

VA

RESEARCH CURRENTS

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



Inroads in diabetes prevention 6

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WHAT'S INSIDE

Fast Findings 2



PTSD nightmares: Is there an effective treatment? 8



A potential grape-based cancer therapy 10



Technology helps upper-limb amputees regain a sense of touch 13



Study links antibiotics with diabetes risk 14



Large genome study leads to better understanding of high blood pressure 16




VA trial testing cannabis-derived compound for PTSD 18



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Any health information in this newsletter is strictly for informational purposes and is not intended as medical advice. It should not be used to diagnose or treat any condition.

Long-term posttraumatic stress tied to changes in brain structure

Posttraumatic stress symptoms can persist decades after trauma exposure and are linked to lower hippocampal volume, according to a study featuring VA San Diego Healthcare System researchers. The study assessed PTSD symptoms in 247 men at two times: when each man was an average age of 38, and again when they were an average age of 62. Participants were Veterans who served during the Vietnam era and had experienced trauma before the first assessment. At the first time point, 8 percent of participants met criteria for presumptive PTSD. At the second time point, 6 percent did, showing that PTSD symptoms remained mostly stable over the 24-year period. Posttraumatic stress symptoms at both times were linked to lower volume of the hippocampus and other brain regions. Participants who had worse symptoms at time 2 had smaller hippocampal volume than they had at time 1. The study confirms what other research has shown, that posttraumatic stress symptoms are present years after trauma, even in the absence of a PTSD diagnosis. The results show that this symptom persistence is highly related to changes in brain structure, say the researchers. (*Brain Imaging and Behavior*, March 4, 2019)



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TBI and PTSD increase tinnitus risk

Traumatic brain injury and PTSD increase the risk for tinnitus, found a VA San Diego Healthcare System study. Tinnitus refers to hearing sound—such as ringing in the ears—when no external sound is present. Researchers assessed the hearing of 2,600 Marines before and after combat deployment. They found that both PTSD and TBI, particularly blast TBI, were linked to worsening tinnitus. Tinnitus progression also increased with hearing loss. Pre-deployment tinnitus was also likely to continue or worsen after deployment. Screening for PTSD, TBI, and hearing loss may allow for more focused treatment for tinnitus, say the researchers. (*Military Medicine*, Feb. 22, 2019)



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Study sheds light on pesticides-Alzheimer's link

A team including two VA researchers have found a possible mechanism for how exposure to pesticides increases the risk of Alzheimer's disease. Occupational exposure to organophosphate pesticides—such as experienced by agricultural workers—has been shown to increase the risk of Alzheimer's disease. The researchers exposed rats to the chemical chlorpyrifos to simulate this pesticide exposure. Exposure resulted in dysregulation of microglial cells (a type of cell involved in the immune defense of the brain and spinal cord). Exposed rats showed accelerated neurodegeneration. The neurodegeneration was more severe in male rats,

and only male rats showed cognitive impairment over 20 months. The results suggest that future treatments to preserve or restore the microglia could help prevent Alzheimer's disease in people exposed to pesticides, according to the researchers. (*NPG Aging and Mechanism of Disease*, Jan. 22, 2019)



Testosterone replacement with exercise boosts muscle mass after spinal injury

Low-dose testosterone replacement therapy paired with resistance training can lead to improved muscle mass and health in spinal-cord-injured patients, according to a Hunter Holmes McGuire VA Medical Center study. Loss of muscle mass is often a problem in patients with spinal cord injury. Patients underwent twice-weekly resistance training for 16 weeks, using ankle weights and electrical stimulation to activate the paralyzed muscles in their legs. They were also given testosterone

replacement therapy via a patch. Patients receiving both testosterone and resistance training had improved body lean mass, muscle mass, and knee extensor strength. The patients also showed trends in less body fat, increased metabolic rate, glucose effectiveness, and inflammatory response. The results suggest that low-dose testosterone replacement therapy could ease the negative muscle and metabolic effects of spinal cord injury. (*Journal of Neurotrauma*, Feb. 22, 2019)



Loved ones' support helps keep Veterans in PTSD treatment

Support of loved ones is important to keeping Veterans from dropping out of PTSD treatment, found a Minneapolis VA Health Care System study. Researchers interviewed Veterans undergoing prolonged exposure therapy or cognitive processing therapy—two forms of psychotherapy considered the gold standard for PTSD care—at four VA medical centers. They found that Veterans whose loved ones encouraged them to participate in treatment and face distress were twice as likely to remain in PTSD treatment, compared with those without such support. The

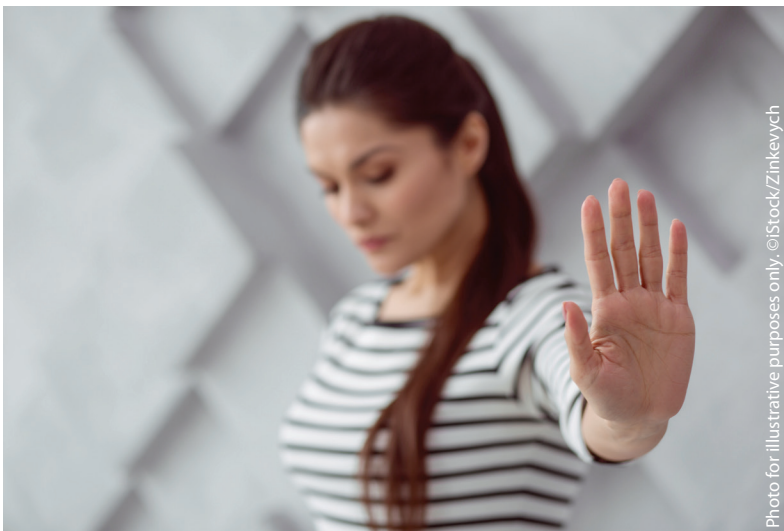
researchers concluded that providers should routinely assess how much support for treatment Veterans are getting at home. (*Journal of Consulting and Clinical Psychology*, March 2019)



Rat study: Brain injury can cause PTSD without psychological stressors

A mouse study by James J. Peters VA Medical Center researchers found that PTSD can occur after a traumatic brain injury even without a corresponding psychological trauma. PTSD and TBI often occur together in Veterans, but it is difficult to separate their effects. The researchers exposed rats to repetitive low-level blasts while the rodents were under anesthesia. The rats showed anxiety and PTSD-like behavior for at least nine months after the exposure, even though they had been spared significant psychological stress because of the

