

Future directions in PTSD research and care

In a recent survey by the RAND Corporation of nearly 2,000 veterans of operations Enduring Freedom and Iraqi Freedom, half the respondents reported they had a friend who was killed or seriously wounded. Nearly half—45 percent—said they saw dead or seriously injured non-combatants. Not surprisingly, the rate of respondents who met the diagnostic criteria for post-traumatic stress disorder (PTSD) or depression was relatively high, at 18.5 percent. Based on these data, RAND estimates that some 300,000 veterans who have returned from Iraq and Afghanistan are suffering from PTSD or major depression.

For an overview of key issues and emerging trends in PTSD research and care, *Research Currents* spoke with Terence M.

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The hidden scars of war—According to VA's National Center for PTSD, "...the frequency and intensity of exposure to combat experiences is strongly associated with the risk of chronic PTSD."



Stress and the heart—Dr. David Sheps checks in with a patient about to undergo SPECT imaging to detect cardiac ischemia. Looking on is technologist Dorian Lucey.

Study links gene variation to cardiac effects of mental stress

Researchers with VA and the University of Florida have identified a gene variation in some heart disease patients that makes them especially vulnerable to the physical effects of mental stress—to the point where blood flow to the heart is greatly reduced.

"Searching for the presence of this gene may be one way to better identify patients who are at an increased risk for the phenomenon," said David S. Sheps, MD, MSPH, associate director of the division of cardiovascular medicine and director of nuclear cardiology at UF's College of Medicine, and a staff cardiologist at the Malcom Randall VA Medical Center in Gainesville.

According to Sheps and colleagues, who published their findings in the April 14 *Archives of Internal Medicine*, those with the gene variation are three times more likely to experience dangerous decreases in blood flow to the heart—a condition known as cardiac ischemia—than heart disease patients without it. Ischemia increases the chance these patients will suffer a heart attack, heart rhythm abnormalities or sudden death.

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More is not better: VA-NIH study yields surprising finding on treatment for acute kidney injury

More intensive treatment—for example, dialysis six times instead of three times per week—failed to produce any added benefit for patients with acute kidney injury in a large clinical trial sponsored by VA and the National Institutes of Health. The results appeared online May 20 in the *New England Journal of Medicine*.

In acute kidney injury, the kidneys suddenly shut down, causing a dangerous buildup of fluids and waste products in the body. The condition occurs most often in hospital patients who have experienced trauma, toxic side effects from drugs, or infection following surgery. The risk is higher in older patients and in those with chronic kidney disease, high blood pressure, diabetes, heart disease, or vascular disease.

Despite advances in care in recent decades, acute kidney injury is costly to treat and has a high death rate—50 to 80 percent. It affects about 3 percent of VA patients and anywhere from 1 to 15 percent of hospitalized patients in general.

VA Research Currents

is published 10 times per year for the Office of Research and Development of the U.S.

Dept. of Veterans Affairs by
VA R&D Communications

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Seeking better therapy—Dr. Paul Palevsky of the Pittsburgh VA chaired a VA multisite study, in collaboration with the National Institutes of Health, that tested whether patients with acute kidney injury would benefit from more intensive treatment.

Five earlier single-center trials had yielded mixed findings as to whether more intensive dialysis might save lives. But the new VA-NIH trial included more patients than the previous five studies combined and is expected to influence how doctors manage the condition.

“This is an important study that will change our practice,” Harvard Medical School professor Ajay Singh, MD, told *U.S. News and World Report*.

NIH director Elias A. Zerhouni, MD, said: “We now have definitive evidence that intensive treatment of acute kidney injury is no more beneficial in improving treatment outcomes than the usual level of care. As a result, the findings of this well-designed study may help prevent unnecessary medical expenditures.”

The VA-NIH study, conducted from 2003 to 2007, included 1,124 critically ill patients at 17 VA hospitals and 10 university hospitals. Patients were randomly assigned to either intensive or less-intensive treatment. The exact type of renal therapy

Acute kidney injury has a death rate of 50 to 80 percent.

depended on the patient’s condition. Patients who did not need drugs to maintain their blood pressure were given conventional hemodialysis—three times per week in the less-intensive arm, six times per week in the intensive arm. In hemodialysis, a machine does the job of the kidneys and filters toxins and extra fluid from the blood. Patients who needed drugs to increase their blood pressure were given gentler forms of renal replacement therapy, in either higher or lower doses or frequencies. Patients were able to switch between forms of renal replacement therapy as their clinical condition changed, while staying within the lower- or higher-intensity treatment arm.

