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VA RESEARCH CURRENTS

Research News from the U.S. Department of Veterans Affairs

Photo by Tommy Leonardi

Curbing hypertension 6

Group care, home telehealth, and other innovative approaches are driving steady improvements in blood pressure among VA patients.

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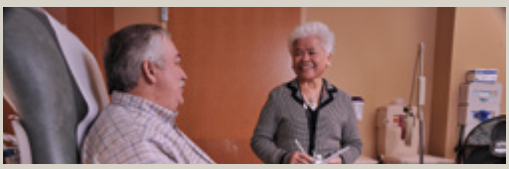

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Study finds depression, anxiety rates roughly equal among older Vets, non-Vets

Physical health problems, transitions out of the work force, changes in family roles, the loss of family members and longtime friends—these and other factors put older adults at greater risk of depression and anxiety, compared with younger people. But what if that older adult is also a Veteran?

A study of nearly 7,000 men aged 50 or older found that Veterans were no more likely than non-Veterans to have depression or anxiety.

"Veterans, particularly those who served in combat, generally experience more stress and trauma compared with non-Veterans," write Dr. Christine Gould, a psychologist with the Geriatric Research, Education, and Clinical Center at the Palo Alto VA Healthcare System, and Dr. Sherry Beaudreau, a research health scientist at the Sierra Pacific Mental Illness, Research, Education, and Clinical Center, also based at the Palo Alto VA. "Given what we know about the role of lifetime stress in depression and anxiety, we expected to see higher rates of depression among Veterans."

Instead the researchers found just the opposite. Older Veterans actually scored better than non-Veterans in the same age group. Only 11 percent of Veterans reported elevated depression, compared with 12.8 percent of non-Veterans. The pattern held true for anxiety as well, with 9.9 percent of Veterans reporting elevated anxiety, versus 12.3 percent for non-Veterans. The differences between the groups were not statistically significant.

"Contrary to expectation, no significant differences in rates of elevated depression and anxiety symptoms were found for Veterans versus non-Veterans," wrote the authors.

(*International Journal of Geriatric Psychiatry,* online Aug. 22, 2014)

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Dr. Seth Brodie, with VA and Emory University, is studying genetic patterns that predict response to chemotherapy.

Genetic finding may help predict response to chemotherapy

Researchers at the Atlanta VA Medical Center and Emory University found that an alteration in a common gene could help predict how well patients with lung cancer respond to treatment.

The study found that patients with non-small lung cancer (NSLC) who had variations of the gene caveolin-1 tended to respond more favorably to chemotherapy than those without the alteration. Those patients also tended to have higher survival rates.

Caveolin-1 is a membrane-bound protein that is a key structural component of the caveola—Latin for "little cave." The caveola's job is to act as a sort of gatekeeper to help regulate traffic and out of the cells. Highly active caveolae mean more traffic; depressed ones mean less.

The study showed that cells with inactivated caveolin-1 tended to be more sensitive to a specific type of chemotherapy commonly used to treat NSLC.

"We discovered that hyper-methylation of the caveolin-1 gene in advanced lung cancer is a marker for taxane sensitivity," says Dr. Seth Brodie, a postdoctoral fellow with VA and Emory.

Bottom line: The more sensitive cancer cells are to chemotherapy drug, the more effective that drug will be. "Right now taxane-based chemotherapy is the first-or second-line drug to be used in lung cancer," says Brodie. "If we can predict which patients will be most receptive to the treatment, then we can bolster effectiveness and limit the number of patients who have to deal with the side effects of chemotherapy."

(*PLOS One,* Sept. 15, 2014)

Gene that controls blood pressure tied to cognitive decline

Research shows that the smaller the brain's hippocampus, the greater the chances of cognitive decline and Alzheimer's disease later in life. Studies also show that certain mental activities can enlarge the hippocampus.

Now, researchers with Duke and Vanderbilt universities and the VA Tennessee Valley Healthcare System have pinpointed genetic factors that appear to directly affect hippocampus size.

Their study followed 138 older adults four years. It found that variants in a gene responsible for regulating blood pressure and commonly tied to late-life cardiovascular problems may also cause shrinking of the hippocampus.

The researchers zeroed in on three variants of the AGTR1 gene, which is part of the renin-angiotensin system, or RAS. RAS is a hormone system responsible for regulating blood pressure and fluid balance.

The variants were associated with greater changes in hippocampal volume, and with memory problems. The shrinkage occurred only in the right hippocampus; the left side was unaffected. Each side of the structure handles somewhat different functions, with the right side relating more to navigation.

"Variants in the RAS could heighten the risk for developing dementia by accelerating age-related changes in the brain," says study coauthor Dr. Warren Taylor, with the Mood Disorders Program at Vanderbilt University's Center for

Cognitive Medicine and VA's Geriatric Research, Education, and Clinical Center in Nashville.

Taylor hopes the gene variant can serve as a biomarker for future risk of memory loss or other mental conditions. Ideally, it will also provide clues to guide new treatments.

(*American Journal of Psychiatry,* online Aug. 15, 2014)

Dr. M. Neale Weitzmann, a research biologist at the Atlanta VA Medical Center, studies how the immune system drives bone formation and breakdown.

Lab tests show promise for bone-regenerating injection

Rheumatoid arthritis can be debilitating. A chronic inflammatory autoimmune disease, RA leads to bone loss around inflamed joints, and progressive loss of bone density across the entire skeleton. This can result in osteoporosis, which leaves patients at higher risk of fractures and other injuries.

The key to preventing this downward spiral, says Dr. M. Neale Weitzmann, a biologist at the Atlanta VA Medical Center, is the immune system and its role in bone formation and breakdown. In a recent study, Weitzmann, also with Emory University, wanted to see if by blocking a specific receptor on immune T cells, he could alter their effect on bone turnover.

"The CD28 receptor on a T cell provides the stimulation necessary for them to activate," says Weitzmann. "In effect, we wanted to see if we could suppress them temporarily to keep them from degrading a patient's skeletal system."

Over 12 weeks, Weitzmann's team studied the effects on mice of an anti-inflammatory drug called CTLA-4-Ig, which reduces T cell activation. CTLA4-Ig was indeed found to increase bone density. Surprisingly, though, this resulted from an increase in new bone formation, rather than reduced bone breakdown.

"Almost all the drugs currently in use for osteoporosis work by preventing further bone breakdown," says Weitzmann, "but they do not function effectively in regenerating the skeleton. So these findings were of great interest."

The results suggest that bone loss associated with RA and other diseases could be stopped, and possibly even reversed, by suppressing CD28 signals to T cells.

The potential therapy needs to be further studied, but Weitzmann is confident.