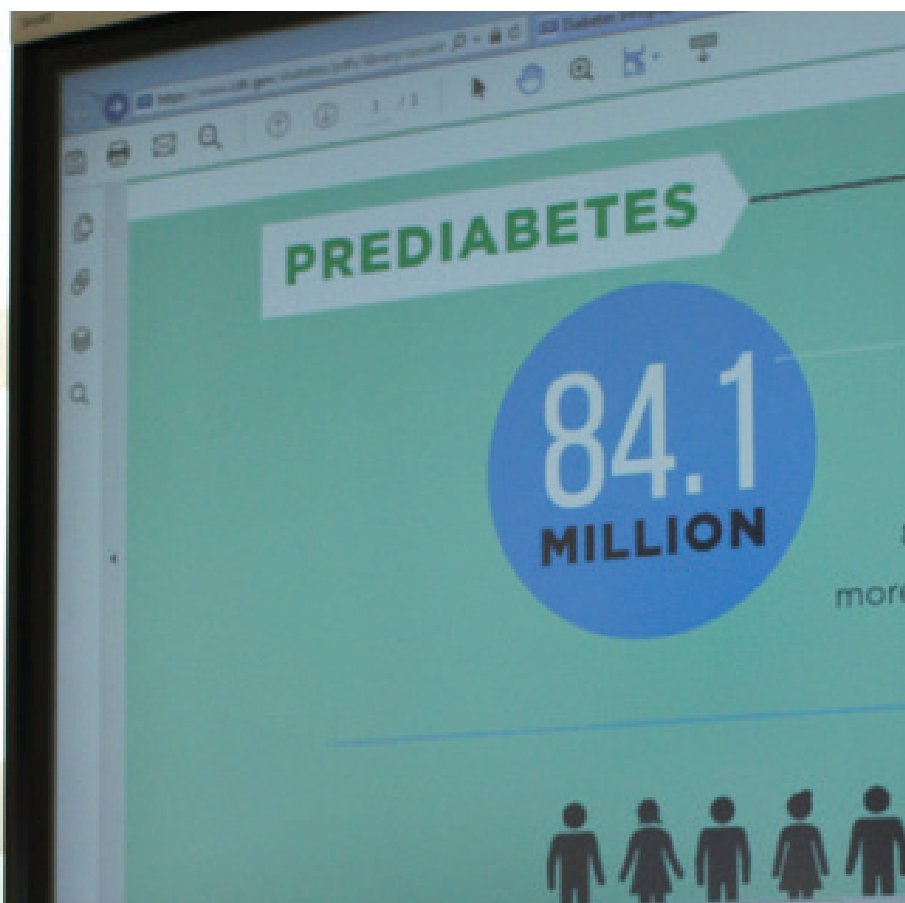
anesthesia. Exposing the rats to predator scent stress months after the blast exposure also caused a PTSD response. This showed the researchers that mild TBI may make the brain more sensitive to future psychological stress. The researchers also found that a specific experimental compound reversed PTSD-related behaviors in the blast-exposed mice, suggesting that it could one day be used to treat such injuries in humans. (*Neuropharmacology*, February 2019)



Harassment of women Veterans by male Veterans common at VA medical centers

Harassment of women Veterans by male Veterans at VA medical centers is prevalent, found a VA Greater Los Angeles Health Care System study. Researchers surveyed more than 1,000 women Veterans who used VA health care at any one of 12 facilities. One in four women said they experienced inappropriate or unwanted comments or behavior from male Veterans on VA grounds. The negative interactions included catcalls, sexual remarks, and denigration of

Veteran status. Reports of harassment were more common among women with histories of military sexual trauma; other trauma exposure; anxiety, depression, or PTSD; and poorer health. Not surprisingly, women experiencing harassment were significantly less likely to feel welcome at VA and were more likely to not feel safe. Importantly, they were also more likely to delay or miss care. More efforts are needed to make VA health care facilities more inclusive, welcoming, and respectful of women Veterans, say the researchers. (*Women's Health Issues*, Jan. 24, 2019)



Dr. Tannaz Moin, an endocrinologist at the VA Greater Los Angeles Healthcare System, led a study comparing different approaches to weight loss and diabetes prevention.

Online program helps Veterans lose weight, potentially prevent diabetes

VA researchers compared an online version of the Diabetes Prevention Program to an in-person DPP and to MOVE!, VA's flagship weight management program.

More than 80 million adults in the United States have prediabetes, meaning their blood sugar levels are elevated to the point where they may be at risk for full-blown Type 2 diabetes. Diabetes, a chronic condition in which the body is not properly making or using the hormone insulin, is a leading cause of blindness, kidney disease, amputation, and death.

A major risk factor for diabetes is obesity. Nearly 80 percent of Veterans in the VA health system are overweight or obese.

With research showing it's possible for people with prediabetes to prevent or delay diabetes by improving diet, losing weight, and exercising more, VA researchers tested the effectiveness of an online version of the Diabetes Prevention Program (DPP) that features those three elements. They compared the online DPP to an in-person DPP and to MOVE!, VA's flagship weight management program. Those participating in the study were overweight or obese Vets with prediabetes.

The Veterans in the online DPP lost an average of 10.6 pounds at six months and 8.08 pounds at one year, compared with 2.4 pounds at six months and 0.2 pounds at one year for the MOVE! participants. There was no statistically significant difference in weight loss between the Vets in the online and in-person DPP groups, prompting the researchers to conclude: “An intensive, multifaceted [online] DPP intervention may be as effective as in-person DPP and help expand reach to those at risk.”

Dr. Tannaz Moin, an endocrinologist at the VA Greater Los Angeles Healthcare System, was the lead author of the study. It appeared in the *American Journal of Preventative Medicine* in November 2018. This is the first time, she says, researchers have compared the online DPP to the in-person DPP and to MOVE!, which is also an in-person program. The online and in-person DPPs included essentially the same key program elements: emphasis on a low-fat diet focusing on seven percent weight loss, at least 150 minutes of moderate physical activity per week, such as fast walking, and a calorie-reduction goal that depended on the starting weight of the participant.

Veterans keep each other accountable in online program

Moin and her team weren't surprised that the online and in-person DPPs, which follow recommendations made by the U.S. Centers for Disease Control and Prevention (CDC), led to similar degrees of weight loss. Both programs included identical features that helped to engage the participants: a human coach who gave one-on-one feedback; the regular delivery of educational materials on healthy eating and exercise to build skills and confidence toward achieving weight-loss goals; and closed group sessions in which

the same participants maintained physical activity and diet logs and kept each other accountable.

Closed groups and self-monitoring, including dietary and physical-activity logging, are key components of the CDC standards in the DPPs.

Unlike the in-person DPP and MOVE! programs, the online DPP offered features that increased flexibility and convenience for the Veterans. Online participants could remotely connect to the program at any time., and a human coach monitored online

group interactions and gave feedback to the Veterans. The participants interacted with coaches mostly by phone or private online messaging or both and could post online messages to group members.

