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VA Research Currents

RESEARCH NEWS FROM THE U.S. DEPT. OF VETERANS AFFAIRS

In Purple Heart, researchers seek clues to resilience

War-wounded Veterans who survive into later life—especially those who do not develop posttraumatic stress disorder—may provide valuable clues as to the factors that confer resilience to combat stress.

So says a team of VA researchers who studied more than 10,000 Veterans of World War II and the Korean War. The findings appear online in the journal *Depression and Anxiety.*

The study found decreased mortality among aging Veterans who had earned a Purple Heart—meaning they had been injured in action—compared with those who had not earned the medal. Whether the Purple Heart holders had chronic PTSD or not, they were about twice as likely to still be alive after some 10 years of follow-up, compared with those with no Purple Heart and no PTSD.

The study included Veterans who were 65 or older in the late

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The ups and downs of measuring blood pressure

You've just been to the doctor and your blood pressure is a bit high. *Or is it?*

A recent study at the Durham VA Medical Center and Duke University confirms that people's blood pressure tends to be higher at the doctor's office than when they check it themselves at home.

The difference can often be as much as 10 or 15 points in the systolic, or top, number. So if your reading at the doctor's office is hypertensive—say, 140 over 90—it could well be only pre-hypertensive at home—130 over 85, for example. That's a bigger spread than the five-point gap between home and clinic that clinical guidelines recognize

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Photo by Robert Turtil

Photo by Jeff Bowen

A lot of heart—Edward Schnug (left), who passed away in 2008 at age 85, was photographed at a 2005 Veterans Day parade in which he represented the Military Order of the Purple Heart. He earned three Purple Hearts serving with the Marines in World War II, Korea, and Vietnam. Dr. Tim Kimbrell (above) and other VA researchers believe the same emotional resilience that enables some war-wounded Veterans to ward off PTSD may also contribute to longer life.

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and advise doctors to account for in their decision-making.

But that's only part of the story. The VA-Duke study also suggests that regardless of where blood pressure is taken, the best way to get an accurate reading—to know a patient's "true" pressure—is to take at least five or six measurements on different days and use the average.

According to lead author Benjamin Powers, MD, MHS, an internist with VA and Duke, the only realistic way to get multiple measurements is to rely on home monitoring.

"Practically speaking, we can't bring people into the clinic more frequently to do this, and taking blood pressure five times during a single clinic visit is not going to accomplish the same thing."

Study compared readings across different settings

The VA-Duke hypertension study involved several hundred Veterans. It was mainly intended to test the effects of home blood pressure monitoring and phone calls from nurses that aimed to help patients improve behaviors such as diet, exercise, and prescription adherence.

The newest phase of the analysis, published in the June 21 *Annals of Internal Medicine,* zeroed in on the ideal way to measure blood pressure. How can providers get the most accurate information on which to base treatment decisions? The study compared results obtained through three methods: clinic measurements, home monitoring, and measurements by research assistants as part of a carefully controlled study protocol.

Editorial describes scope of problem in everyday care

An editorial that accompanied the VA-Duke article, by a group with Johns Hopkins University, painted a disturbing picture of how hypertension treatment decisions are commonly made for U.S. adults. Aside from "white coat syndrome"—most patients' pressure spikes higher at the doctor's office, usually because they are nervous about their appointment—there is a fair degree of variation, and sloppiness, in how clinic readings are typically taken.

"In practice, blood pressure measurement is remarkably casual," wrote the Hopkins team. "As clinicians and patients, we have personally observed major deviations from accepted standards: Cuffs are applied over clothing, [blood pressures] are obtained without allowing the patient to rest for 5 minutes, and measurements are taken while the patient sits hunched over an examination table with his or her legs dangling. Training is minimal, and monitoring to check technique is nonexistent. Devices, even if initially validated, are not checked and, if needed, recalibrated."

Citing several studies that back their conclusion, the Hopkins authors say the


Photo by April Elkers

result is that "suboptimal measurement of [blood pressure] is remarkably commonplace."

