

VA

RESEARCH CURRENTS

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



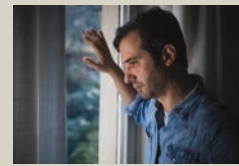
Photo by Jeff Bowen

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Many Veterans with suicidal thoughts not receiving mental health care

More than 3 in 5 Veterans who have suicidal thoughts are not engaged in mental health treatment, according to a VA study. Researchers looked at data from 2011 on more than 3,000 Veterans. About 7% said they have suicidal thoughts. Only 36% of those were receiving mental health treatment. Younger Veterans; women; those with current depression; and those with more lifetime suicide attempts, lifetime trauma, and medical problems were more likely to be in treatment. Mistrust of mental health providers and fear of damaging one's reputation were linked to lower mental health treatment. The results highlight a need to find new ways to engage Veterans at risk for suicide in mental health care, say the researchers. (*Journal of Psychiatric Research*, July 29, 2020)




Photo: ©iStock/vadimguzhva

Cover photo: Dr. Prasad Padala simulates repetitive transcranial magnetic stimulation for mapping the brain of a research assistant at the Central Arkansas VA. *Read more on page 6.*

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VA



U.S. Department
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Yoga a cost-effective treatment for back pain

Yoga can be a cost-effective treatment for Veterans with chronic low back pain, found a VA San Diego study. Patients were assigned to either 60-minute yoga sessions twice a week for 12 weeks or delayed treatment, in which they would receive the yoga treatment after the study. Yoga instruction could be provided for about \$300 per participant. An analysis indicated that the costs of this program are offset by long-term reductions in health care costs for participants. Research suggests that yoga may have health benefits similar to physical therapy and can likely be delivered at a lower cost. The study suggests that yoga could be a useful non-opioid option for patients with chronic low back pain, say the researchers. (*Medical Care*, September 2020)



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American Indian/Alaskan Native Veterans have higher risk of death

American Indian/Alaskan Native Veterans had higher death rates than other ethnic groups, found a VA Greater Los Angeles study. Researchers looked at health and census data on more than 5 million Veterans. They found that American Indian/Alaskan Native Veterans had a 7% higher risk of death from any cause in a given year, compared to Black and white Veterans. Mortality rates were similar between other ethnic groups when controlling for other factors. Neighborhood segregation was a large contributor to this

disparity. American Indian/Alaskan Native Veterans who lived areas with greater non-Hispanic Black segregation had a lower risk of death than those in other areas. Living near tribal reservations also seemed to lessen the disparity. The results suggest that social characteristics of neighborhoods need to be examined to address racial disparities, say the researchers. (*Health Services Research*, October 2020)

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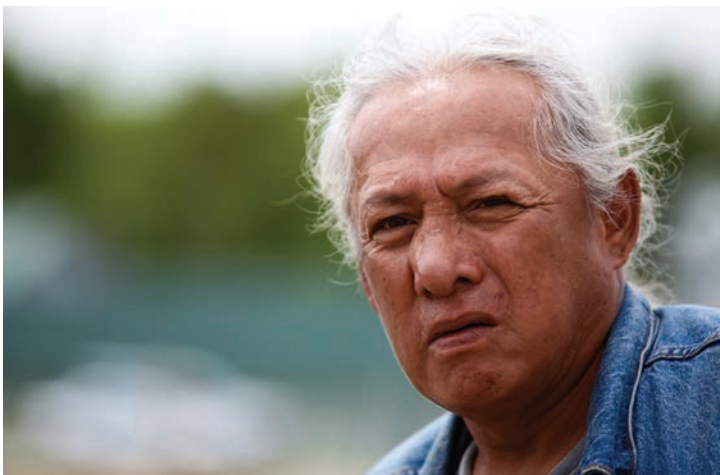
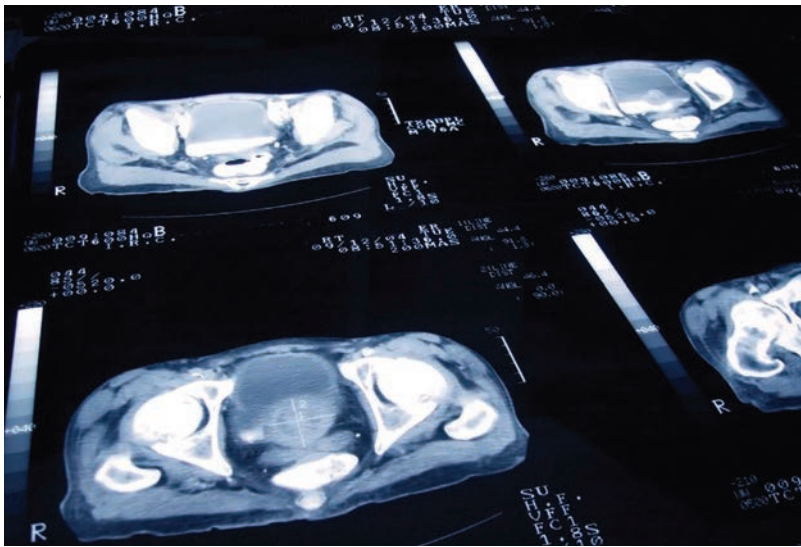