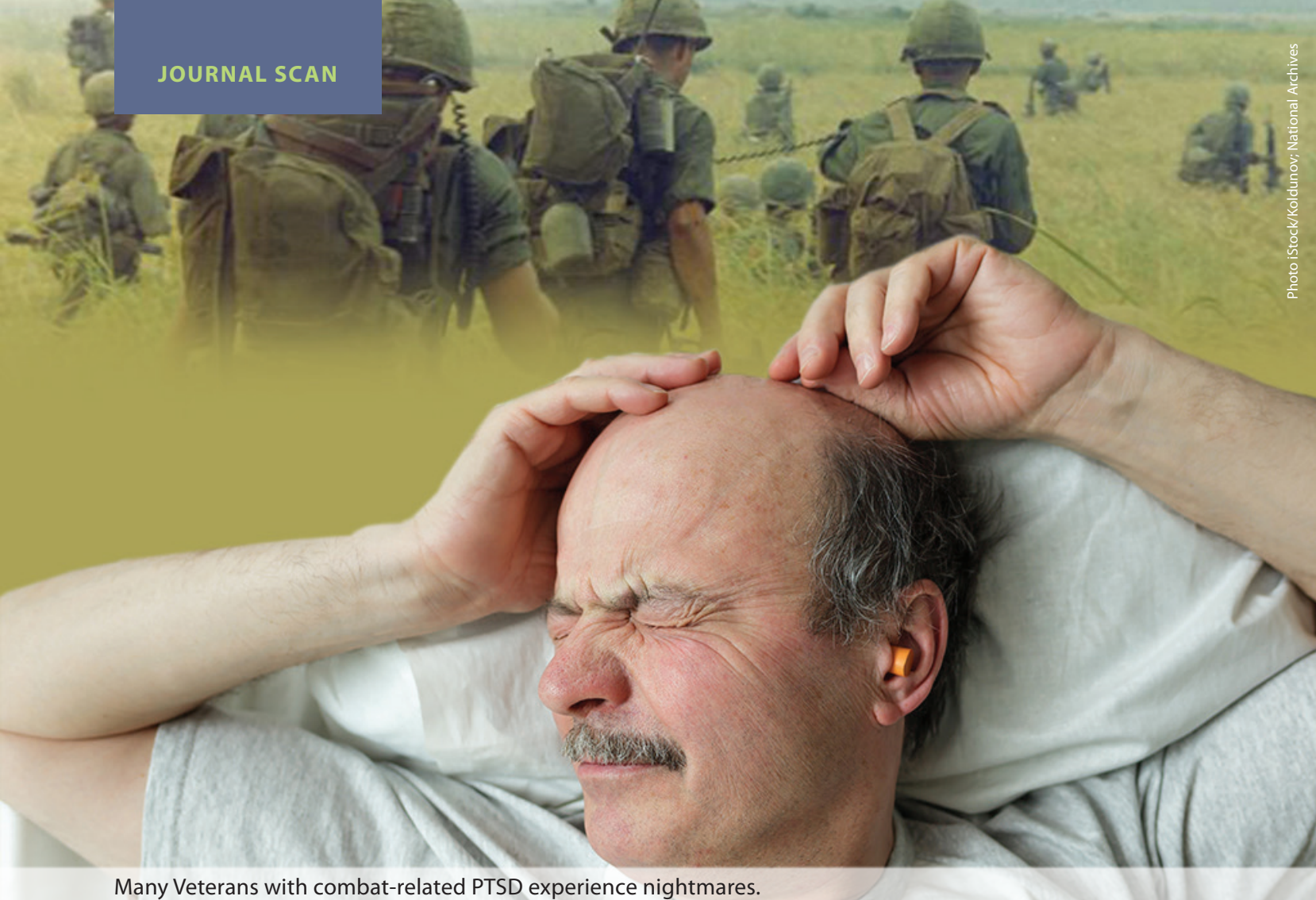
Plus, only the online participants received a wireless digital scale, allowing the coaches to remotely track everyone's weight. Veterans in the in-person DPP and MOVE! programs traveled to a VA site to get weighed, one reason participation was greater in the online program, Moin says.

“The online participants knew someone was looking at this information,” says Moin, who is also an assistant professor at the University of California, Los Angeles. “Some of those Veterans told us in interviews that they felt someone cared and was following their progress. So there was accountability in the online program like there was in the in-person DPP.”

Veterans in the online DPP could also complete sessions anywhere and anytime, another element of convenience that the in-person DPP and MOVE! participants didn't have.

“Participants felt like they were part of a community in which they can connect with other people in the group and with their coach.”

Read more at www.research.va.gov/currents ★



Many Veterans with combat-related PTSD experience nightmares.

PTSD nightmares: Is there an effective treatment?

A recent review article by a VA clinician-researcher explored why nightmares are a hallmark of PTSD and discussed treatment options and research needs.

The scientific community has made major strides in recent years to untangle PTSD, a mental health condition that can trigger flashbacks to a traumatic event or cause one to feel distant and angry. Advancements have been made to understand the reasons behind PTSD, where the condition takes hold in the brain, and which therapies work best.

But uncertainty exists in how to best treat nightmares, a hallmark symptom of PTSD. Research results on therapies for PTSD patients who are experiencing nightmares have been inconsistent. That shortcoming applies to Veterans, active-duty service members, and civilians, all of whom have been diagnosed with the disorder.

Dr. Ali El-Solh, a pulmonologist and sleep specialist at the VA Western New York Healthcare System in Buffalo, is hoping to improve the lives of Veterans with PTSD who are battling nightmares. He authored a review that explores why nightmares are a characteristic of PTSD, examines the health risks linked to PTSD and nightmares, elaborates on psychological and drug treatments for these nightmares, and identifies future research needs.

El-Solh's review appeared online in the journal *Nature and Science of Sleep* in November 2018. He discussed his work with *VA Research Currents*.

Why is it important to highlight the connection between PTSD and nightmares?

I wrote the review largely because of the profound impact of nightmares on the quality of life of Veterans with PTSD and the inconsistent results of available treatments for this disorder. It's of great concern that Veterans who have nightmares are at higher risk for suicide and suicidal thoughts. Understanding the origin of nightmares may offer clues in how to address the serious consequences that stem from these distressing events. But the disheartening reality is that our approach to the treatment of nightmares is limited by the fact that we have no objective tools [like a brain scan] to assess their extent and severity. In addition, it's more apparent that nightmares are not experienced alike. They are shaped by the traumatic events and underlying behavioral and medical conditions of each person.

You say there's no single strategy that holds the most promise for alleviating nightmares in people with PTSD. Why is that?

It's hard to single out one therapy because the choice of the therapy depends on a patient's preferences and the availability of expertise to deliver the treatment. We recommend starting with one of the behavioral treatments when a patient has access to a qualified therapist and is willing to commit to that therapy. We also advocate lifestyle modifications that promote good sleep, such as stress relief exercises, an avoidance of alcohol and caffeine, and a refrain from using electronic media close to bedtime. A drug can also be prescribed. In order to promote adherence to medications, we go over the expectations intended from the patient and discuss potential side effects.

Frequent monitoring following completion of any therapy is key to assessing whether a satisfactory response has been achieved or whether another treatment should be used.

Such complementary techniques as acupuncture, herbal medicine, yoga, massage, and support groups have been described as other potential therapies for treating nightmares. However, these reports are anecdotal and included a limited number of participants. Nonetheless, patients are encouraged to pursue complementary therapies if they alleviate nightmares.

“We recommend starting with one of the behavioral treatments when a patient has access to a qualified therapist and is willing to commit to that therapy.”

Your review notes that imagery rehearsal therapy (IRT) is considered the “preferred empiric treatment” for PTSD-related nightmares. What is IRT?

Imagery rehearsal therapy is a behavioral therapy that's based on the premise that nightmares can be altered through daytime rehearsal of dreams. In other words, the script of a reoccurring nightmare can be modified into a new scenario with a non-frightening ending. The new script is rehearsed daily and can be practiced in a group or individual format. In contrast to medication, imagery rehearsal therapy has been shown in randomized controlled trials to ease the anxiety emanating from nightmares. The beneficial effect can last for more than 12 months and unlike drugs used for nightmares, IRT has no side effects. Other behavioral therapies for nightmares like systematic desensitization and exposure, relaxation, and rescripting therapy have been as effective as IRT. But head-to-head comparisons between those treatments are rare. The choice of the behavioral therapy depends on the doctor's expertise, the willingness of the patient to return for follow-up visits, and the patient's ability to cope with the stressful response that may result from recalling distressing events.

