peers from other VA research programs facing similar challenges.

Sharma, of Kansas City, said he picked up tips on how to be a more effective ACOS for research: “Most of the successful ACOSs I talked with suggested that you need to communicate regularly with your investigators through informal meetings. Problems occur only when you don’t communicate well.”

John Stagner, PhD, research compliance officer at the Louisville VA, agreed on the value of networking: “The main thing to take away from the meeting, if you stay busy, is you start interacting with your colleagues and you find out who’s more experienced, who to call up and ask when you have questions.”

Cates told attendees that another goal of the meeting was to “provide you and us [VA’s national Office of Research and Development] with a giant focus group, so we can leave with your ideas on how we need to move forward.”

Jacqueline Parthemore, MD, chief of staff at the San Diego VA, one of VA’s largest research sites, said this two-way

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The faces of local accountability—Among the more than 600 VA professionals attending the 2009 Local Accountability for Research meeting were (from left): Ram Sharma, PhD, MHSA, acting associate chief of staff for research, Kansas City (Mo.); John Stagner, PhD, research compliance officer, Louisville; Michael Merritt, research compliance officer, Las Vegas; Jacqueline Parthemore, MD, chief of staff, San Diego; and Bradley Bender, MD, chief of staff, Tampa.

VA study to expand on ‘Spouse Battlemind’

A team at the Memphis VA has been funded by the Department of Defense to adapt and expand a readjustment training program for soldiers and spouses to ease the transition home after deployments.

Linda Nichols, PhD, and colleagues will conduct a clinical trial titled “Reintegration: The Role of Spouse Telephone Battlemind,” based on the Spouse Battlemind program developed at Walter Reed Army Medical Center. The study will test a telephone-based, prevention-focused therapy that includes education, support, cognitive behavioral therapy and skills-building.



Photo by Brandon Steinkamp/US Navy

Coming home—Aviation Machinist’s Mate 2nd Class Donnie Stokes greets his wife and son at the naval station in Norfolk, Va., after returning in December 2007 from a six-month deployment in support of operations Iraqi Freedom and Enduring Freedom.

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constipation, and in SCI, bowel function is already decreased. But if someone finds benefit from a treatment, including opioids, without having significant adverse effects, I think that’s wonderful.

Q: Can psychotherapy help?

A: There are cases where cognitive behavioral therapy and similar therapies seem to be effective, but large-scale studies are lacking in this patient population.

Q: What about alternative treatments?

A: A few years ago, when we asked people which pain therapies they perceived as effective, they rated massage very highly. But as far as I know, there have not been rigorous clinical trials on this.

Q: Which research projects relating to SCI pain at the Miami VA do you find particularly promising?

A: Dr. Mary Eaton’s group is doing cell therapy research that’s very exciting. They’re using genetically engineered cells

that deliver the body’s own natural pain-relievers, like GABA (gamma-aminobutyric acid) or serotonin. We’re planning to collaborate on these projects.

And our imaging studies on the brain—particularly the thalamus and the cingulate cortex—may give us important insights into the mechanisms that underlie the perception of pain in SCI patients.

Also, I’m chairing an international group on pain assessment in SCI, and together we’ve developed a basic pain data set as part of the International SCI Data Sets. This is a standardized outcome measure of pain for both clinical practice and research that we hope will facilitate collaboration between clinical centers. It is easy to use and has generated a lot of interest. It was just published in *Spinal Cord*. It may be of special interest to VA because it could potentially be incorporated into the electronic medical record.

Q: What’s the main message you hoped to convey as guest editor of *JRRD*’s special issue on SCI pain?

A: I wanted to bring together an international community of clinical and basic researchers. My goal was to emphasize the importance of collaboration—not just within VA, but nationally and internationally. One of the problems is that there are relatively few people with SCI, compared with other medical conditions. Through collaborations, we can translate basic research findings into the clinic and conduct studies that are large enough to draw conclusions and develop treatments faster. —G

Call for papers on data quality

The VA Information Resource Center invites abstracts for potential publication in an upcoming issue of VA’s *Journal of Rehabilitation Research and Development*. The issue will focus on the quality of databases used in research to improve veterans’ health care. Abstracts will be due by April 20, 2009. For details visit www.rehab.research.va.gov/jour/08/45/8/pdf/call-for-papers.pdf.

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communication was crucial. “The important part of this meeting was not just the educational talks that we heard, but the opportunity for us in the field to provide feedback to those in [Central Office] about the ways in which they can assist us in achieving what we all want.”

Plenary sessions during the meeting included wrap-ups of the breakout sessions, plus talks by Gerald Cross, MD, VA’s principal deputy undersecretary for health; Joel Kupersmith, MD, chief research and development officer; and Timothy O’Leary, MD, PhD, acting deputy chief research and development officer.

Cross said he views research as “the jewel of VA’s accomplishments” and charged the group with maintaining impeccable standards. “Your responsibility and mine is to make sure that VA research is done with such care, precision, and attention to ethical issues and all other requirements, that we ensure that our research program continues to flourish.”