About half the patients in both groups died within the first two months of dialysis. The difference in death rates was not

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statistically significant, according to the authors. There were also no significant differences between the groups in recovery of kidney function, the rate of failure of organs other than kidneys, or patients' ability to return to prior living situations.

“What we have shown is that the more intensive therapy is not better than the less intensive strategy,” said study chairman Paul M. Palevsky, MD, chief of the renal section at the VA Pittsburgh Healthcare System and a professor of medicine at the University of Pittsburgh School of Medicine. Palevsky added that “unlike earlier studies that used only a single method of therapy, our use of an integrated strategy of continuous and intermittent methods of therapy allows us to apply these study results more readily to clinical practice. What is important about these results is that they outline the limits of effective therapy.”

The study was cosponsored by VA's Cooperative Studies Program and NIH's National Institute of Diabetes and Digestive and Kidney Diseases. —

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The researchers studied 148 older patients with coronary artery disease. After being injected with a safe radioactive dye, the volunteers had to give a three-minute speech in front of a small audience—a task used commonly in research to induce anxiety. Afterward, they lay down inside a gamma camera—similar in appearance to a CT or MRI scanner—and underwent imaging that would trace the isotope in their bloodstream and thus show blockages in blood flow to the heart. They underwent a similar test when not in a stressed state and also had blood samples taken for genetic analysis.

About a quarter of the patients experienced reduced blood flow to the heart as a result of the mental stress, and about two-thirds of these patients had a particular variation of the adrenergic beta-1 receptor genotype. This receptor typically helps the body respond to stress by regulating blood pressure and heart rate, but a variation apparently makes certain patients more vulnerable to the effects of psychological stress.

According to Sheps: “We may be able in the future to be more specific about what kind of treatment might work better in certain patients depending on their genetic makeup. That is one of the important things happening in [medicine]. There are many diseases that already have been shown to respond differently to different types of treatment based on genetic differences.”

The research was supported by VA; the National Heart, Lung and Blood Institute; and the UF colleges of Pharmacy and Dentistry. —

CONFERENCE HIGHLIGHTS

VA conference brings together experts on traumatic brain injury

By Joel Kupersmith, MD
Chief Research and Development Officer



Many of our newest veterans are returning home from Iraq and Afghanistan with multiple complex injuries. One such injury—traumatic brain injury (TBI)—is referred to as the “signature injury” of the current conflicts. While VA is committed to providing the best health care to these veterans, there are many challenges and knowledge gaps regarding TBI. To foster progress in this area, VA's Office of Research and Development (ORD) brought together a multidisciplinary group of experts in Arlington, Va., last month for a state-of-the-art conference titled “Research to Improve the Lives of Veterans: Approaches to Traumatic Brain Injury Screening, Treatment, Management and Rehabilitation.”

A planning committee chaired by Henry Lew, MD, PhD, director of polytrauma research at the Palo Alto VA, commissioned background papers for workgroup discussions. The papers examined topics such as the pathology of blast-related brain injury, diagnosis, comorbidities (for example, mental health issues, sensory deficits, infections, seizures, and pain), brain imaging, care management, community reintegration, and the role of veterans' families in TBI care.

Six workgroups focused on different aspects of TBI and then presented summaries of their findings and research recommendations for discussion with the entire group. Among other objectives, the recommendations called for enhanced access to TBI data through a central database, increased recruitment of TBI researchers into the VA system, and additional support for clinical trials focused on TBI.

ORD is already acting on many of these recommendations. We will be supporting a polytrauma and TBI fellowship program through VA's Office of Academic Affiliations, and a soon-to-be-released request for study proposals will reflect several research priorities discussed at the conference. Also, papers from the event are being prepared for journal submission.