Powers concurs: "When people have looked at how well providers follow protocol in routine practice, it's usually pretty disappointing. Even small differences in the patient's arm position can make a difference of a few millimeters of mercury."

Many patients could be misdiagnosed

In the VA-Duke study, only one in three patients was consistently classified across all three methods used in the study. Based on home measurements, for example, about half the patients were found to have well-controlled pressure. Based on clinic measurements, the figure dropped to below one-third.

If such a trend were taking place at medical practices across America—as it likely is—millions of patients could be on hypertension drugs they don't really need. Powers, an assistant professor of medicine

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103 S. Gay Street, Rm. 517
Baltimore, MD 21202
(410) 962-1800, ext. 223
research.publications@va.gov

Editor: Mitch Mirkin

Taking blood pressure: Does your clinic get it right?

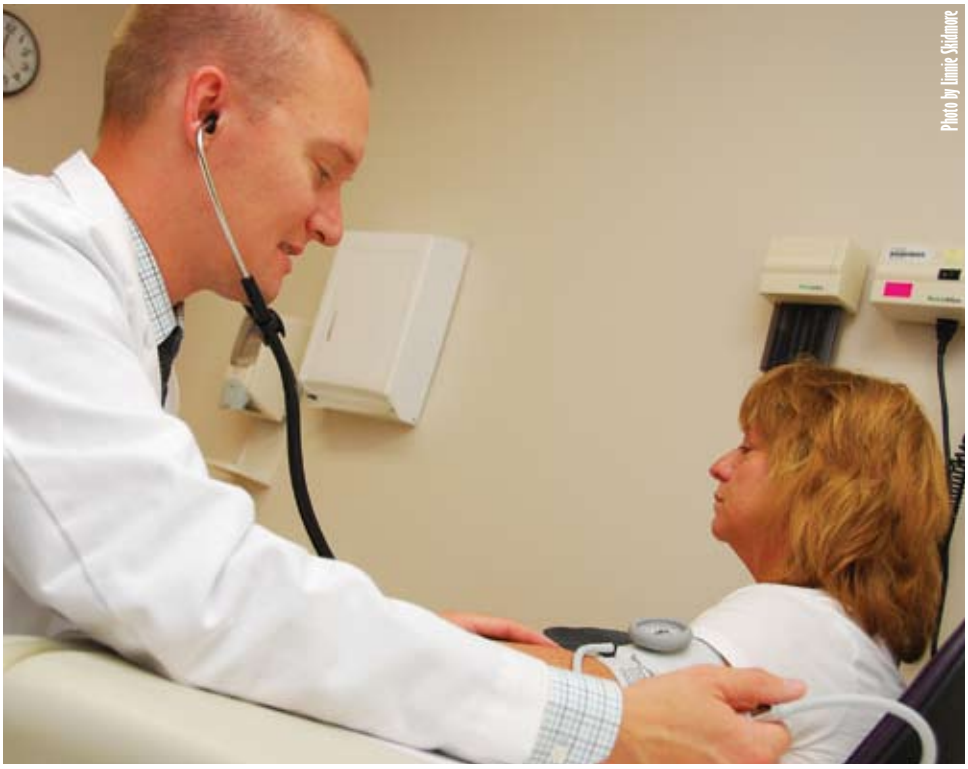
The American Heart Association and other organizations issue guidelines for clinicians on how to properly measure blood pressure. Here are some key points:

• Patients should not exercise, drink caffeine, or smoke for at least a half-hour before their visit. They should sit quietly for at least five minutes before the reading.

(Powers offers an example of how real-world practice often deviates from the guideline: Some patients rush into a doctor's office feeling stressed after having circled the parking lot for 10 minutes looking for a spot, and their blood pressure is taken right away.)

• During the measurement, patients should sit comfortably with their back supported, feet flat on the floor, and arm supported at the level of the heart. Their sleeve should be rolled up. They shouldn't converse with the clinician during the procedure.