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Exploring gene expression in prostate cancer

A team including Southeast Louisiana Veterans Health Care System researchers found multiple gene expression trends linked to prostate cancer. Gene expression refers to the creation of proteins based on genetic instructions. The team studied data from three large genomic databases. They found that gene expression of the protein FBXW7 was significantly lower in prostate cancer, compared to in normal prostate tissue. Expression of several related proteins (FBXW8–10) was higher in prostate cancer, as well. The study

also found higher expression of several different FBXW proteins in metastatic castration-resistant prostate cancer, a hard-to-treat form of the cancer, compared with more common prostate cancers. The results help explain the role genes play in prostate cancer risk, say the researchers. They also suggest that FBXW7 has potential as a treatment to suppress tumor growth. (*American Journal of Clinical and Experimental Urology*, Aug. 15, 2020)

DOD photo by Lance Cpl. Immanuel Johnson



Blast exposure linked to attention problems

Blast pressure from an explosion contributes to cognitive problems caused by traumatic brain injury (TBI), found a VA Mid-Atlantic Mental Illness Research, Education, and Clinical Center (MA-MIRECC) study. Explosions cause a pressure wave in the air that can strike people near the blast. More than 250 post-9/11 Veterans completed cognitive tests and surveys about blast exposure. Those with a mild TBI performed worse on cognitive tests than those without TBI. The

severity of blast pressure seemed to control this relationship. In Veterans with mild TBI, those who had experienced more severe blasts showed lower performance on a simple attention task, even with the same TBI diagnosis. The results show that severe pressure waves could lead to persisting attention difficulties that impede cognitive function in Veterans with TBI, say the researchers. (*Neuropsychology*, July 16, 2020)



3D-printed masks can be decontaminated of coronavirus using standard methods

VA researchers identified several methods that effectively decontaminate 3D-printed mask material of the virus that causes COVID-19. The researchers tested viral activity on mask material using multiple disinfectants. They found three solutions that inactivated the virus: bleach, quaternary ammonium sanitizer, and hydrogen peroxide. Likewise, exposing the material to dry heat for 30 minutes inactivated the viruses. The liquid alcohol isopropanol was not as effective. The cleaning methods tested did not interfere with the integrity of the 3D-printed

material. Standard decontamination methods can be an effective way to allow for reuse of 3D-printed material when surgical mask supplies are limited, conclude the researchers. (*Infection Control and Hospital Epidemiology*, Aug. 12, 2020)



Veterans Choice Program did not reduce appointment wait times

Giving Veterans the choice to receive specialty care from non-VA community providers did not lower appointment wait times, according to a VA Boston study. The Veterans Choice Program, passed in 2014, allowed Veterans to access care in the community if they live far from a VA facility. Researchers looked at data from 2013 to 2019 to study wait times in four specialties: cardiology, gastroenterology, orthopedics, and urology. The data included 6.9 million VA consultations and 869,000 community visits. The results showed that average wait times

for appointments within VA were shorter than those in the community. Administrative delays did not account for the difference. Wait times in VA declined during the study period. However, the decline began before Veterans Choice was implemented. Geographical areas with the highest VA wait times also had the highest community wait times. The results suggest that increasing eligibility for community care may be insufficient to lower Veterans' wait times, say the researchers. (*JAMA Network Open*, Aug. 3, 2020)

Brain stimulation improves condition of patients with Alzheimer's



Photo courtesy of Southern Nevada VA

Dr. Prasad Padala simulates repetitive transcranial magnetic stimulation for mapping the brain of a research assistant at the Central Arkansas VA, Ashlyn Jendro.

A VA pilot study finds that a brain stimulation therapy provided to patients with Alzheimer's disease improved their state of apathy, a profound loss of motivation and initiative and a feeling of social withdrawal. Apathy is the most common behavioral problem in people with Alzheimer's disease, the No. 1 form of dementia. The results appeared online in the *Journal of Alzheimer's Disease* on Oct. 13, 2020.