All in all, this work should lead to a better understanding of TBI and ultimately improve the care provided to the courageous men and women coping with this condition. —



Photo by Mitch Altman

No couch potato—Navy veteran Marty Segal, 65, who relies on the Baltimore VA for health care, stays fit by exercising regularly at home, as well as outdoors and at a local gym. (Photo not intended to show specific exercise or technique recommended in VA study discussed below.)

Primary care counseling spurs home-based workouts

In a study involving 224 men aged 60 to 85 at the VA medical center in Jackson, Miss., brief counseling sessions with a nurse during primary care visits were effective in getting the veterans to do more walking and strength training at home. The study was published May 12 in the *Archives of Internal Medicine*.

After 10 months, veterans who had received exercise counseling during three primary care visits were averaging about 41 minutes per week of strength and flexibility training at home, doing exercises such as arm curls, arm raises and calf stretches. This compared with about 15 minutes per week among veterans who received only general health education during their doctor visits. The exercise-counseling group was also walking more than the other group—about 61 minutes per week, versus 46 minutes.

According to lead author Patricia M. Dubbert, PhD, the study shows that a simple, low-cost intervention can go a long

Veterans in the study did exercises such as arm curls, arm raises and calf stretches at home.

way in building healthy exercise habits for older veterans. “Our study helps show that clinicians can prescribe strength training in addition to walking at home for patients, and that with the kind of patient counseling we used, these interventions can be safe and effective.”

Dubbert’s team based the exercise counseling on materials produced by the National Institute on Aging. She notes that the methods used in the study—face-to-face counseling and telephone follow-ups—are “recommended components” of VA’s “MOVE!” program, a nationwide initiative aimed at promoting exercise and healthy

eating among veterans. She adds though, that while “many providers recommend walking, which is good, fewer are aware of the potential benefits of strength training.”

The participants in the study didn’t necessarily shed pounds as a result of their increased exercise, but they did report better performance on a variety of health and fitness measures.

“People who increase their exercise, especially strength-building exercise, may lose body fat but gain muscle weight, so that they firm up but do not lose weight on a scale,” explains Dubbert.

The study also did not track the effects of the increased exercise on body metrics such as blood pressure or cholesterol. According to Dubbert, “VA primary care patients often have well-controlled blood pressure, lipids and blood sugar, and it would be difficult to show an effect of exercise in addition to the medications being prescribed.”



High-tech therapy—Among the newer PTSD treatments being evaluated by VA investigators is the use of computer-generated virtual reality environments (as seen in the image above) as an aid to prolonged exposure therapy. At right, Dr. Sarah Miyahira of the Honolulu VA works with a service member just back from Iraq.



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Keane, PhD, associate chief of staff for research at the VA Boston Healthcare System and director of the behavioral science division of VA’s National Center for PTSD, headquartered in White River Junction, Vt. He is also a professor of psychology and professor and vice chairman of the division of psychiatry at Boston University School of Medicine. He is recognized internationally as a leading expert on trauma and PTSD and has authored numerous books, journal articles and clinical guidelines on PTSD. Keane served as guest editor for the current issue of VA’s *Journal of Rehabilitation*



Research and Development (JRRD), which focuses on PTSD.

Research Currents: VA Secretary Peake has spoken of the need to properly diagnose and treat PTSD but not “over-label” returning veterans with diagnoses that may no longer be appropriate as these men and women move forward and readjust. Is that a difficult balance to achieve?

Terence Keane: Yes. We need to mitigate the stigma that’s associated with a diagnostic label at the same time that we encourage people to come forward to get appropriate treatment. That’s a balancing act on the best of days. Most importantly, we need to do the right thing by the returning veterans—whether that means providing diagnosis and intervention early on, or adopting a wait-and-see attitude. I think both approaches have a place.

Increased focus on PTSD— Dr. Terence Keane says the new generation of U.S. war veterans is driving expanded research on the roles of traumatic brain injury and psychological stress in health outcomes.

RC: The Department of Defense has stepped up efforts to remove the stigma of PTSD treatment—for example, by changing its security-clearance procedure so that applicants need not disclose past mental health care that was “strictly related to adjustments from service in a military combat environment.” Do you think this will have a positive impact on PTSD care?