Stressing individual responsibility and preventive, proactive approach

Kupersmith outlined the unique value of VA research—among many examples, its large “comparative effectiveness” trials that help doctors in VA and throughout the world determine the best medical treatments. He also stressed the importance of fostering a culture of prevention, proactiveness and individual responsibility.

O’Leary struck a similar theme in his talk, titled “How We Can Transition from a Reactive to a Proactive System.” He challenged participants with the questions: “How can we make compliance with regulation and policy easier than non-compliance?” and “How do we build a culture in which human subject protection and animal welfare are second nature, rather than obstacles to overcome?”

Another highlight of the meeting was a presentation by VISN directors Randy Petzel, MD, and Jack Hetrick on the ongoing Research Administrative Review that ORD initiated in early 2008. They said the goal of the process is to “develop recommendations to respond to the challenge of effective management and strengthen research activities at local VA facilities.” Members of the review team are focusing on tasks such as reducing inefficiencies, easing administrative burdens and enhancing recruitment.

Slides from the meeting can be viewed at www.research.va.gov/programs/PRIDE/conferences/accountability.cfm. ➔

VA RESEARCHERS IN THE NEWS



Diabetes, dementia and the brain—

Suzanne Craft, PhD, of the University of Washington and the Geriatric Research, Education and Clinical Center at the Puget Sound VA, was quoted in a Jan. 12 *Reuters* article on her study on how diabetes changes the effects of dementia on the brain, published online last month in the *Archives of Neurology*.

Richard Weindruch, PhD, of the University of Wisconsin and the Geriatric Research, Education and Clinical Center at the Madison VA Medical Center, was featured in a CBS “60 Minutes” segment about his research on caloric restriction as an anti-aging measure. The piece aired on Jan. 25.

Jonathan Myers, PhD, a health research scientist at the Palo Alto VA, was quoted in a Jan. 2 *Scientific American* article titled “Does Exercise Really Make You Healthier?” Myers explained how “exercise has a favorable effect on virtually all risk factors of cardiovascular disease.”

Lisa Schwartz, MD, MS, and **Steven Woloshin, MD, MS**, both with the Dartmouth Medical School and the VA Outcomes Group at the White River Junction (Vt.) VA, were interviewed on the Jan. 9 “Science Friday” segment of National Public Radio’s “Talk of the Nation” show about their new book, *Know Your Chances: Understanding Health Statistics*. H. Gilbert Welch, MD, MPH, of VA and Dartmouth was also a coauthor of the book.

Lisa V. Rubinstein, MD, MSPH, director of the Center for the Study of Healthcare Provider Behavior at the VA Greater Los Angeles Medical Center and president of the Society of General Internal Medicine, was quoted in a Jan. 9 *New York Times* article titled “In Search of a Good Doctor.” Rubinstein, who is also with RAND and the University of California, Los Angeles, recommended that patients play an active role in decision-making with their doctors because it “will help raise the quality of care given by any clinician.” ➔

It's about teamwork

Studying how nurses, doctors work together

Funded by a \$300,000 grant from the Robert Wood Johnson Foundation, researchers with VA and the University of Minnesota (UM) aim to fine-tune the teamwork among nurses, doctors, social workers and others in VA who care for veterans with chronic heart failure (CHF).

In CHF, the heart can't pump blood adequately to the rest of the body. The condition is a common cause of hospital stays—and mortality—in VA's health system and the nation at large.

Every VA medical center has a CHF care group—a multidisciplinary team that cares for CHF patients. The new study will look at how these teams work together. How well do they communicate and share knowledge? How are disagreements handled? What type of leadership is there? How efficient and well-organized are they? The focus will be on the relationship between nurses and doctors—as the team coleaders—and how they set the tone for the rest of the group.

“How do small groups of nurses and doctors work together? That's the key. They both have important knowledge necessary to improve care,” said Douglas Wholey, PhD, of UM's School of Public Health. He is leading the study with UM nurse researcher Joanne Disch, PhD, RN.

Spearheading the effort for VA are cardiologist Paul Heidenrich, MD, MS, and health services investigator Anju Sahay, PhD, both in Palo Alto. They are with VA's Quality Enhancement Research Initiative (QUERI), which helps translate research findings into clinical practice. VA has nine such groups, focusing on high-risk or highly prevalent conditions.



Focus on nurses—Nurses such as this cardiac team at the Pittsburgh VA will be the focus of a research collaboration between VA and the University of Minnesota aimed at improving care for heart failure.

Sahay and Heidenrich have also formed a group called the Heart Failure Network to further boost communication among VA providers who care for CHF patients. Sahay said the network will be an effective way to spread the new study's findings about what works best.

“The CHF QUERI through the Heart Failure Network will disseminate the findings through our bimonthly live meetings,” she said. “These findings will also be disseminated throughout VA through posters, presentations and publications.” Sahay added that the findings will also be shared with VA's offices of Patient Care Services and Quality Performance.

To learn more about QUERI visit www.queri.research.va.gov 