Read more at www.research.va.gov/currents ★



Dr. Tamaro Hudson is studying the effect of muscadine grape extract on prostate cancer. (Non-muscadine grapes shown for illustrative purposes.)

A grape-based cancer therapy?

A team at the Washington DC VA is testing an extract made from the skins of muscadine grapes against aggressive forms of prostate cancer in the lab.

For years, the American Cancer Society and other groups have advised eating a colorful mix of fruits and veggies to help ward off cancer. At the same time, scientists continue to hunt for specific chemicals within plants that have special tumor-busting power.

Does the antioxidant-rich muscadine grape harbor one of those compounds? That question is being pursued by a group that includes Dr. Tamaro Hudson at the Washington DC VA Medical Center.

Hudson is also an assistant professor of pharmacology department at Howard University. He is doing experiments in cell cultures and mice, and collaborating with a Johns Hopkins team on a clinical trial.

The lab experiments have been promising. In January of this year, Hudson and colleagues published a study in the Elsevier journal *Heliyon* showing that an alcohol-based extract made from the skin of muscadine grapes decreases the growth of prostate cancer cells, through a process called cell cycle arrest.

“We were able to show the ability of the grape extract to reduce tumor growth,” says Hudson.

The experiments used a cell line, known as PC3, that originated back in 1979 in a 62-year-old Caucasian man with

aggressive prostate cancer that had spread to the bone. The cells have been an important resource for cancer and drug labs worldwide.

Hudson's team applied the grape-skin extract to cells in Petri dishes, and to tumors that had grown in mice injected under the skin with a saline solution containing the cancer cells.

One of the collaborators on the research is Dr. William D. Wagner, a professor at Wake Forest School of Medicine. He owns a company called Muscadine Naturals that makes dietary supplements from muscadine grapes grown locally in North Carolina. But Hudson's study used an extract from a different source, from purple muscadine grapes grown in south Georgia.

Related clinical trial ongoing at Hopkins

Hudson and Wagner are also part of a group conducting a phase 3 clinical trial. It's sponsored by the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University in Baltimore. The trial has other sites, as well, but none within the VA system.

The trial involves 80 men who had prostate cancer in the past and underwent treatment, but now have the disease again, as evidenced by their rising PSA (prostate-specific antigen) levels. About 15 to 40 percent of men who go through an attempt at curative therapy for prostate cancer—such as surgery or radiation—will develop recurrent disease.

According to the researchers, these men have limited conventional treatment options. As such, "they are excellent candidates for innovative treatments hypothesized to slow the progression of clinical prostate cancer and delay the development of metastatic disease."

The men are taking eight capsules daily, each containing 500 mg of dried, powdered muscadine skins. Even if the grape product slows the spread of the cancer but doesn't eradicate it entirely, that might buy the men additional years of symptom-free living.

The trial also has an interesting genomics, or

personalized medicine, aspect. An earlier phase 2 trial by the group—designed to confirm the safety of the grape therapy and establish the most effective dose—failed to show a statistically significant difference in outcomes between men who got the grape product and those receiving a placebo. The researchers gauged success by how long it took the men's PSA levels to double. That's a standard measure used in men with recurring prostate cancer. The longer it takes for the PSA number to double, the better. That means the cancer is slower-growing.

But a subgroup of men in the phase 2 trial who had certain variant of a gene called SOD2 did show a measurably better response. There weren't enough of these men to sway the overall outcomes of the earlier trial, but the current phase 3 trial includes only prostate cancer patients with this genotype. Some will get the grape capsules, and others a look-alike placebo.

"This will indicate whether it was a true effect," Hudson says.

The gene variant at play is the alanine/alanine SOD2 allele.

Hudson says researchers aren't sure yet roughly what percentage of men with prostate cancer in the general population have this gene variant.

Drilling down to the active constituents

Meanwhile, Hudson and others are working to identify what exactly in the skin of the muscadine grape combats cancer. He's pretty sure it's not the well-known compound resveratrol. Muscadine, unlike most other red grape varieties, has only very modest levels of that super antioxidant. But it does have plenty of other compounds shown in lab studies to have anti-cancer activity, such as ellagic acid, kamperfol, and quercetin.

In fact, there are dozens of compounds, or phytochemicals, in these dark-skinned grapes, as there are in any fruit. Isolating which ones affect cancer is tedious

"We were able to show the ability of the grape extract to reduce tumor growth."

Continued on next page

work, says Hudson. But if scientists can isolate the most relevant compounds, in theory they can develop a more potent therapy. It could also make it more feasible for patients to consume the requisite amount. After all, if a person set out to eat enough muscadine grapes to equal the amount given in capsules to the clinical trial participants, they'd have to eat more than 10 pounds daily.

Hudson does note that as his group chemically breaks down the dried and pulverized grape skin into its various components, and tests those against cancer cells, the therapeutic effect wanes.

“The issue becomes whether you want to remove those components from the plant [or fruit] itself. If you isolate it out, does that increase the [anti-tumor] activity?”

Consistent with his lab's findings so far, it could be that the final product will in fact be as close as possible to the whole grape skin, as it exists in nature, with all its various polyphenols and other compounds intact.

“The field is slowly moving away from [a more fractionated approach],” he adds. “If you can keep



Photo by Mitch Mirkin

Dr. Tamaro Hudson is a researcher with the Washington DC VA Medical Center and Howard University.

those constituents together, in the natural environment of the plant, they all work in concert.”

Hudson has received funding from the Charles and Mary Latham Fund, as well as a Historically Black Colleges and University Research Training Award from VA. ★

For an overview of the latest VA research on PTSD, traumatic brain injury, or any of 36 high-priority topics affecting Veterans' health, visit our web topic pages at www.research.va.gov/topics/default.cfm.



VA research on POSTTRAUMATIC STRESS DISORDER (PTSD)

In earlier wars, it was called "soldier's heart," "shell shock," or "combat fatigue." Today, clinicians recognize the issues described by each of these terms as a distinct medical condition called posttraumatic stress disorder, or PTSD.

ABOUT PTSD

- PTSD can occur after a traumatic event like combat, sexual, or disaster. While stress is common after a trauma, for those with PTSD reactions such as reliving an event that is mild and feeling distant or angry do not go away over time, and can even get worse.
- While PTSD can affect people who have experienced a wide range of life-threatening events, in Veterans the condition is commonly associated with combat trauma. It has taken a significant toll on many war Veterans who currently use VA health care, including Iraq and Afghanistan Veterans. Military sexual assault or harassment can also lead to PTSD.
- and couples. Veterans of all eras are included in these studies.
- Ongoing studies range from investigations of the genetic or biochemical foundations of the disorder to evaluations of new or existing treatments.
- VA National Center for PTSD (NCTSD)** is a world leader in research and education programs focusing on PTSD and other psychological and mental consequences of traumatic stress. It currently consists of seven VA academic centers of excellence across the United States, with headquarters in White River Junction, Vermont.
- VA National PTSD Brain Bank** is a brain tissue repository that supports research on the causes, progression, and treatment of PTSD. The bank is responsible for tissue acquisition and preparation, diagnostic assessment, and storage. Most of the brains stored in the bank are from people once diagnosed with PTSD. Others are from donors who had major depressive disorder. Other brains are from healthy controls. The goal is to help to pinpoint how PTSD affects brain structure and function.
- In 2013, VA and the Department of Defense (DoD) announced that the two departments together were committing more than \$100 million to fund [research](#).