Twenty Veterans with Alzheimer's disease and apathy took part in the double-blind study. Half received repetitive transcranial magnetic stimulation (rTMS), and the other half a form of sham stimulation. Through patient and caregiver interviews, the researchers documented a "significantly greater improvement" in apathy levels in those who received brain stimulation, compared with those in the control group. The positive effects of rTMS continued up to three months from baseline, according to the research team.

The key conclusion was that repetitive transcranial magnetic stimulation "may be safely used in people with Alzheimer's disease and may improve apathy, function, and some aspects of cognition." The researchers said "may" and not something more definitive mainly because of the study's small sample size, says Dr. Prasad Padala, a geriatric psychiatrist at the Central Arkansas Veterans Healthcare System who led the study. He and his team also did not carry out multiple statistical comparisons that would have been made with a much larger study group, he notes.

At least 70% of patients with Alzheimer's disease show signs of apathy

Padala is one of many VA researchers who are interested in a therapy for patients with neurodegenerative diseases, including pre-dementia or full-blown dementia. He explains that VA patients have a much higher risk of these health conditions than the general public partly because their rate of diabetes, a chronic disease in which the body can't produce or properly use insulin, is three times higher. Research has shown that older adults with poorly controlled diabetes are at greater risk for Alzheimer's and other forms of dementia.

About 70% to 80% of patients show apathy at some stage of Alzheimer's, says Padala, who works in the Geriatric Research Education and Clinical Center at the Central Arkansas VA and directs the facility's Memory Disorders Consultation Clinic. He has been researching treatments for apathy in people with Alzheimer's disease for about 15 years and has found that the stimulant methylphenidate (trade name Ritalin) works well in treating apathy in those with Alzheimer's, not the disease directly. But some patients cannot tolerate the drug because of its side effects, mainly heart problems and weight loss, he adds.

The U.S. Food and Drug Administration has approved repetitive transcranial magnetic stimulation for treating cases of depression that won't respond to other treatments. The therapy is in the investigational stage for treating apathy in people with dementia. Padala has been experimenting with rTMS over other forms of brain stimulation because much research supports its use for patients with schizophrenia, another cohort in which apathy is a common symptom. Schizophrenia

is a mental disorder involving a breakdown in the relation between thought, emotion, and behavior, leading, in part, to a withdrawal from reality.

Researchers interested in areas of brain that control motivation

The 20 Veterans in the study averaged 77 in age; nearly all of them were men. They had all received an Alzheimer's diagnosis based on a memory test and other assessments. Padala and his team administered rTMS or the sham stimulation nearly 45 minutes per day for 20 days over a four-week period, with 3,000 stimulations each session. The total of 60,000 brain stimulations with a highly focused 3 Tesla magnet—the strength of a standard MRI (magnetic resonance imaging) scanner—was key.

The researchers targeted an area of the brain called the dorsolateral pre-frontal cortex, which has many connections to parts of the brain that control

motivation. "Since we are focusing on apathy, that was an area of interest," says Padala, who is also affiliated with the University of Arkansas for Medical Sciences. In addition to observing a much greater improvement in apathy

at the four-week mark in the patients who received rTMS, the researchers recorded a "significantly greater improvement" in memory, attention, and cognition in the rTMS patients at four weeks. Although not as much as the brain stimulation group, those who received the sham treatment also showed improvement in apathy, a trend that could be attributed to the "placebo effect" and that is similar to results in medication trials, Padala says.

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

Different emotions may drive male, female Vets to attempt suicide



Photo for illustrative purposes only. ©iStock/tommaso79

"Women feel personally like they are not worth anything, and men feel like the world has sort of let them down," says the study's lead author, Dr. Lauren Denneson.

A new study finds that a much different set of emotions may have driven male and female Veterans to attempt suicide.

The findings appeared online in the journal *Social Science & Medicine* in September 2020.

In interviews with the researchers, 25 male Veterans and 25 female Veterans who had made a recent suicide attempt discussed their suicidal thoughts. In the moments before they tried taking their lives, the women recalled feeling "shameful," "tainted," and "worthless." The men talked about feeling overwhelmed and remembered thinking, "it just wasn't worth it," "I've had enough," and "screw this."

The researchers also found that experiences related to self-concept, power, relationships, coping, and stress were key contributors to the Veterans' suicide attempts. These experiences often differed by gender.

Dr. Lauren Denneson, a specialist in social psychology and public health at the VA Portland Health Care System, led the study.

"Our findings suggest that women and men have very different precipitating thoughts when they decide to take their own lives," she says. "Women feel personally like they are not worth anything, and men feel like the world has sort of let them down."