TK: It may take some time to gauge the real impact, but I think this is a major step forward for DoD and a very optimistic change in policy. I’m convinced that DoD leadership is invested in the mental health fitness of their workforce and has every reason to promote the use of treatment resources. From my point of view, what’s important is making sure these policies are implemented all the way up and down the line.

RC: Where are we today with PTSD care in relation to the Vietnam era?

TK: We’re so much better equipped today than even after the first Persian Gulf War, let

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Scientists cited for work in cancer, diabetes, schizophrenia

Three VA investigators were honored for their groundbreaking medical research on behalf of veterans at a special VA Research Forum held May 23 at the agency's headquarters in Washington, DC. The event, held in connection with this year's National VA Research Week, featured remarks from VA Secretary James Peake and other dignitaries, as well as talks and demonstrations from researchers on topics such as women's health, brain-computer interfaces, prosthetic limbs, and wheelchair technology.

Andrew V. Schally, PhD, of the Miami VA Medical Center and University of Miami, received a Meritorious Service Award from VA for his work on innovative cancer treatments. Winner of the Nobel Prize in Physiology or Medicine in 1977, Schally discovered and synthesized three hormones—all peptides, or chains of amino acids—produced in the hypothalamus region of the brain. The discoveries had a significant impact on reproductive medicine, among other areas, leading to the development of fertility and contraceptive compounds. More recently, his research has focused on the development of “smart” chemotherapy that targets tumors but leaves surrounding tissues unharmed. The approach involves combining cancer drugs with synthetic versions of hormones and then targeting tumors that have receptors for those hormones.

Schizophrenia pioneer—

Dr. Robert Freedman's work has identified new potential targets for schizophrenia therapy called nicotinic acetylcholine receptors. An experimental drug that acts on these receptors has shown promise in early clinical trials.



Revealing insulin's

role—Dr. Daryl Granner's research has shed light on insulin's role as a regulator of gene expression. New drugs based on his findings are being developed by several pharmaceutical companies.



Honored for cancer research—VA researcher and Nobel Prize winner Dr. Andrew Schally (center) is presented with VA's Meritorious Service Award by Chief Research and Development Officer Joel Kupersmith, MD (left), and Under Secretary for Health Michael Kussman, MD, during the Research Forum event at VA headquarters on May 23.

Also at the May 23 event, the 2007 Middleton Award, VA's highest award for biomedical research, was awarded to **Robert Freedman, MD**, and **Daryl K. Granner, MD**.

Freedman, of the Denver VA Medical Center and University of Colorado Health Sciences Center, studies the molecular and genetic underpinnings of schizophrenia, which affects some 100,000 veterans who use VA's health system. In research over the past three decades, Freedman's team has developed a promising new drug that targets the same molecular receptors as nicotine and appears to improve sensory processing and mental function in patients with schizophrenia. The drug is now in early clinical trials.

Granner served as a VA clinician-scientist for more than 25 years, retiring recently from the Nashville VA Medical Center. He is now a professor emeritus at Vanderbilt University and a visiting professor at the University of Iowa. Granner has been noted internationally for his pioneering research on the mechanisms of insulin, the main hormone involved in the body's processing of glucose. As a result of his studies, cited by other scientists more than 4,000 times in the past 15 years, several companies are now developing compounds known as “glucokinase activators” as a potential treatment for type 2 diabetes, which affects some one million veterans who use VA health care. —

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alone Vietnam, Korea or World War II. We now have screening instruments, real-time information about the psychological status of returning troops, diagnostic interviews, and new treatment models and methods. We now need to apply these models consistently across the entire country and disseminate the evaluation and treatment tools that have been developed in and outside VA.

RC: To what extent has closer collaboration between VA and DoD helped to enable these advances?

TK: I was on a Web broadcast this morning with Col. [Elsbeth Cameron] Ritchie, a psychiatrist for the Army in DC, and there were over 500 people across the country taking part and interested in learning about returning war vets. This would not have happened 15 or 20 years ago. The fact that so many professionals tuned in to hear this program represents the great progress that's been made, in part through increased collaboration between VA and DoD.

RC: What steps have been taken to ensure uniform assessment of PTSD?