VA RESEARCH ON PTSD: OVERVIEW

- VA has a continuing commitment to fund efforts to understand, prevent, and treat PTSD. The wide-ranging nature of current PTSD research includes studies of Veterans at large, subgroups of Veterans, families,

(Continued on back)



VA research on TRAUMATIC BRAIN INJURY

VA research related to TBI is wide-ranging. Among the goals of VA researchers working in this field are to shed light on brain changes in TBI, improve screening methods and refine tools for diagnosing the condition, and develop ways to treat brain injury or limit its severity when it first occurs.

ABOUT TRAUMATIC BRAIN INJURY

- The CDC defines a TBI as "a disruption in the normal function of the brain that can be caused by a bump, blow, or jolt to the head, or penetrating head injury."
- After a TBI, the person may experience a change in consciousness that can range from becoming dazed and confused to loss of consciousness. The person may also have a loss of memory for the time immediately before or after the injury.
- The DoD estimates that 22 percent of all combat casualties from Iraq and Afghanistan are brain injuries. TBI is a significant cause of disability outside of military settings, most often as the result of assaults, falls, automobile accidents, or sports injuries.
- TBI can include a range of conditions, from headaches, irritability, and sleep disorders to memory problems, slower thinking, and depression. These symptoms often lead to long-term mental and physical health problems that impact Veterans' employment and family relationships, and their reintegration into their communities.
- While most people with mild TBI have symptoms that resolve within hours, days, or weeks, a minority may experience persistent symptoms that last for several months or longer. Treatment typically includes a mix of cognitive, physical, speech, and occupational therapy, along with medication to control specific symptoms such as headaches or anxiety.

VA RESEARCH ON TRAUMATIC BRAIN INJURY: OVERVIEW

- Beyond studying how to better treat TBI, researchers are also developing improved methods to assess the effectiveness of treatment and learning the best ways to help family members cope with the effects of TBI and support their loved ones.
- VA TBI Model System (TBIMS)** is a longitudinal multicenter research program that examines the recovery course and outcomes of Veterans and active duty service members with TBI. The goal of the system is to conduct research that contributes to evidence-based rehabilitation interventions and practice guidelines that improve the lives of people with TBI.
- VA Transitional Research Center for TBI and Stroke Disorders (TRAC-TBI)** conducts studies to understand the complex changes in the brain, thinking, and psychological well-being that result from TBI and posttraumatic stress disorder (PTSD). These studies will lead to more understanding and better treatment options for returning Veterans with TBI and PTSD.

(Continued on back)



VA research on MULTIPLE SCLEROSIS

Multiple sclerosis is a complex neurologic disease that affects the central nervous system, including the brain, spinal cord, and vision pathways.

ABOUT MULTIPLE SCLEROSIS

- MS is the immune system attacks the myelin sheath, the fatty tissue that surrounds and protects nerve fibers, as well as the nerve fibers themselves. Damage from these attacks is called demyelination. When any part of the myelin sheath or nerve fiber is damaged or destroyed, nerve impulses traveling to and from the brain and spinal cord are distorted and interrupted, causing a wide variety of symptoms.
- Sometimes the myelin can repair itself and the MS symptoms go away after the immune attack. Over time, however, the myelin and underlying nerve fibers cannot recover and suffer permanent damage. The cause of MS is currently unknown.
- Symptoms vary depending on the location of the lesions in the brain and spinal cord. They may include tingling, numbness, painful spasms, slurred speech, or blurred or double vision.
- Some people experience muscle weakness, poor balance, poor coordination, muscle tightness or spasticity, tremors, or temporary or permanent paralysis. Problems with bladder, bowel, sexual function, or mood are also very common.
- Fatigue is a major concern for most people with MS, as are challenges with memory, attention, and concentration. Symptoms may come and go, appear in any combination, and be mild, moderate, or severe.
- Many symptoms—such as fatigue, insomnia, mood, cognition, mobility, spasticity, and bowel function—are a very response to self care. Lifestyle changes such as increased activity, in addition, medication therapies and other interventions are available to help manage MS symptoms.

VA RESEARCH ON MULTIPLE SCLEROSIS: OVERVIEW

- Medical care for Veterans with MS, whether or not their illness was service-connected, can include disease-modifying therapies, other medications, physical and occupational therapy, and other health care services and medical equipment.
- Current VA research includes investigations into the biology of MS, targets for intervention, impacts of spasticity, fatigue and fall management programs, health services and the care delivery to evaluate and improve mood and fatigue, and telehealth interventions to improve access to care and symptom management, among others.
- VA Multiple Sclerosis Centers of Excellence (MSCEs)** are dedicated to furthering the understanding of MS and its impact on Veterans and developing effective treatments to help manage the disease and its symptoms. MSCE-East is located in Baltimore, and MSCE-West is jointly located in Seattle and Portland, Oregon.
- VA has also established a national integrated network of dedicated MS health care professionals for care and referral within the VA health care system.

SELECTED MILESTONES AND MAJOR EVENTS

- 2003 - Founded the [Multiple Sclerosis Centers of Excellence](#).
- 2014 - [Announced](#) that military deployment to the first Gulf War was not a risk factor for developing MS.
- 2017 - [Found](#) that high doses of lipoid acid can significantly slow brain atrophy, reduce falls, and improve walking times in some MS patients.

(Continued on back)

Study: Technology helps upper-limb amputees regain a sense of touch

Artificial hands have come a long way since the days of the simple mechanical hook. Nearly 50 years ago, at a time when engineers were only dreaming of what is possible today, VA prosthetics expert Dr. Eugene Murphy wrote: “Though engineers and prosthetists have made substantial contributions, they need perspective and humility to inspire and guide the very long, sustained efforts required to replace even a few of the roles of the hand.”

Fast-forward a half-century, and today devices like the LUKE arm (formerly known as the DEKA arm), developed in part through VA research, feature hands that do in fact replace many roles of their natural counterparts. They boast features like multiple degrees of freedom, pre-programmed multiple grip patterns, and grip-force sensors. In 2018, an Air Force Veteran using the technology, Ron Carrier, said at a news conference, “I feel like I have my hands back again.”

Even with all the progress in prosthetic hands, some features have remained a challenge. One is restoring a natural sense of touch to users. This has largely to do with somatosensory functions, part of the nervous system that gives us the perception of touch, pressure, pain, temperature, position, movement, and vibration. Somatosensory feedback of the hand is key to gaining a feel for objects.

That’s why Veterans and others with upper-limb prostheses often struggle to determine the size of an object in their prosthetic hand and the amount of pressure to put on it.