"If everything goes as we plan, we could provide effective regenerative measures to repair damaged bone, rather than just preventing further bone loss," he says. "The standard of care for osteoporosis could change completely."

(*Arthritis & Rheumatology,* April 2014)

Study highlights risks of putting off PTSD care

A recent VA study of Veterans with posttraumatic stress disorder found was that those who waited longer to get into care tended to fare worse. The Veterans who sought and received care earlier rather than later had lower rates of PTSD upon follow-up a year after they initiated care.

The study analyzed the records of nearly 40,000 Veterans of Iraq and Afghanistan who received VA mental health care between 2001 and 2011 and had a post-deployment diagnosis of PTSD. Of those, 75 percent, or around 30,000 Veterans, screened positive for PTSD when they eventually started

mental health treatment.

The researchers looked at PTSD symptoms at baseline appointments and at subsequent follow-ups. They also looked at how much time had elapsed between the end of each Veteran's service and his or her first mental health appointment.

"Veterans who waited longer to get mental health treatment were less likely to experience PTSD symptom improvement," says lead author Dr. Shira Maguen, a staff psychologist at the San Francisco VA Medical Center.

For each year that a Veteran waited to initiate treatment, there was about a 5 percent increase in the odds of either not improving or worsening on the PTSD screen a year or more later. In other words, a Veteran who waited five years had 29 percent greater odds of screening positive for PTSD at follow-up, compared with a Veteran who began treatment immediately.

"The sooner we can get these Veterans into care, the better their chances are for improving before their lives, relationships, and jobs suffer," says Maguen, also an associate professor at the University of California, San Francisco.

(*Psychiatric Services,* online Aug. 1, 2014)

Fish oil as remedy for diabetic neuropathy?

Fish oil, one of the best sources of omega-3 fatty acids, has been shown to help a range of health problems, from heart trouble to low mood. Should diabetic neuropathy be added to the list?

A new animal study from the Iowa City VA suggests the answer is yes.

Diabetes affects about one million VA patients, and more than half have symptoms of neuropathy, which include pain and numbness in the feet. This diabetes complication is the cause of most non-trauma-related amputations, as it often leads to serious foot ulcers that don't heal.

Dr. Mark Yorek's team with VA and the University of Iowa fed a diet rich in fish oil to rats with type 1 diabetes and diabetic neuropathy. They measured various signs of nerve health in the rats, such as their sensitivity to heat, and how well the nerves conducted electrical signals. Across several parameters, the rats showed improved nerve function.

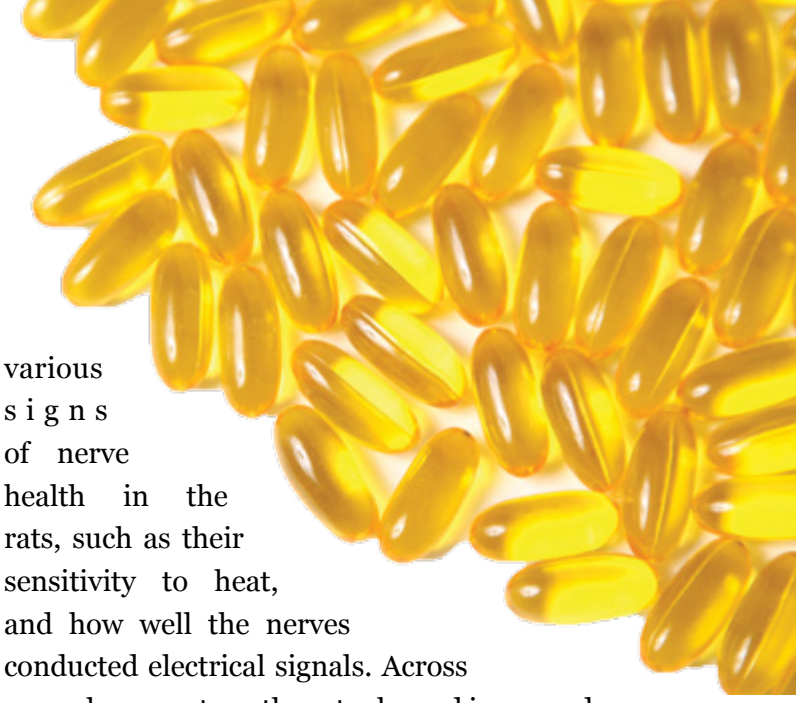


Photo: ©iStock/Kameleon007

"We found that supplementing the diet...with menhaden oil improved a variety of endpoints associated with diabetic neuropathy," wrote Yorek's group. "These results suggest that enriching the diet with omega-3 fatty acids may be a good treatment strategy for diabetic neuropathy."

Importantly, says Yorek, the treatment appeared to both prevent and reverse neuropathy in the series of experiments his lab performed.

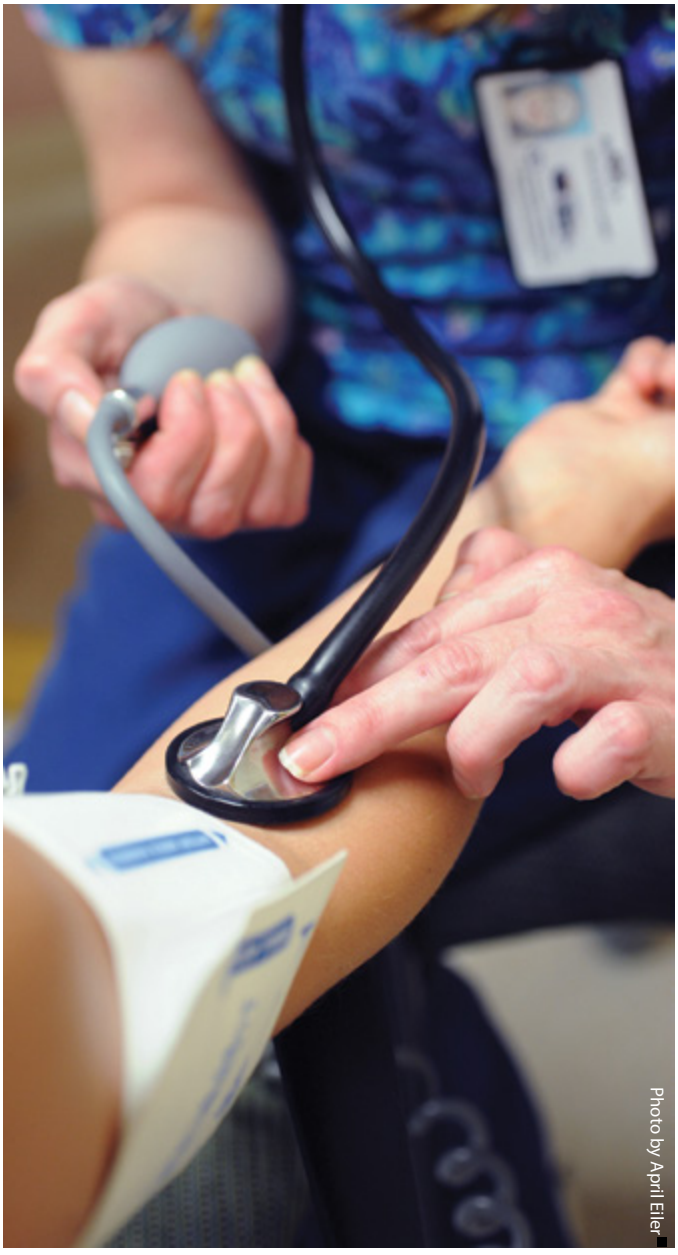
He adds that fish oil is a treatment that can potentially be very easily translated into everyday care. "It requires only a capsule or two, similar to a vitamin. Some people envision that they have to take a smelly fish oil syrup, like castor oil."