• The cuff should fit right. Heavier, larger-boned patients require a bigger cuff.



Promoting proper pressure procedures—Dr. Ben Powers of Duke University and the Durham VA Medical Center led a study on how providers can obtain the most accurate blood pressure readings for patients. Here, he checks Janet McMillion's pressure.

• At a first visit, two readings should be taken. If they differ significantly, a third should be taken. (Here again, though, says Powers, taking multiple readings at a single office visit is not as valuable as having the patient do several readings at home, on different days.)

at Duke, uses the analogy of diabetes. "What if you had to make your treatment decision for your patient with diabetes based on one random blood sugar measurement that you got in the clinic, and based only on that, you had to determine how to change their medication?"

He points out that hypertension is even more common than diabetes, and that the scope of the problem is potentially huge. "This occurs all the time," he says. "High blood pressure is the most common reason older adults visit the doctor. We've been able to measure blood pressure for a long time and treat it, and some of the things covered in our article are fairly well-known, but I don't know that on a regular basis we as clinicians in the U.S. are very mindful of the inherent error in measurement and the inherent variability in blood pressure, and how that impacts clinical decision-making."

VA in good position to tackle problem

VA, says Powers, is uniquely positioned to tackle the problem. With its shift to a model of primary care known as patient-aligned care teams (PACT), the agency will increasingly rely on home-based self-monitoring for hypertension and other chronic conditions. Telehealth staples such as phone follow-up and secure email and Internet contact will play a bigger role. The goal is to improve access and continuity of care, especially for those who live in rural areas or otherwise can't travel to VA care sites.

Powers has already figured out how to make good use of home monitoring with his hypertension patients.

"I get them a monitor that's validated, that fits, that works for them. I ask them to get me some info on their home blood pressure. Those who are Internet-savvy can send me a secure message through myHealtheVet. Others write it down and bring it to me at the clinic visit. So even

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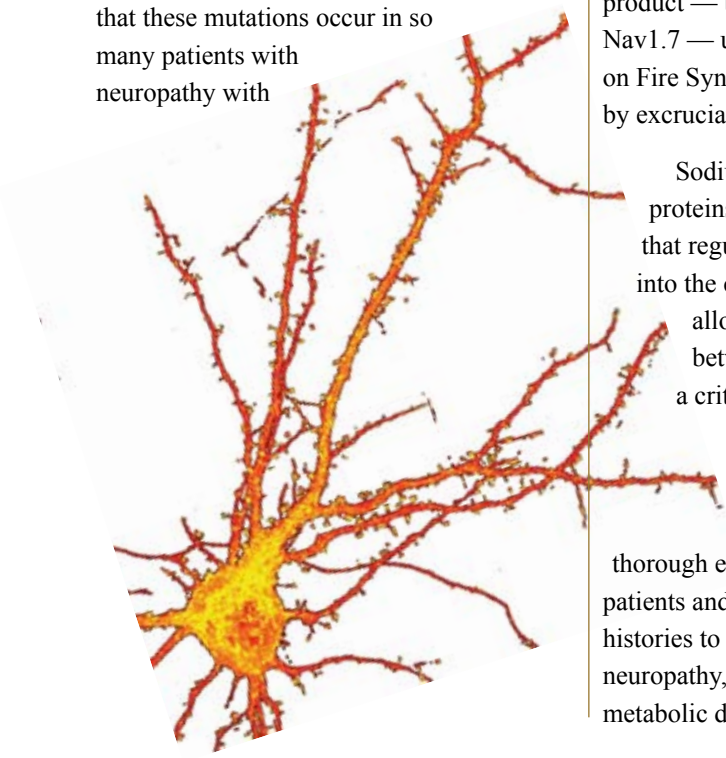
Gene discovery sheds light on mystery nerve pain

An estimated 20 million people in the U.S. suffer from peripheral neuropathy, marked by the degeneration of nerves and in some cases severe pain. There is no good treatment for the disorder, and doctors can find no apparent cause in about a third of cases.