VA researchers and collaborators have been drawing closer to this goal. One leading site is the lab of



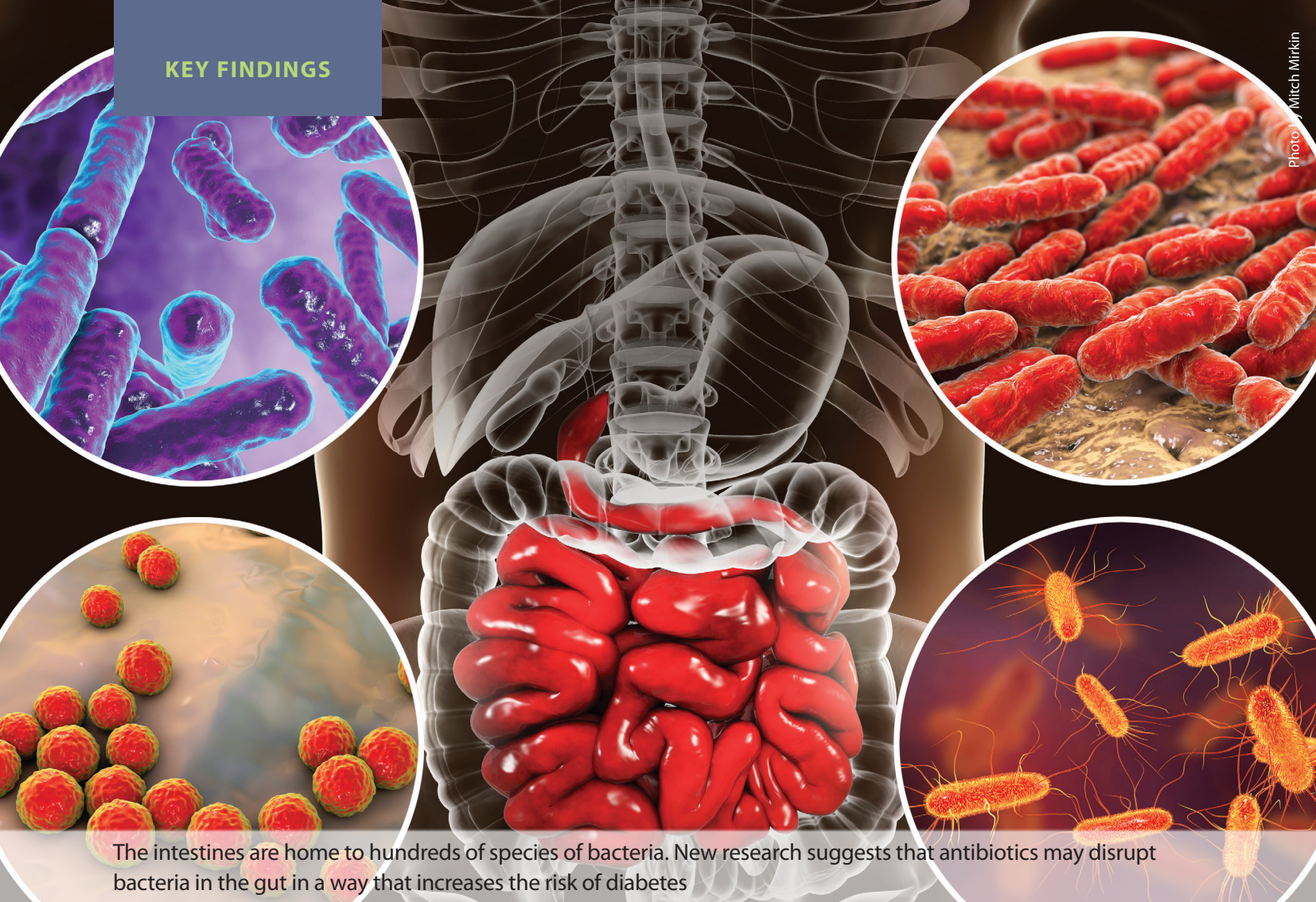
Research participant Keith Vonderhuevel demonstrated a prototype artificial hand, featuring a sense of touch, at a 2017 Capitol Hill event sponsored by Friends of VA Medical Care and Health Research.

Dr. Dustin Tyler, a biomedical engineer and a principal investigator with VA’s Advanced Platform Technology Center in Cleveland. A team there carried out a trial of a technology that has been in development in recent years. The team tested the potential of artificial sensory feedback to restore lost feeling in two people with prostheses, one that starts at the wrist and the other in the forearm. The ultimate goal was to improve the ability of amputees to function normally at home, work, and in the community.

Dr. Matthew Schiefer, formerly with the Advanced Platform Technology Center, led the trial, published in December 2018 in the online journal *PLoS One*. His research focuses on neural engineering, a sub-field of biomedical engineering that’s based on understanding nerve response. He hoped that through electrical nerve stimulation, the amputees would regain a sense of touch so they could determine the size and hardness of foam blocks.

Read more at www.research.va.gov/currents ★

KEY FINDINGS



The intestines are home to hundreds of species of bacteria. New research suggests that antibiotics may disrupt bacteria in the gut in a way that increases the risk of diabetes

VA study links antibiotics with diabetes risk

A study from the VA New York Harbor Healthcare System found that Veterans with a history of antibiotic use were more likely to develop Type 2 diabetes.

Adding to a growing body of evidence linking antibiotic exposure to diabetic risk, a study from the VA New York Harbor Healthcare System shows that Veterans with a history of antibiotic use are more likely to develop Type 2 diabetes.

The results appeared in the February 2019 issue of the journal *Primary Care Diabetes*.

The study, which analyzed data on more than 14,000 Veterans seen in VA primary care over an 11-year period, only points to an association between antibiotics and diabetes. It does not prove cause and effect. But the researchers say a causal link is plausible from a biological standpoint, given how antibiotics disturb bacteria in the gut.

“There is strong experimental evidence from animal studies showing that the gut microbiome is vulnerable to dramatic changes in the distribution of species [of bacteria] when exposed to antibiotics,” says senior author Dr. Mark Schwartz. “Some of these changes can be permanent. And these changes, in turn, are linked to metabolism. This has been shown to lead to obesity, diabetes, and metabolic syndrome in animals. So I think there’s a strong biological argument here.”

Schwartz is a physician-researcher with VA and New York University. He's also a professor in the department of population health at NYU.

Acknowledging antibiotics' good side

The internist is quick to emphasize the lifesaving nature of antibiotics. "We live much longer now, in large part because of the ability of these drugs to cure infections."

But like many in the medical community, he is working to stem the tide of overreliance on antibiotics. The trend has spawned deadly "super bugs" that resist treatment. Despite campaigns in recent years urging doctors and other health care providers to be more cautious in how they prescribe the drugs, research shows that about 1 in 3 prescriptions for antibiotics are inappropriate. For upper respiratory infections, the ratio gets worse: 1 in 2.

"The vast majority of those patients [with upper respiratory infections] do not have bacterial infections, and even for the ones that do, it's not certain we're doing more good than harm by prescribing antibiotics," says Schwartz.

Antibiotics per se are effective only against bacteria, not viruses. As many as 9 in 10 upper respiratory infections are thought to be caused by viruses.

Following up on a couple of European studies

A small handful of epidemiological studies outside of the U.S., such as one from Denmark and one from an Israeli group that used U.K. data, both published in 2015, had begun to explore the antibiotic-diabetes connection before Schwartz's group began their work on the question. The new VA study is among the first U.S. database studies published on the topic.

Schwartz's team used VA's Central Data Warehouse to examine medical records and health care utilization data on patients who had received primary care at the VA New York Harbor Healthcare System between 2004 and 2014. They excluded those with any prior history of diabetes. They traced which Veterans

developed diabetes during the study period—as indicated by a diabetes diagnosis, or prescriptions for drugs used only to treat diabetes.

Out of 14,631 included in the study, 1,413 developed diabetes.

More than two-thirds of the Veterans in the study had been prescribed one or more courses of antibiotics. The researchers found that any exposure to antibiotics—even one course during the 11-year study period—statistically raised the odds of diabetes, by 13 percent. For several classes of antibiotics, more exposures translated to greater diabetes risk. For most classes, higher average daily doses of the medications also raised diabetes risk.