The researchers didn't examine the exact mechanisms behind fish oil's effect, but Yorek says it could relate to a lowering of inflammatory stress, or a more direct effect on the nervous system: It's possible the omega-3s in the fish oil boost the body's output of compounds that help protect or regenerate nerve cells.

(*Journal of Neurophysiology,* online Nov. 5, 2014) ★

Curbing hypertension: What works?

Group care, home telehealth, and other innovative approaches are driving steady improvements in blood pressure among VA patients, according to new research.



A variety of innovative treatment strategies are helping to improve blood pressure among VA patients, says a new study.

VA is getting better when it comes to managing Veterans' hypertension due to comprehensive, and sometimes creative, treatment methods. That's the gist of a new study aimed at quantifying the success of various behavioral interventions VA has in place to improve hypertension and blood pressure control.

Hypertension is the most common chronic condition in the VA population, affecting nearly 4 in 10 Veterans. It can lead to stroke and other deadly complications.

"High blood pressure can have all kinds of negative ramifications. It can exasperate existing comorbid conditions like diabetes," says Dr. Leah Zullig, a core investigator at the Center for Health Services Research in Primary Care at the Durham VA Medical Center in North Carolina. "It really is a silent killer, potentially decreasing people's lifespan, and it's easy to overlook because it can be symptomless at the early stages."

Zullig, also an assistant professor of medicine at Duke University, reviewed the results of 15 trials on hypertension control in VA. Specifically, she looked at what kind of behavioral interventions were in play at various VA facilities and what their success rates were.

The results appeared in the *Journal of Clinical Hypertension* in November 2014.

Behavioral interventions target modifiable risk factors

"When it comes to blood pressure and hypertension, there are things we can't control, like genetics. But with behavioral interventions, you're talking about diet, exercise, and other such factors

"At VA, we deal with complex patients, but we do so taking that into consideration."

that can make a difference in a person's health," says Zullig.

The indications overall are that VA is doing better at treating hypertension and controlling high blood pressure. Zullig cites a large VA study published in *Circulation* in 2012 that found that from 2000 to 2010, blood pressure control rates improved in VA from about 46 percent to 76 percent.

Part of that success, Zullig writes, is thanks to innovative behavioral approaches taken at many VA facilities. VA follows the Eighth Joint National Committee, or JNC-8, guideline for hypertension management, which uses the latest evidence to outline adult hypertension treatment. Nevertheless, there is flexibility within VA. Individual facilities may focus more on one treatment method over another.

"It really varies from institution to institution," says Zullig. "Durham might include telemedicine while another focuses more on group patient education. It's not always comparing apples to apples, and that's why this study is so important."

Group care a big hit

Zullig's research involved analyzing results from group hypertension treatment, self-monitoring by patients, medication-adherence plans, telehealth, early intervention, and even relaxation therapies.

"At VA, we deal with complex patients, but we do so taking that into consideration. The really successful treatments reflect that stance. They involve behavioral counseling, medication management, self-monitoring, and more. They address multiple issues."

While the solutions to high blood pressure and hypertension are as varied as the patients themselves, Zullig's research did identify common trends—such as increased frequency of contact. Also, group care was a big hit, with patients not only receiving access to clinical staff, but also having the opportunity to build peer support systems and friendships.

In one study involving 239 Veterans in North Carolina and Virginia with poorly controlled diabetes and hypertension, patients were assigned to seven- or eight-person groups led by a pharmacist, primary care internist, and nurse or other diabetes educator. Twelve months later, mean systolic blood pressure had improved by 13.7 mm Hg in group participants and by only 6.4 mm Hg in the usual-care patients.

Two other studies also evaluated group care. In one, four to eight participants underwent small-group training sessions for an hour. Led by a nurse, nutritionist, physical therapist, or pharmacist, the sessions proved more effective at controlling blood pressure than individual therapy, and at lower cost.

Other treatment methods involved nurse-administered home telehealth, remote monitoring, ramped-up education, personalized letters containing behavioral strategies, and more. According to Zullig, no matter how different the methods, they have one thing in common: an innovative mindset on the part of the providers, and a desire to improve Veterans' quality of life. ★

Photo courtesy of Portland VA Medical Center

Cody Goheen, a Navy Veteran who served in the Gulf War and today works as a research coordinator at the Portland VA, demonstrates the OtoID.

New device helps halt hearing loss for cancer patients

Some chemotherapy drugs can be toxic to cells in the ear, resulting in permanent hearing loss. A new device from Portland VA researchers catches the problem early on, so therapy can be adjusted.

When cancer strikes, doctors do what they can to save lives. Chemotherapy drugs are potent weapons against cancer cells, but they can have serious and permanent side effects. One of them is hearing loss.

Researchers at the VA Portland Health Care System have developed technology to help prevent this side effect. They call it the OtoID, and so far the system has been tested with the help of 110 volunteers, with promising results.

The technology itself doesn't treat the hearing loss caused by some chemotherapy drugs, but it enables patients to easily and reliably test their own hearing, so the first signs of damage can be caught early on.

In most cases, doctors will be able to adjust the dose of the drug, or perhaps use a different one.

"Our experience with [the oncology department] is that treatment regimens are changed, or less toxic drugs are substituted, when ototoxicity [toxic damage to the ear] is found and tumor response to the treatment has been good. This means that it is medically reasonable to change the regimen," says researcher Dr. Marilyn Dille. She says colleagues are now doing a formal study of how many patients have had their treatment plan changed thanks to the OtoID.

Dille and the project's other lead investigators, Drs. Peter Jacobs and Dawn Konrad-Martin, are all

with the Portland-based National Center for Rehabilitative Auditory Research. The center is funded by VA Rehabilitation Research and Development.