An international team of scientists headed by researchers from Yale University, the VA Medical Center in West Haven, and the University Maastricht in the Netherlands found that mutations of a single gene are linked to 30 percent of cases of unexplained neuropathy. The findings, published online June 22 in the *Annals of Neurology,* could lead to desperately needed pain treatments to help those struggling with the disorder.

"For millions of people, the origin of this intense pain has been a frustrating mystery," says Stephen Waxman, MD, PhD, director of VA's Center for Neuroscience and Regeneration Research and a professor of neurology, neurobiology, and pharmacology at Yale. "All of us were surprised to find that these mutations occur in so many patients with neuropathy with unknown cause." Waxman was a senior co-author on the paper.



Nerve center—Work by a group at VA's Center for Neuroscience and Regeneration Research may help explain cases of peripheral neuropathy that have no apparent cause.

The study focused on mutations of a single gene — SCN9A — that is expressed in sensory nerve fibers. Waxman's group had discovered that mutations in this gene's product — the protein sodium channel Nav1.7 — underlie inherited cases of "Man on Fire Syndrome," a rare disorder marked by excruciating burning pain.

Sodium channels are specialized proteins in the membrane of brain cells that regulate the flow of sodium ions into the cell. They act like a battery to allow electrical impulses to travel between neurons and appear to play a critical role in pain sensations.

Following up on the findings from Waxman's lab, colleagues in the Netherlands conducted thorough examinations of neuropathy patients and scrutinized their medical histories to rule out all known causes of the neuropathy, such as diabetes, alcoholism, metabolic disorders, or exposure to toxins.

The SCN9A gene appears to be the culprit in some cases of severe nerve pain.

The researchers then did a genetic analysis of 28 patients with neuropathy with no known cause. They found 30 percent of these subjects had mutations in the SCN9A gene. The researchers found that the mutations cause nerve cells to become hyperactive, a change they believe eventually leads to degeneration of nerve fibers.

"These findings will help us as clinicians to a better understanding of our patients with small fiber neuropathy and could ideally have implications for the development of future specific therapies," says Catharina Faber, MD, PhD, one of the lead authors from the Netherlands.

The research was funded in part by VA and the Erythromelalgia Association. Erythromelalgia is the medical term for Man on Fire Syndrome.

Can the omega-3 fatty acid DHA ward off dementia?

A lab study presented by Greg Cole, PhD, and colleagues with VA and the University of California, Los Angeles, at the recent International Conference on Alzheimer's Disease suggests that DHA—a type of omega-3 fatty acid linked to cardiovascular and brain health—may be a potent agent against dementia, but mainly for prevention and not for treatment.

Past clinical trials on DHA have yielded mixed results. A trial funded by the National Institute on Aging and led by Joseph Quinn, MD, of the Portland VA Medical Center and Oregon Health and Science University, failed to find a cognitive benefit overall for more than 400 older people with Alzheimer's. However, in a sub-analysis, those patients who lacked a gene called ApoE4—a risk factor for Alzheimer's—did show a slower rate of decline. Another clinical trial, conducted by a firm that makes DHA supplements derived from algae, found benefits for older people with only mild memory impairments, as opposed to full-blown Alzheimer's disease.

Taken together, the trials "raise the possibility that treatments [such as DHA] must be given very early in the disease for them to be truly effective," said William Thies, PhD, scientific director of the Alzheimer's Association, when results from the two studies were first presented in 2009.

Striking a similar theme, Cole and colleague Sally Frautschy, PhD, both with the Geriatric Research, Education and Clinical Center at the West Los Angeles VA Medical Center, asked the following pointed question in a commentary in *Alzheimer's Research and Therapy* earlier this year: "Should a drug [DHA] be discarded for prevention if it fails to modify progression?" Their latest study provides more evidence to support their line of research. Using genetically engineered mice, they found that DHA does thwart dementia, even in mice carrying the ApoE4 gene—but only if it used as a very early intervention, before disease has set in. The effect was seen both in performance in a maze used to test mice's memory, and biological markers of beta-amyloid, a protein that accumulates in the brain in Alzheimer's. Next steps will likely include a study on older mice to confirm whether DHA's therapeutic benefits are in fact lost at later stages of the disease process. So far, say Cole and Frautschy, "Our data support consideration of DHA for prevention trials."