While the researchers tried to control for as many variables as they could, Schwartz acknowledges other factors may have confounded the results. In other words, it could be that the Vets who developed diabetes were more likely to have taken antibiotics, but it wasn't the drugs themselves that elevated their risk.

One possibility is that having prediabetes—a condition in which blood sugar is elevated, but not to the point of full-blown diabetes—may weaken the immune system and make people more susceptible to infections. That would mean that the same Veterans who eventually developed diabetes would have incurred more infections in the years leading up their diagnosis—and presumably would have used more antibiotics.

Schwartz elaborates on another feasible scenario: "It's entirely possible that it's the underlying infection, and not the antibiotic, that increases diabetes risk—especially if the infection is intestinal, perhaps, or respiratory, where much of our microbiome live."

Read more at www.research.va.gov/currents ★



Dr. Adriana M. Hung, a coauthor on the new blood pressure study, meets with patient Rodney Stewart at the Tennessee Valley Healthcare System.

Genome study leads to better understanding of high blood pressure

An international study using Million Veteran Program data has identified more than 200 gene variants related to high blood pressure.

A large, international genetic study using Million Veteran Program data has identified more than 200 gene variants that could contribute to high blood pressure. The study also identified over 200 drugs currently used to treat other diseases that could potentially be repurposed to treat high blood pressure.

Dr. Todd Edwards of the VA Tennessee Valley Healthcare System—one of the senior authors on the study and himself a Veteran—explained the significance of the findings. “We’re redrawing the map of blood pressure genetics,” he said in a Vanderbilt University press release.

Nearly 100 researchers from around the world collaborated on the study, including 24 VA researchers. The results appeared in the January 2019 issue of the journal *Nature Genetics*.

Each person has different variations of genes at specific locations on their genome. These variations are mostly inherited. The idea behind genome-wide association studies such as this one is that people who share the same gene variants could have similar risks for diseases.

Study group included more than 300,000 Veterans

While lifestyle choices—such as smoking, diet, and alcohol use—influence the risk of high blood pressure, doctors have known for some time that a significant part of a person’s risk comes from the genes inherited from parents.

Previous genome studies reported more than 250 genome locations that affect blood pressure. In this study, the researchers identified 201 new locations on the genome that affect blood pressure. They also identified 304 locations that had been identified by previous studies.

They found these new gene associations by looking at the genomes and blood pressure data of more than 300,000 Veterans who participate in MVP, along with more than 140,000 participants from the UK Biobank.

By comparing genomes across this large participant group, the researchers identified the gene variants shared by those with high blood pressure.

Once they had identified the new gene locations, the researchers compared their results with the genomes of more than 300,000 participants from the International Consortium for Blood Pressure and Vanderbilt University’s BioVU. The comparison confirmed the findings from the MVP data.

Findings may lead to new drug treatments

Beyond identifying new gene locations affecting blood pressure, the study yielded several other interesting results. Once the researchers had identified genome locations related to blood pressure, they cross-checked those genes against a list of genes targeted by drugs used to treat diseases other than hypertension. This analysis pointed to over 200 drugs that interact with the identified genes, meaning that those drugs

could potentially be repurposed for treatment of high blood pressure. The study also identified 40 new genes that could be the focus of new drug development to treat high blood pressure.

The researchers also compared the genetic effects on blood pressure between black, white, and Hispanic Veterans in the MVP database. They found that the effects of gene variations were similar among ethnic groups.

Another phase of the study focused on the genetic underpinning of kidney function. The kidney is an important organ for blood pressure regulation. The researchers looked at gene expression in mouse kidney cells to identify which cell types are most involved in regulating blood pressure. They found that structures in the kidney called tubules are the most important for

blood pressure. Genes identified by the study were most expressed in tubule cells.

“We’re redrawing the map of blood pressure genetics.”

Developing a hypertension risk score

Finally, the researchers used the new genomic data obtained in the study to create a score for predicting high blood pressure in patients. The score counts the number of gene variants related to high blood pressure that are present in an individual patient’s genome. The higher the score, the greater the genetically predicted burden of high blood pressure for a given individual. The researchers checked these scores against the electronic medical records of over 250,000 Veterans. On average, individuals with higher scores were more likely to have high blood pressure, as well as kidney disease, stroke, complications related to diabetes, and aortic aneurysms, as well as a number of other conditions.

Read more at www.research.va.gov/currents ★



Hemp and marijuana both refer to the cannabis sativa plant and its products. Different varieties of the plant, however, can contain different levels of chemical compounds, and that is what distinguishes hemp from marijuana.

VA trial testing cannabidiol—a compound derived from cannabis—for PTSD

Researchers at the VA San Diego Healthcare System aim to see whether CBD can ease symptoms, when given along with evidence-based psychotherapy.

Researchers at the VA San Diego Healthcare System aim to see whether cannabidiol, or CBD—a compound derived from cannabis plants—can help ease PTSD. The study will give CBD as an add-on to prolonged exposure therapy, a proven psychotherapy for PTSD.

The \$1.3 million VA-funded study will enroll 136 Veterans, from all service eras.

Dr. Mallory Loflin, a research scientist with VA and assistant professor of psychiatry at the University of California, San Diego, is leading the study. Loflin, with VA's Center of Excellence for Stress and Mental Health, specializes in studying new mental health treatments that target the body's endocannabinoid system. CBD and related compounds from cannabis bind with receptors—proteins on the surface of cells—that are part of this system.

Loflin says past research suggests that CBD can increase extinction learning in PTSD. This has to do with people “unlearning” unhelpful responses and behaviors they've developed in the wake of trauma. This, she says, could boost

the speed and effectiveness of prolonged exposure therapy, which helps patients gradually work through their traumatic memories. She says CBD could also ease insomnia and over-arousal. Those types of effects are beneficial on their own, but they could also further boost Veterans' engagement and retention in treatment.

VA Research Currents interviewed Loflin to learn more about the trial, which plans to start recruiting patients by March 2019.

It seems there is a lot of confusion and misinformation floating around on the internet about CBD, and cannabis in general. Does that present special challenges for this study?

I certainly get more questions from prospective participants! In particular, folks have a lot of questions about whether it's legal for them to participate in the study, and whether they could get in trouble with their work. Because I have a Schedule 1 license, under the Controlled Substances Act our participants are 100-percent legally allowed to receive the study drug. The challenge, though, is with the work question. Just because something is legal doesn't mean that one's workplace allows it, so we do have to advise them to do their homework to find out if their employer prohibits use of cannabidiol, even in the context of a research study and for medical treatment. That's obviously something we wouldn't have to think about with other medication trials.

While there has been legitimate research showing health benefits from CBD, there's also been hype about how it's good for virtually anything that ails a person. Is there a concern that this might lead to a stronger-than-usual placebo effect?

Yes, and this isn't just an issue for CBD either. This is a common problem for cannabinoid research in general. Folks talk about cannabis and cannabinoids being cure-alls for everything from Alzheimer's to warts, which creates a huge demand on participants



Photo by Kevin Walsh

Dr. Mallory Loflin is leading a VA study in which Veterans with PTSD will receive capsules containing CBD—a compound derived from cannabis—or a lookalike placebo, along with evidence-based psychotherapy.

to see improvement when they're in a "cannabinoid research study." Unfortunately, what we then see is that even folks in the placebo condition in these trials tend to see greater benefit from the inactive treatment than folks would usually see from an active treatment outside the study! This strong placebo effect creates headaches for researchers because it makes it very difficult for our experimental condition (the study drug) to outperform the placebo, increasing the likelihood that the trial will fail.