Right now, the team plans to have the device deployed mainly on chemotherapy wards, so cancer patients can get a pre-treatment baseline measure of their hearing and follow-up periodically to check for changes. The plan is for the OtoID to eventually be used by Veterans and others at home, as well.

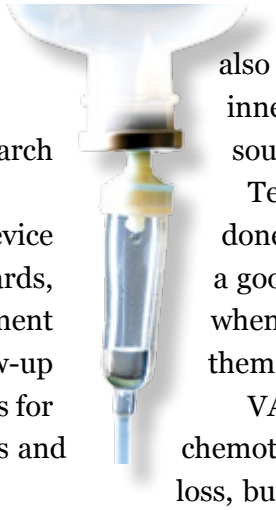


Photo: ©iStock/sippakorn

The system, which runs off a tablet such as an iPad, allows test results to be transmitted back to a VA clinic via a secure wireless network. Audiology staff can then enter those results into patients' electronic health records, for sharing with oncologists and other care team members.

The most common chemo drug linked to permanent hearing loss is cisplatin. The platinum-based drug is used to treat head, neck, and lung cancers, as well as other tumors.

Up to half of Veterans who receive the treatment will incur some permanent hearing loss, and up to 40 percent will experience tinnitus—ringing or other noises in the ear that can become highly distressing and debilitating.

Dille says that as cancer survival rates improve, health care providers are increasingly focusing on quality of life—both during treatment and afterward. That means easing side effects, both temporary and permanent, is more of a priority than in the past.

"Health-related quality of life is now a central goal of cancer treatment," she points out. "This patient-centered approach to oncological care is one reason why methods to reduce and manage ototoxicity are receiving increased attention."

First and foremost, the OtoID tests high-frequency hearing. That's the range where chemo-related damage typically occurs. Users listen to tones via headphones and use a touchscreen to indicate which tones they hear.

The latest version of the OtoID, now in the works, also tests low-level sounds produced within the inner ear, the cochlea, as it turns incoming sound into signals for the brain.

Testing these "otoacoustic emissions" can be done even while a patient sleeps. Dille says it's a good indicator of hearing changes, especially when patients' overall poor health prevents them from reliably completing standard tests.

VA oncologists recommend that chemotherapy patients be monitored for hearing loss, but it often doesn't happen. "Feedback from VA audiologists indicates that this is infrequently done, largely due to logistics relating to testing patients, and limited access to evidence-based, time-efficient tools and protocols," notes Dille. "The OtoID was developed to directly address these obstacles."

DoD partnering on other uses for OtoID

Asked if the technology might become obsolete if a new generation of less toxic chemo drugs emerges, Dille suggests there is likely to be a continuing need, even with improvements in care.

"Cancer treatment is always advancing," she acknowledges. "Certainly less toxic drugs would be an outstanding improvement. We hope that happens." But a more near-term development, she says, will likely be drugs designed to be given along with existing chemotherapy agents to prevent, lessen, or reverse the ear damage they cause.

"The OtoID will certainly be relevant for testing the efficacy of these pharmaceutical approaches, and for other uses, such as hearing conservation programs that monitor the hearing of workers and soldiers in excessively loud noise or explosion," says Dille. Her group recently provided the Department of Defense with two OtoID devices for this purpose.

With the help of VA's Technology Transfer office, the OtoID has a patent application in the works, and commercial partners are being sought to license and manufacture the system. ★

Photo by Cpl. Alejandro Pena/USMC

U.S. Marine Crops Cpl. Daniel Pritchett performs dumbbell incline presses in the fitness center on Camp Leatherneck in Helmand province, Afghanistan, in 2013. A new VA study aims to pinpoint the specific chemicals generated during exercise that boost brain health.

Could exercise bring some muscle **to the fight against Alzheimer's?**

Through an NIH Director's Transformative Research Award, a team of VA and Stanford investigators aims to find out what exactly it is about exercise that benefits the brain.

Exercise has long been sold as a cure-all for what ails us. Walk briskly and you might stave off Parkinson's disease. Exercise regularly and your chances of heart disease go down. Run a few miles on the treadmill and not only will your depression ease, you just might live longer. There are literally thousands of studies that show the health benefits of regular exercise.

Now VA and Stanford researchers are taking it a step further–studying what exactly it is about exercise that is so beneficial–in the hopes that this mystery factor might prove to be a fountain of youth, perhaps even preventing common aging-related diseases, like Alzheimer's and other dementias.

Dr. Tony Wyss-Coray and Dr. Thomas Rando, both research health scientists at the VA Palo Alto Health Care System and winners of a 2013 National Institute of Health Director's Transformative Research Award, imagine a world where the elderly, the infirm, and those with spinal cord or other debilitating injuries could take a medicine derived from the actual chemicals that exercise produces.

But how does working up a sweat in the gym, on the basketball court, or on the road exert such a positive influence on our brain? Finding out, according to Wyss-Coray, is the first step.

Muscles secrete molecules that benefit brain

"We know that during exercise muscles secrete molecules that are beneficial to the body and the brain," says Wyss-Coray. Within those molecules are hormones, growth factors, and small proteins called cytokines that are integral for cell signaling. "We can see them, but they've never been really studied in a systematic fashion to tie the factor to an effect," he says.

Wyss-Coray and Rando plan to use a technique known as parabiosis to couple the circulatory systems of physically active mice with those of mice that are less active. "If we take the blood of an exercised animal and inject it into an unexercised animal, we should see positive effects," says Wyss-Coray.

> "Today many of us are almost completely sedentary. What effect does that have on our brains?"

The duo, also Stanford University professors, plan to then analyze the blood to identify what factors are responsible for the changes. According to Wyss-Coray, it stands to reason that if a certain molecule results in positive changes within the brain and body when it is present, then deleting it should have the opposite effect.

"It gets to the question of what normal is," says Wyss-Coray. "Thirty-thousand years ago humans were doing a lot of running around. Today many of us are almost completely sedentary. What effect does that have on our brains? And as we age and can no longer exercise, or when we're sick, or injured, such as Veterans with spinal cord damage, what are the consequences of being immobilized?"

Building on past research

The new study isn't entirely different from one published by Wyss-Coray and others in the journal *Nature Medicine* in June 2014 that showed blood from young mice could reverse cognitive aging in older mice. That study followed up on centuries of speculation about the effect young blood can have on the elderly. Now, says Wyss-Coray, the focus isn't just on young blood in general, but on the specific factors in the blood that have an effect on the brain.