DHA maven—Dr. Greg Cole is studying DHA, already taken in softgel or other supplement form by millions of Americans, for its potential use in preventing dementia. A liquid chromatography-mass spectrometry tool (left) in Cole's lab helps measure blood levels of DHA in animal models or human study volunteers.


Photo by Michael Moody

Protected status—Former Marine Jeremiah Oertel, seen here taking part in a study at VA's National Center for Rehabilitative Auditory Research, is among thousands of Veterans who volunteer each year for VA research studies and whose rights, safety, and privacy are protected through an array of federal and VA-specific policies and regulations.

Accreditation means extra safeguards for research volunteers

VA's Central Office Human Research Protection Program, which helps ensure high ethical and scientific standards for research projects that involve Veterans or their health information, has been accredited by the nonprofit Association for the Accreditation of Human Research Protection Programs (AAHRPP).

A key component of the Human Research Protection Program is the VA Central Institutional Review Board, launched in 2008. It oversees large clinical trials and other human research projects conducted at multiple VA medical centers and often involving hundreds or even thousands of Veterans. More than 100 VA sites have approval to conduct human research projects, and study teams at several sites often collaborate on studies. The VA Central IRB was established to improve the quality of review of such large, complex multi-center research projects while ensuring that local issues are addressed.

The new recognition from AAHRPP means the VA Central IRB and the other facets of the agency's Human Research Protection Program surpass federal policies and regulations and meet even higher standards.

In addition to its recognition of the VA Central Office-based program, AAHRPP has also accredited the local human research protection programs at the more than 100 VA sites nationwide that conduct research involving Veterans.

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though I might be seeing them in the clinic, I'm still making a decision based on their home measurements—ideally, several of them." He notes that through VA's electronic medical record system, multiple blood pressure readings could be easily tracked and combined for patients.

Also, unlike the private sector, VA is free to use telehealth wherever and whenever it makes the most sense for patients.

"It's been difficult for private primary care providers to do because we're still working out how to pay private fee-for-service doctors for care that doesn't involve face to face interactions with patients," says Powers. "We are free from that constraint in VA, and we can provide the highest quality, most efficient care possible without having to rely on seeing people face to face in order to get paid."

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1990s. It tracked their survival through 2008.

"Among the older Veterans we studied, those with Purple Heart citations had half the mortality rate of those without Purple Heart citations," said lead author Tim Kimbrell, MD, a physician-researcher with the Center for Mental Health and Outcomes Research, based at the Central Arkansas Veterans Healthcare System.

It's estimated that more than a million service members received a Purple Heart in World War II, and nearly 119,000 in the Korean War. In recent years, researchers with VA and the Department of Defense have sought insight into the psychological and neurobiological factors that enable some troops to withstand traumatic events and not develop PTSD. The authors of the new VA study say Purple Heart holders who survive long past their war experience without PTSD may be the ideal population on which to focus such research.

"Our theory was that there are many factors that contribute to resilience to PTSD, and these same factors may increase survival," said Kimbrell.

Actually, the researchers were surprised to find that among Purple Heart recipients, those with PTSD had slightly lower mortality than those without PTSD. That contradicts several studies that have shown a link between chronic stress conditions such as PTSD and worse survival. Kimbrell and colleagues suggest this finding is due to "early attrition": Those who had been physically injured in World War II or Korea and suffered PTSD may have been less likely to survive to age 65 in the first place. So the PTSD-Purple Heart group included in their study may have been an exceptionally healthy and hearty cohort of Veterans.