Read more at www.research.va.gov/currents ★



Dr. Mark Logue, an Army Veteran, is a statistician in the National Center for PTSD at the VA Boston Healthcare System.

VA Researchers Who Served: Dr. Mark Logue

Dr. Mark Logue, an Army Veteran, is a statistician in the National Center for PTSD at the VA Boston Healthcare System. His research interests include the genetics of psychiatric disorders and neurological traits, such as PTSD, Alzheimer's disease, dementia-associated neurodegeneration, and panic disorder. He's also an associate professor of psychiatry at the Boston University School of Medicine. He has authored and co-authored more than 75 research papers, and his work has been published in dozens of academic journals.

What motivated you to join the military?

After being admitted to the University of Oregon in the mathematics program, I looked for ways to help pay for college. I considered ROTC but decided that joining the Army Reserves would be a good way to cover the costs of school. Also, doing basic training over the summer months between high school graduation and my freshman year at Oregon sounded more exciting than getting a standard summer job

What inspired your research career?

While working on my PhD in statistics, I became involved in a genetics project, and I really liked the way it allowed me to use my mathematical and programming skills to address real health problems. I've been working on genetic studies ever since.

Did you have mentors who inspired you in life, the military, or your research career?

I don't know if I can say that I've been inspired. But I have had a few mentors and colleagues who have played large roles in getting me to where I am today. My PhD thesis advisor, Dr. Veronica Vieland, was a big influence on

my career. She somehow determined that me asking questions from the back of her classes indicated that I was paying attention and interested rather than being difficult. She was the person who made me interested in psychiatric genetics.

Another person who has been influential in my career is Dr. Mark Miller. I work with him in the behavioral sciences division of the National Center for PTSD. We started collaborating on the genetics of PTSD when I was an associate professor at Boston University. He encouraged me to look for a position in the National Center for PTSD. Also, the administration of the National Center for PTSD has been very supportive of my research and career development. There are many others—too many to name individually—who have generously shared their time and expertise to help guide my career.

Describe your military experience.

I joined the Army Reserves after completing high school in 1989. As a medical supply specialist, I was assigned to a reserve combat support hospital unit in Vancouver, Washington. My work was largely that of a clerk dealing with medical supplies: stocking, doing inventory, ordering replacement parts, and performing other similar tasks. My reserve unit was activated in December 1990, in support of Operation Desert Shield, the lead-up to Operation Desert Storm [the Persian Gulf War]. I was sent to a hospital in Stuttgart, Germany, that was gearing up to handle casualties air-lifted from the Middle East. I worked there to increase capacity by ordering more medical supplies, setting up equipment, and retrofitting rooms to have a larger patient capacity. Fortunately, the high casualty load we were preparing for never arrived. I was released back to the reserves in March 1991, where I stayed until I was discharged in 1997.

What kinds of research are you involved in? How does it potentially impact Veterans?

I work on genetic studies examining the impact of genes on PTSD and Alzheimer's disease. Because my



Logue joined the Army Reserves after completing high school in 1989.

background is in statistics, my primary focus is on the computation side of things. That means my lab is in an office with a bunch of computers, not a bunch of freezers and test tubes. I write programs and computer scripts to collate and analyze genetic data from hundreds or even thousands of subjects at a time. I then interpret the results. My team is looking at genetics across multiple levels, including genetic variation that is inherited from your parents, epigenetic marks that may control which genes are turned off and on, and the activity of the genes themselves in blood samples and brain tissue. Hopefully, identifying genes and biological pathways related to PTSD and Alzheimer's disease will lead to new treatments and to better identification of Veterans at risk.

Read more at www.research.va.gov/researchers_who_served ★

Cigarette Smoking among Rural Veterans



- VA researchers looked at data on **3,229 Iraq and Afghanistan Veterans** to learn about the links between **cigarette smoking, rural residence, and mental health.**
- They found **higher smoking rates** among **rural Vets**, compared with urban Vets, and among those with **psychiatric diagnoses.** Those living in **“extremely rural areas”** and those with **psychiatric conditions** were also **“more severely dependent on nicotine.”**
- The findings “underscore the need to **reduce barriers for treatment** both for **smoking cessation** and **mental healthcare** for **veterans residing in the most rural areas.”**

From [“Cigarette smoking rates among veterans: Association with rurality and psychiatric disorders,”](#) *Addictive Behaviors*, March 2019. Infographic by VA Research Communications, January 2019. Photo: © iStock/ImagineGolf.

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Listen to the Voices of VA Research podcast series:

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The homelessness-suicide link

• **Dr. Jack Tsai** with **Yale University** and the **VA New England Mental Illness Research, Education, and Clinical Center** led a study on the association between **suicide attempts** and **homelessness** in **Veterans** and **non-Veterans**.

• The study included data on more than **36,000 U.S. adults**.

• Among **non-Veterans**, there was a **fourfold higher likelihood** of **past suicide attempts** among those who had been **homeless**. Among **Veterans**, the association was even stronger, with an **eightfold higher likelihood**.

• The researchers concluded that **“strategies to synergize homeless and suicide prevention services, particularly in the Veterans Health Administration, may benefit high-risk individuals.”**

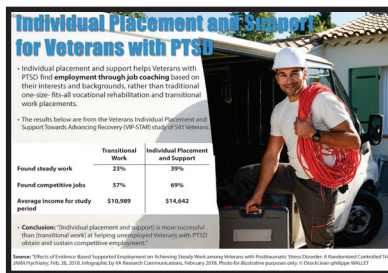
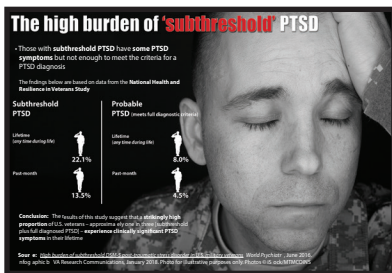
From **“Association between suicide attempts and homelessness in a population-based sample of US veterans and non-veterans,” *Journal of Epidemiology and Community Health***, online Jan. 2, 2019.

Infographic by VA Research Communications, September 2018. Photo: © iStock/Srdjanns74.



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RESEARCH CURRENTS

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

Learning from 'bright spots' in nursing home care

What began as a research pilot at the Edith Nourse Rogers Memorial Veterans Hospital in Massachusetts now impacts care at 135 VA Community Living Centers (CLCs) across the country. The **Bright Spots Program**, rolled out nationally by VA in 2017, trains staff to huddle at the frontline about quality-of-care issues, and to focus on four steps, known by the acronym **LOCK**: 1) Look for the bright spots, 2) Observations by everyone, 3) Collaborate in huddles, and 4) Keep it bite-sized. For example, in a 10-minute huddle, CLC staff might **review risk factors for pressure ulcers**, and talk about residents who are at risk but do not have pressure ulcers, in order to learn from these "bright spots."

For more examples of VA research innovations being translated into everyday care, visit www.research.va.gov/research_in_action.



Photo by Jeff Bowen

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