"We're talking about possible epigenetic changes in the brain. Exercise releases these molecules and, at the DNA level, they reprogram tissue in the brain, making it more active, resistant to detrimental factors, essentially, making it younger," says Wyss-Coray. "Now ultimately, if we can isolate the factors and produce them, we'll be able to treat any number of ailments." ★

Illustration: ©iStock/Henrik5000

Alzheimer's research in VA

In the 1970's VA began planning to meet the challenges of caring for aging World War II Veterans. VA research leaders developed Geriatric Research, Education and Clinical Centers (GRECCs) to increase basic knowledge of aging and the diseases commonly associated with growing older.

Today, there are 19 GRECCs at VA facilities throughout the nation. Their research staffs publish hundreds of peer-reviewed articles on aging, and provide thousands of hours of geriatric education. Many of these articles are on diseases commonly related to aging, including Alzheimer's disease.

To read more about Alzheimer's research underway at GRECCs and at other VA sites nationwide, visit www.research.va.gov/topics.

Study of guardsmen ties **deployments to risky driving**

In a study of Ohio guardsmen, prior deployment was associated with increased rates of drinking and driving, passing on the right, running red lights, and ignoring seatbelts.

Just inside the main gate at Fort Campbell, Ky., home of the Army's famed 101st Airborne Division, is a large sign counting the days between fatalities. Reach 101 death-free days, and the soldiers receive a day off. But these aren't combat fatalities. The sign is counting motor vehicle accidents, and unfortunately, the days off are few and far between.

"Motor vehicle accidents are a leading cause of death and disability in U.S. military populations," says Dr. Katherine Hoggatt, a research health scientist at VA's Greater Los Angeles Center for the Study of Healthcare Innovation, Implementation, and Policy. "And recently deployed soldiers and Veterans may have particularly high rates of risky driving."

The soldiers in the 101st receive post-deployment training on risky driving, as well as safety briefs and near-constant reminders about the hazards they face on the road. The Army even distributes a brochure titled "Post-Combat Driving: The American Road." The brochure includes a self-assessment, statistics on risky driving among returning soldiers, and mitigation techniques based on the recommendations of fellow soldiers.

Photo: ©iStock/aijohn784

But not every soldier returning from deployment has such a robust support system. "There haven't been many studies into risky driving behavior among National Guard soldiers and reservists," says Hoggatt, also an adjunct assistant professor at UCLA. "They've played a large role in active military operations and may actually be at greater risk of deployment-related stress and mental health problems than their active duty counterparts."

Driving study included more than 2,600 guardsmen

Hoggatt and her colleagues set out to research risky driving behavior and its relationship to mental health conditions and deployment-related trauma among members of the Ohio Army National Guard. The findings appear in the Jan. 2, 2015, issue of the journal *Traffic Injury Prevention*.

The study included data from 2,616 Ohio Army National Guard soldiers who answered questions such as:

- How often do you use seat belts when you drive or ride in a car?
- In the past 30 days, how many times have you driven when you've had perhaps too much to drink?
- In the past year, have you disregarded speed limits late at night or early in the morning?

Responses to these and a handful of other questions were then analyzed against combat-related trauma, PTSD, alcohol and drug use, and other mental illnesses. Overall, 12 percent reported rarely using a seatbelt or drinking and driving in the last 30 days, 25 percent reported disregarding speed

Nicholas Bartolomeo, who served three tours with the Marines in Iraq and now works at VA's Center of Innovation on Disability and Rehabilitation Research in Gainesville, Fla., demonstrates a driving simulator.

limits, and 26 percent reported passing cars on the right often.

Deployment to a conflict was associated with an increased rate of drinking and driving, passing on the right, running red lights, and ignoring seatbelts. Although there was some variability, these risky driving behaviors were more common for Veterans with exposure to a greater number of deployment-related traumatic events.

"There are several theories for why Veterans may engage in risky driving after deployment to conflict areas," says Hoggatt. "One is that they're continuing learned driving behaviors that were actually helpful in combat situations. Another is that they might be predisposed to risky behavior, as evidenced by their volunteering for combat-related jobs in the first place, or they may be recreating feelings experienced in high-stress combat environments. Risky driving might also be a consequence or expression of other mental health conditions that are exacerbated after deployment."

Hoggatt believes more research is needed to understand the effect of deployment on risky driving across different military populations. At the same time, there are already initiatives to address risky driving among Veterans.

"VA and the Defense and Transportation departments have developed driving programs tailored for a young military audience, and VA researchers can do further testing to see how we can get the message to soldiers as early and effectively as possible," says Hoggatt. "We pay a lot of attention to various mental health consequences and hazards for soldiers returning from combat—risky driving is a big one, but it can be prevented." ★

VA, University of Florida use simulators to study effects of TBI, PTSD on driving

In 2009, VA announced that motor vehicle accidents were the primary cause of death for recently returned Veterans. To help reduce the number of driving fatalities, researchers across VA have studied a number of variables, from posttraumatic stress to increased drinking.

Now researchers at the North Florida South Georgia Malcom Randall VA Medical Center, in conjunction with the University of Florida, plan to study the effectiveness of a new occupational therapy driving intervention program on Veterans with TBI, PTSD, or depression. The study will use the DriveSafety CDS-250 simulator mounted in a Dodge Sprinter van and focus on Veterans with mild traumatic brain injuries.

Considered the hallmark injury of the wars in Iraq and Afghanistan, traumatic brain injuries have been found to have a variety of long-lasting and often subtle effects on Veteran health. Unfortunately there is very little research on how TBI can affect future driving behavior or how those with certain injuries respond to traditional traffic safety education.

The study is an extension of earlier research conducted in Gainesville with the STISM M500W fixed-base driving simulator. It compared the driving habits of 18 post-deployment combat Veterans with those of 20 participants who had no combat experience. In that study, combat Veterans made more critical driving errors than their peers, particularly when it came to reckless behavior such as speeding. The work was published in July-August 2011 in the *American Journal of Occupational Therapy.*