Stormy seas—A VA study found that some 11 percent of OEF/OIF Veterans enrolled in VA care had an alcohol or drug use diagnosis, and that these diagnoses were strongly linked to PTSD and depression. Here, a sailor stands watch on the USS Carl Vinson in the Arabian Sea in November 2010.

Study tracks drug, alcohol use in OEF/OIF Veterans

Reviewing data on more than 456,000 Iraq and Afghanistan Veterans who enrolled in VA health care between 2002 and 2009, a team with VA and the University of California, San Francisco, found that around 11 percent of the patients had received a diagnosis of an alcohol or drug use disorder. The study appeared in July in *Drug and Alcohol Dependence.*

About 1 in 10 Veterans had an alcohol use disorder and 1 in 20 had a drug use disorder. Male sex, age under 25, never-married or divorced status, and greater combat exposure were linked with higher rates of drug and alcohol disorders. Of those with an alcohol or drug use disorder, up to three-quarters also received a diagnosis of PTSD or depression. In other terms, those with PTSD or depression were around four times more likely to have a drug or alcohol problem. The rates found in the study were close to those seen in earlier studies of Vietnam Veterans.

Karen Seal, MD, MPH, and colleagues say their findings support the need for "increased availability of integrated treatments that simultaneously address [alcohol and drug use disorders] in the context of PTSD and other deployment-related mental health disorders."

In a related study, published online in June in the *Journal of General Internal Medicine,* Seal's group tested whether an integrated clinic combining primary care with mental health and social services increased the use of all these services among Iraq and Afghanistan Veterans. The study, which included 526 Veterans, compared an initial three-part visit to the integrated clinic with usual care, in which patients saw a primary care provider and received referrals for the other services as needed. While the integrated clinic improved the likelihood of an initial mental health and social services evaluation for Veterans, it did not boost long-term retention in psychotherapy or other mental health care.

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VA Research Communications
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Inside: **The ups and downs of measuring blood pressure**

Gastric bypass surgery and high-risk patients

A study that tracked outcomes for more than 42,000 mostly older, male, severely obese Veterans found that those who underwent a common form of bariatric surgery did not live more years, on average, than similar patients who did not opt for surgery. The results appeared June 15 in the *Journal of the American Medical Association.*

The authors, led by Matthew Maciejewski, PhD, at VA's Durham, N.C.-based Center for Health Services Research in Primary Care, stressed that the study tracked only mortality outcomes, and that gastric bypass surgery may hold other benefits for patients, even those at higher risk because of age, severity of obesity, and medical complications. They pointed out that the study tracked patients only about seven years, and that further follow-up will be conducted to see if the surgery patients do live longer than non-surgery patients over the longer term—say, 12 or 14 years.

Most previous studies have found a survival advantage to obesity surgery, but those studies looked mainly at younger, lower-risk patients.

Doctors doing research are more satisfied with jobs

In a survey of more than 7,000 physicians at 135 VA medical centers, those who conduct research in addition to carrying out their clinical duties reported higher job satisfaction than those with no research involvement. The study is now online in *Academic Medicine,* the journal of the Association of American Medical Colleges.

According to authors David Mohr, PhD, and James Burgess Jr., PhD, VA physicians with at least 20 percent research involvement provided higher ratings with regard to new skill development opportunities, feedback from supervisors, job autonomy, and work and family balance. In terms of overall job satisfaction, 78 percent of doctors who do research reported a favorable rating, compared with 72 percent of those not involved in research.

Mohr and Burgess concluded that "as an application of our findings, we suggest that health care organizations place an emphasis on research activities and allow protected physician time for research. While this may come at a cost in the ability to see patients, in the long run, the time may lead to more organizational commitment, job satisfaction, and tenure."

Mohr and Burgess are with Boston University and VA's Center for Organization, Leadership and Management Research.

Happier physicians—Dr. Roy Aaron directs a research center of excellence at the Providence VA and teaches orthopedics at Brown University. A study has found that physicians in VA who conduct research have higher levels of job satisfaction than those involved only in clinical care.