TK: Brian Marx, Paula Schnurr, Matthew Friedman [of the National Center for PTSD] and I are involved in a project that will disseminate evidence-based approaches to the assessment of PTSD nationwide. We've developed a Best Practice Guideline for the assessment of PTSD. Following a recommendation from the Institute of Medicine, VA will disseminate these best practices nationwide to bring uniformity to the process of evaluating veterans seeking compensation for psychological war injuries.

RC: In your *JRRD* editorial, you write that "silo-based studies of PTSD may have contributed to the current state of knowledge, but what is needed now is greater integration across disciplines and specialties." Could you elaborate?

TK: I was calling for the integration of molecular biology, genomics, proteomics, clinical psychology, and psychiatry. That's the next direction that has to be explored. These are the kinds of things that will yield important and fruitful directions for PTSD.

RC: One of the major themes emerging for clinicians and researchers is the overlap and interplay between PTSD and traumatic brain injury (TBI)—sorting out the effects of each and identifying the best treatments. How is that problem being addressed?

TK: This particular cohort of war veterans is going to stimulate much greater research on the role of traumatic brain injury and the role of psychological stress in health outcomes, much as the Vietnam veterans served to improve recognition, diagnosis and



Drs. Hui Qi Tong (left) and Wang Zhen.

VA research fellows play role in China earthquake relief

Two postdoctoral fellows in the San Francisco VA lab of PTSD researcher Charles Marmar, MD, along with a psychology extern from the center, were key players in the wake of the earthquake disaster in Sichuan, China, on May 12.

The fellows—Hui Qi Tong, MD, MS (also a predoctoral psychology intern), and Wang Zhen, MD—had been doing collaborative research in Shanghai. George Hu, MA, was doing an externship in another Chinese city. After the quake, the VA team realized that Chinese first responders urgently needed guidance on how to provide psychological first aid. The researchers helped organize a translation of a 152-page manual developed by the National Child Traumatic Stress Network, VA's National Center for PTSD and other experts, designed to aid children, teens and adults in the aftermath of disaster and terrorism. With the help of more than 40 volunteer translators from both sides of the Pacific, the translation was completed in four days and quickly made available for distribution to professional and lay volunteers working with survivors. —

treatment of people with PTSD of all sorts. We're looking very carefully at trying to understand blast injury, TBI and stress concurrently. But the answers aren't there yet. There will need to be a lot of cross-disciplinary collaboration and some public sector and private sector integration—VA, DoD, the National Institutes of Health and the private sector all have a role to play in trying to help provide the best possible assessment and treatment for people with these conditions.

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RC: VA recently gave an additional \$2 million in funding to the National Center for PTSD. What are the current research priorities for the center?

TK: Our priorities are the development of a PTSD registry, the development of telehealth and Internet-based interventions, and the dissemination of existing evidence-based assessment instruments and treatment tools. Keeping in mind that VA has hired hundreds of new mental health providers in the last couple of years, it seems important that we provide outstanding mentorship and education for these new people so they benefit from the prior generation's experiences in developing these instruments and treatments. ➡

Web feature on high blood pressure

Hypertension, or high blood pressure, is the topic of a new "Health Spotlight" article on the website of VA's Health Services Research and Development Service. Find the feature at <http://www.hsrdr.research.va.gov/news/spotlight/hypertension-0508.cfm>.

INVESTIGATOR SNAPSHOT



Brain injury and vision—Gregory Goodrich, PhD, a research psychologist at the VA Palo Alto Health Care System, studies visual impairment among veterans with polytrauma, traumatic brain injury (TBI) and PTSD. He is pictured here with a Neuro Vision Technology scanner, used to assess and train patients with brain-related vision problems.

Goodrich: "In mild TBI, patients tend to have normal visual acuities and are often considered to not have vision problems. Our work has highlighted the need to do more comprehensive exams, including binocular function evaluations. Binocular dysfunctions can make reading difficult and cause problems in education and employment. They can also interfere with safe driving, promote eye fatigue, and, if not treated, compound depression and other psychological symptoms. Patients often don't realize their symptoms are related to vision, but they may feel that 'things just aren't quite right.' We hope our research will contribute to more comprehensive vision screening for these patients and better overall care." ➡