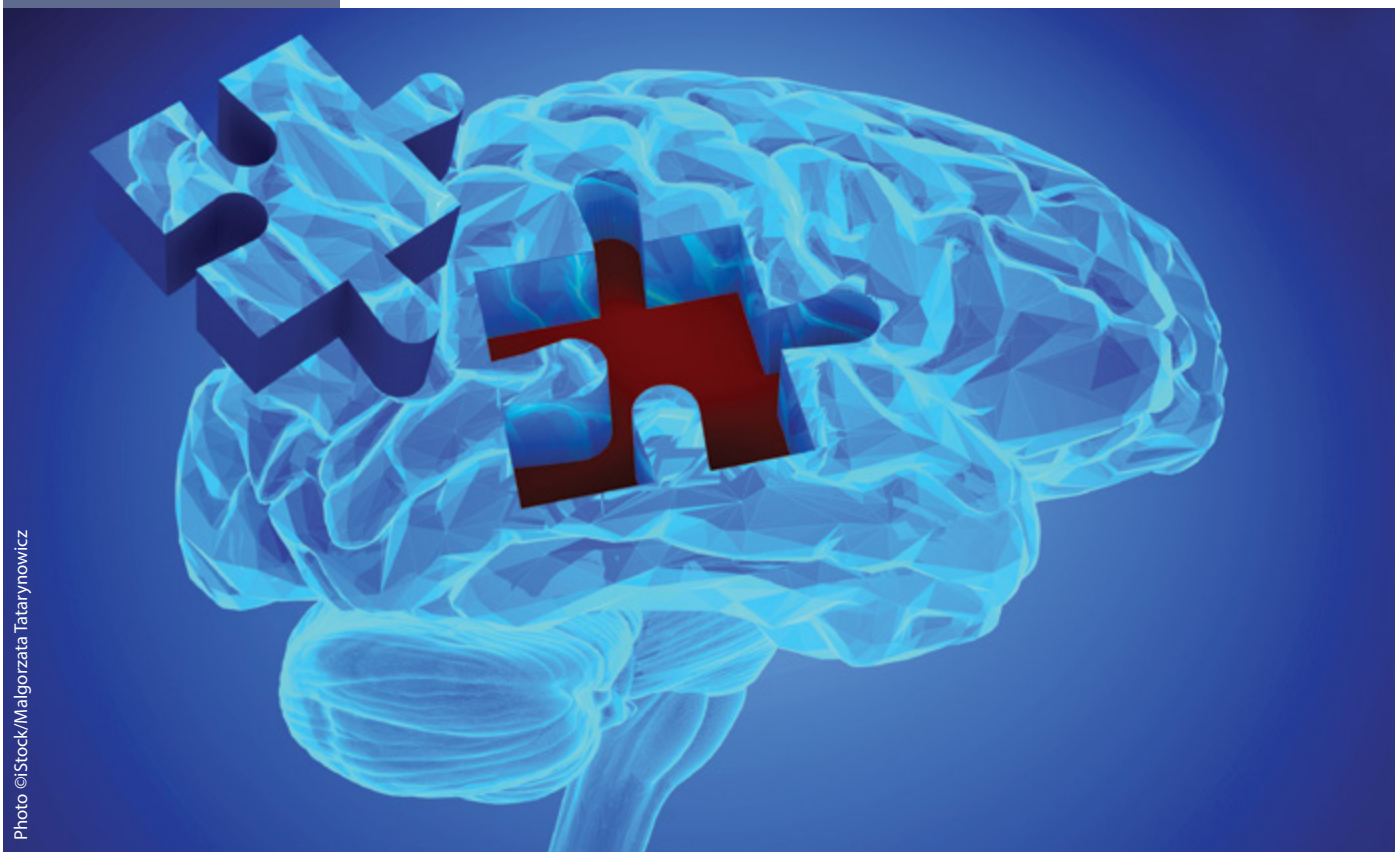


Photo ©iStock/Malgorzata Tatarynowicz

A natural hormone called oxytocin may help restore aspects of social function in people with schizophrenia.

'Love hormone' may have role in schizophrenia therapy

According to a group with VA and UCLA, oxytocin—produced in the brain and sometimes called the "love hormone"—may play a key role in improving the ability of people with schizophrenia to understand others' emotions.

Trust. Empathy. Loyalty. Connection.

These are all good things in human relationships. Can doctors give a drug that increases these qualities?

If there is such an elixir for the social brain, it may just be a natural hormone called oxytocin (not to be confused with the pain drug OxyContin). Because of oxytocin's wide-reaching effects on human bonding and intimacy—both romantic and maternal—it's sometimes called the "love hormone."

Scientists are still learning more about how the hormone works on human emotions, and who might benefit from the substance, which is made naturally in the brain's hypothalamus. It's not yet available as an approved brain treatment in the U.S.

According to research at the VA Greater Los Angeles Healthcare System and the Semel Institute for Neuroscience and Human Behavior at the University of California, Los Angeles, one use for the hormone may be helping those with schizophrenia.

A study involving 27 Veterans and others with schizophrenia showed that oxytocin, delivered via nasal spray to the brain, boosted empathic accuracy—the ability to understand the emotions of others. The study was published in 2014 in the journal *Neuropsychopharmacology*.

Empathic accuracy is impaired in many people

with schizophrenia, says psychiatry researcher Dr. Stephen Marder, with VA and UCLA.

"People with schizophrenia often have deficits in social cognition," he says. "That includes things like being able to recognize emotion in what others are saying, or in their facial expressions, or to recognize sarcasm. This has profound effects on their ability to adjust in the community. It affects their ability to work, to go to school, to develop social relationships."

Oxytocin boosted social skills training

Marder's group didn't administer oxytocin as a primary treatment. Rather, they used it as an add-on to a form of social cognitive training. The nasal spray improved outcomes of the training—particularly in an area in which the training by itself is not as effective.

The 12-session training program was developed a few years ago by Marder's colleagues Drs. Michael Green and Bill Horan. Basically, it teaches people with schizophrenia how to pick up on social cues and read the emotions of others. When those emotions are expressed in more abstract, non-visible ways, that's precisely where patients have trouble—and where the oxytocin made a difference.

"These programs tend to be effective in teaching cue detection—being able to recognize emotion in faces. Where the programs are not as effective is in teaching 'mentalizing'—putting yourself in others' shoes, empathizing.

"In our study we provided training in both cue detection and empathy. In the cue detection, we didn't find an effect from oxytocin, but we didn't need it. The patients learned it anyway. The training itself is effective in imparting that. Where we did find effects was on the measure we call 'empathic accuracy.' That's where the training by itself, without the oxytocin, didn't affect performance."

Video clips help test empathic accuracy

How does Marder's team measure empathic accuracy? They show video clips of volunteers telling stories about real personal experiences—either happy, such as a vacation, or sad, such as the loss of a loved one. The volunteers themselves rate the emotions on a scale. After watching the clips, the training participants rate the same experiences. Typically, even after the unenhanced social skills training, their responses are off the mark.

"This is an area where patients improved only if they received oxytocin," relates Marder. "Those who got no oxytocin showed no improvements in that area."

Marder's team is now exploring the effects further. For one thing, they're pursuing lab work to pinpoint the biochemical pathways that oxytocin affects. On another front, they want to see how far the hormone can go as an adjunct treatment—how much of an impact it can have on the everyday lives of those with schizophrenia. The results could also be relevant for those with autism, who also lack empathy. That itself is a hot area in oxytocin research.

"We want to do a larger study and understand how to better exploit this property," says Marder. "If we can improve empathic accuracy in a study setting, will that extend into the community? It's an important question." ★

More facts about oxytocin

- Oxytocin is released in large amounts in women's bodies during labor, and when their nipples are stimulated. It helps make childbirth and breastfeeding easier.
- The hormone, known by the brand name Pitocin, is injected directly into the uterus to start or strengthen birth contractions for some women.
- Animal research in the 1990s and early 2000s documented the role of oxytocin in monogamous behavior—staying loyal to mates.
- Oxytocin is being explored for a range of potential psychiatric uses, from autism and schizophrenia to social phobia, anxiety, and postpartum depression.

Photo courtesy of VA Summer Sports Clinic

Veterans from across the country participated in the 2014 National Veterans Summer Sports Clinic in San Diego. Along with camaraderie, the annual event provides an introduction to a variety of adaptive sports.

Social support holds little sway in **PTSD treatment-seeking**

It seems logical that people with PTSD who have strong social support would be more likely to seek out treatment. New research suggests that might not be the case.

When it comes to posttraumatic stress disorder, strong social support can often mean the difference between recovery and deterioration. Research has consistently shown that a person's social network—that is, the people he or she can rely on—can play a mitigating role in both PTSD development and severity.

It stands to reason, then, that people with PTSD and strong social networks would be more likely to seek treatment and get help. But new research suggests that might not be the case.

A recent study, published in January 2015 in the journal *Psychiatric Services*, suggests that social support, on its own, has little impact on whether someone with PTSD chooses to seek treatment. More important are the severity of the PTSD; demographic factors like age or marital status; and whether the patient has any other illnesses.

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"PTSD is treatable, and social support is such an important resource."

Study based on more than 2,800 people with PTSD

"This isn't about developing PTSD," says Dr. Rebecca Sripada, a postdoctoral fellow with VA's Serious Mental Illness Treatment Resource and Evaluation Center and the University of Michigan. "We know that lack of social support is associated with an increased likelihood of developing PTSD and with greater severity of PTSD symptoms. What we weren't sure of was how that translated to care. Does having good social support lead individuals with PTSD to seek care?"

The answer, it would seem, is not really. While social support can play a role in whether or not people develop PTSD in the first place, and can play a role in easing symptoms, it may not influence them to seek treatment.

The study involved more than 2,800 people with PTSD from the National Epidemiologic Survey on Alcohol and Related Conditions. In the survey, participants rated their social support on a 12-point scale by indicating their agreement with statements such as, "If I were sick, I know I would find someone to help me with my daily chores," or, "If I wanted to go on a trip for a day, I would have a hard time finding someone to go with me."

Sripada's team calculated the association between level of social support and the likelihood of receiving treatment for PTSD, and adjusted for sociodemographic information. Sripada says sociodemographic factors appeared to play a significant role, but social support did not.

Mobilizing family members and friends

"Traits like age, household income, marital status, geographic region, and race did play a part in whether or not a patient sought treatment for PTSD," she says. Traits linked to a greater likelihood of seeking treatment included having higher education or greater income; being divorced, separated, or widowed; and having greater PTSD severity.

Interestingly, because one of the symptoms of PTSD is withdrawal, symptom severity may adversely impact social support. So worsening PTSD symptoms may result in diminishing social support.

In any case, say the researchers, understanding the role of family, neighbors, and peers is integral to helping Veterans with PTSD manage their symptoms, and to improving treatment rates.

"PTSD is treatable," Sripada says, "and social support is such an important resource. The key is to mobilize [family members or friends], to educate them, so that they encourage their loved ones to get needed care." ★

Veterans enjoy each other's company during VA's 2013 Summer Sports Clinic.

Photo by Larry Gildstad

Rosario Carballo demonstrates the placement of electrodes on Herblay Alonso. Both are on staff at the Epilepsy Center of Excellence at the Miami VA Medical Center.

Study on VA epilepsy centers shows improvements in **access, quality of care**

Preliminary results from a four-year study of VA's 16 Epilepsy Centers of Excellence show the model is working.

Preliminary results from a four-year study of VA's 16 Epilepsy Centers of Excellence (ECOEs) show improvements in Veterans' access to high-quality epilepsy care.

As the result of a 2008 congressional mandate, there are now 16 integrated but geographically dispersed VA facilities designed to treat epilepsy. The centers serve as hubs for their regions, housing expertise and equipment that more rural facilities often lack.

With their focus on regional, coordinated care and interaction with rural physicians, the ECOEs represent a major transformation in the way epilepsy care is delivered, says Dr. Mary Jo Pugh, a research scientist at the South Texas Veterans Health Care System who has been leading the study of their effectiveness.

"The model does appear to be successful," says Pugh. Although the final results of the study won't be available for another six months to a year, Pugh says her research has revealed improvements in access to care, and quality of care.

Condition affects around 1 percent of VA patients

Around 1 percent of VA patients have epilepsy. Older patients are more at risk. Also, studies have now shown that traumatic brain injury can be a significant factor for new-onset epilepsy in younger Veterans.

One such study was published by Pugh's group earlier this year in the *Journal of Head Trauma and Rehabilitation*. "We found the more severe the TBI, the stronger the association with epilepsy," says Pugh. "Even mild TBI is associated with epilepsy."

Pugh says the impact of epilepsy is profound, requiring coordinated care to reduce or eliminate seizures and deal with comorbid conditions.

"If your epilepsy isn't under control, you typically can't drive, have difficulty becoming employed—especially in jobs many young Veterans seek—and quality of life is an issue," says Pugh. "You're afraid to do things and that can affect not only the patient, but also the family. Even people with controlled seizures have higher-than-expected rates of anxiety and depression. Those with uncontrolled seizures can also have cognitive deficits. It is a complex condition requiring coordinated care with a variety of specialists."

For the study, Pugh and her team reviewed the records of Veterans diagnosed with epilepsy from 2008 through 2014. "We were able to collect data both before the implementation of the ECOEs, and after they were fully implemented," she says. By comparing access and quality-of-care outcomes across time, the study should reflect how the program is doing at improving care for Veterans.

Opportunity to identify best practices

From Albuquerque to Gainesville and back up to Baltimore and Seattle, the 16 ECOEs have established relationships with outlying facilities, connecting epilepsy specialists in the ECOE hubs with general neurologists and other epilepsy specialists in the other locations.

"They've done a great job of leveraging the 16 hubs," says Pugh. "Each region has developed their areas of expertise to expand care beyond their own facilities. These connections among clinicians are really important because they build trust and increases referrals, as well as Veterans' access."

More recently, there has been an emphasis by the ECOE clinicians on enhancing mental health services for Veterans with epilepsy—a critical component, since roughly half of Veterans with epilepsy have a comorbid mood disorder.

An even newer focus, identified in December 2014 at the American Epilepsy Society ECOE consortium meeting, is health issues among women with epilepsy. "These are important strides made with a relatively small investment by VA," says Pugh.

"There isn't much known about the quality of care for epilepsy," she adds. "This [study] is unprecedented. Non-VA care for epilepsy is very fragmented, so this is an opportunity to identify best practices and implement them in a nationwide setting." ★

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"[Epilepsy] is a complex condition requiring coordinated care with a variety of specialists."


Photo by Daniel DuVerney/Hines Media Service

Dr. Elly Budiman-Mak administers the Foot Function Index to Ron Hollingsead, who served in the Marines during the Vietnam War.

Index of foot health, developed in VA, has legs worldwide

A brief user-friendly measure of foot health and function, developed by a VA research team in the 1980s, has caught on worldwide among clinicians and researchers. It's been translated into 20 languages.

Dine fodsmerter nar de er vaerst.

Don't worry if you didn't understand that first line. It's Danish for "your foot pain at its worst."

Patients in Denmark who have foot problems can now rate their pain and disability—responding to 23 brief questions in all, each on a scale of 1 to 10—using the Foot Function Index.

The index was developed by VA researchers in the 1980s. It's now been translated into 20 languages—Danish being the latest addition. From Italy and Iran to Turkey and Taiwan, the form is used around the world as a reliable measure of patients' foot health. It applies to patients of all ages and backgrounds, across all types of foot problems.

Dr. Elly Budiman-Mak, with VA's Center of Innovation for Complex Chronic Healthcare, led the effort to develop the index in the 1980s.

"We developed the FFI because there was no outcome measure for foot health and functioning in 1984," she says. "At the time we were working on a

VA-funded study to prevent arthritis foot deformity. We wanted to measure outcomes, so we developed this very useful instrument."

Measure underwent extensive testing

Budiman-Mak says the index may seem simple, but it required much tedious and methodical work. Her team crafted the questions based on input from patients and clinicians. They then field-tested and validated the measure over a few years with different groups of patients.

The measure has three parts. The first part asks about pain, covering several situations: with or without shoes, for example, or in the morning versus the evening.

The second part focuses on disability. It asks patients to rate their difficulty walking in different settings, and going up or down stairs.

The third part asks about limits on activities. For example: "How much of the time do you stay in bed because of [pain in your feet]?"

There are lots of patient self-report measures used by foot surgeons, orthopedists, physical therapists, and other clinicians, but the FFI is one of the favorites worldwide. Budiman-Mak believes it has caught on in large part because of its ease of use and versatility.

'Very easy to apply to patients'

"The instrument is short, user-friendly, and it's written in the English language at the 8th-grade level," she says. "Therefore, it's clinically very easy to apply to patients."

The design, Budiman-Mak points out, is based on the International Classification of Functioning, Disability and Health, a framework developed by the World Health Organization to measure health and disability in individuals and populations.

A revised version of the FFI, developed in 2006, added some psychosocial questions, focused on foot-related quality of life. Now, both the original and the revised version are in wide use. ★

VA rheumatoid arthritis trial **earns Howley Prize**

The National Arthritis Foundation awarded its 2014 Lee C. Howley Sr. Prize for Arthritis Research to the team of investigators who published a study last year titled "Therapies for Active Rheumatoid Arthritis after Methotrexate Failure" in the *New England Journal of Medicine*.

The foundation gives the prestigious award each year to a study team who have "significantly advanced understanding, treatment or prevention of arthritis and related disease," and whose work "will lead to a faster cure."

The study was funded by VA's Cooperative Studies Program and conducted in partnership with the U.S. National Institutes of Health and its Canadian counterpart, the Canadian Institutes for Health Research.

Trial compared second-line treatments

The trial involved 353 patients with rheumatoid arthritis, all of whom had not responded adequately to a common first-line treatment for the disease, methotrexate (sold as Rheumatrex or Trexall).

The drug is considered a "disease-modifying anti-rheumatic drug" (DMARD) because it not only eases pain and swelling, but can also decrease actual joint damage and slow disease progression.

The study compared two follow-up therapies for these patients, both involving methotrexate plus other medications.

The findings suggest that first a relatively inexpensive triple therapy should be tried, consisting of methotrexate plus two other DMARDS: sulfasalazine and hydroxychloroquine. For patients who don't get enough help this way, the authors recommend switching to a more costly regimen consisting of methotrexate plus etanercept (sold as Enbrel, Amgen), an injectable drug that belongs

A group at the VA Boston Health Care System was instrumental in conducting a large multisite VA trial on rheumatoid arthritis that has been recognized by the National Arthritis Foundation for its impact on care.

to a class of agents known as "biologic response modifiers," or simply "biologics." These drugs are genetically engineered proteins that disrupt the body's inflammation process.

Study provided 'critically important insights'

Importantly, the study showed that the less costly triple therapy can do the job for many patients, without the need for the more expensive "biologic" treatment.

The authors wrote, "Our findings suggest that a strategy of first administering triple therapy, with a switch to etanercept-methotrexate in patients who do not have an adequate response to triple therapy, will allow a substantial percentage of patients to be treated in a more cost-effective way without adversely affecting the clinical outcomes."

The study was coordinated through the Cooperative Studies Program Coordinating Center at the VA Boston Health Care System. Staff here substantially contributed to the design, execution and analysis of the trial, which took place at 16 VA medical centers, along with other sites in the U.S. and Canada.

The study chairperson was Dr. James O'Dell, chief of the University of Nebraska Medical Center division of rheumatology and immunology, and chief of rheumatology at the Omaha VA Medical Center.

Experts in the field praised the research. Dr. David Wofsy, of the University of California, San Francisco, said the trial "was a true tour de force of investigator-initiated collaborative research that provided critically important insights into one of the most important clinical challenges in the field of rheumatology."

The study findings were also cited as an important clinical advance at the 2013 Annual Scientific Meeting of the American College of Rheumatology and given special mention in the recent *Annals of Internal Medicine* "Update in Rheumatology." ★

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February is American Heart Month, and few Americans have had as great an impact on heart care as Dr. Michael E. DeBakey (1908 – 2008), in whose honor the Houston VA Medical Center is named. The top surgery consultant for the Army during World War II, DeBakey led or played a major role in the development of many life-saving surgical techniques and devices, including open-heart surgery, arterial grafts, and the artificial heart. He also helped develop the Mobile Army Surgical Hospital, or MASH, and helped lay the groundwork for the expansion of VA research after World War II. One medical historian described him as the greatest physician of the 20th century.

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