Researcher surprised by gender differences

Denneson pursued the study largely because of the growing suicide rate among female Veterans and because suicide prevention research has been based mostly on men. She also felt it important to gain a better understanding of suicide

risk based on the experiences of Veterans with recent suicide attempts. The results were not exactly what she expected.

“I was keeping a very open mind about whether we might see gender differences and what those differences might be,” she says. “I was surprised by how clearly different some of the experiences were by gender.”

Denneson thinks the findings may provide clinicians with a better understanding of women Veterans who are at risk for suicide and how their treatment needs may differ from those of men.

That means, for example, clinicians may take a different approach when using a psychotherapy like cognitive behavioral therapy (CBT), especially with treatment goals or suggested homework, she says. CBT, which is often used in VA, aims to change negative patterns of thinking or behavior that underlie people's difficulties, and to improve the way they feel by challenging unhelpful thinking patterns.

“We saw how much the traumatic experiences women had in relationships, for example, through intimate partner violence and military sexual trauma, and the perceived rejection by others, played a role in their sense of worth,” Denneson says. “Given that, it seems important to increase women's sense of self-worth to reduce their risk of suicide. But perhaps, it would be most impactful if this occurred in the context of positive relationships.

“For the men, we saw how frustrated they were with the many challenges and setbacks they experienced,” she adds. “At the same time, they talked about life being pointless and not worth the struggle. So it seemed that a clearer sense of purpose might make the struggle seem more ‘worth it,’ and having successful experiences may get them closer to feeling like they're living the life they want to live, or at least that they have the ability to get there.”

Suicide prevention is VA's top clinical priority. The agency says an average of 17 Veterans are dying by suicide every day. VA's 2019 National Veteran Suicide

Prevention Annual Report notes that in 2017—the most recent year for which data are available—the suicide rate for Veterans was 1.5 times the rate for non-Veterans, after adjusting for population differences in age and sex, and 2.2 times the rate for female Veterans compared to non-Veteran women.

Plus, the suicide rate among women Veterans rose 61% between 2005 and 2017, compared with 43% for men, according to the VA report.

Many of the participants had mental health conditions

The 50 Veterans in Denneson's study averaged 45 in age, and more than 50% were white. Their military service history spanned from the Vietnam War to the post-9-11 conflicts in Iraq and Afghanistan.

Many of the participants had been diagnosed with mental health conditions, most notably anxiety, depression, personality disorders, PTSD, substance use disorders, or schizophrenia-bipolar disorder. Schizophrenia and bipolar disorder both affect how people think and act, and some of the symptoms are similar. Bipolar disorder can cause huge mood swings, while schizophrenia involves a breakdown in the relation between thought, emotion, and behavior, leading, in part, to a withdrawal from reality.

Large percentages of the sample also had a sleep disorder diagnosis or chronic pain.

In terms of the questions, “We asked the participants what led them to start thinking about suicide and why they decided to try to take their own life,” Denneson says. “We also asked what had changed in their lives since their most recent attempt. We tried to get at strengths and resources, as well, by asking what has helped them or what would help them overcome or handle the challenges they described.”

When the Veterans were asked about the circumstances that preceded their suicide attempt, some themes emerged that were common across the genders. There were also patterns unique to each group.

"I was surprised by how clearly different some of the experiences were by gender."

According to the researchers, the men and women both discussed negative experiences, such as failed or failing relationships, feeling betrayed by others, lacking a sense of purpose, financial problems, health symptoms, or feeling overwhelmed. “Although such concerns contributed to their motivations for suicide, the thoughts participants had just before deciding to attempt suicide centered more on their evaluations of self and their existence in the world,” the researchers write.

‘My self-esteem was so low’

The research team found that feeling worthless or shameful was the most prominent theme and precipitating thought to the suicide attempts among the female Veterans. “Women internalized feelings of powerlessness and poor relationships with others, and they experienced disruptions to their sense of self,

and coping resources, and perceived control over their environment,” the researchers write. “They reported feeling like ‘a throw away,’ often a reflection of how they believed others viewed them.”

A few of their responses are as such:

- “I felt like maybe it’s time for me to just leave this place because I’m shameful. I haven’t done anything in my life. I suck. That moment, I wanted to die.”
- “I felt like such a failure. No relationship worked. I wasn’t productive. I wasn’t doing anything that was good. I was just nonexistent in an existing world. My self-esteem was so low.”
- “... but my mind is telling me, ‘You don’t deserve to be here, you don’t deserve to be anything.’”

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

Gender differences in suicidal thinking

WOMEN

“I felt like such a failure.”
“I’m worthless.”
“You don’t deserve to be anything.”



MEN

“I was just tired of life.”
“Screw this.”
“It just isn’t worth it.”



Above is a sampling of gender-specific themes that arose when VA researchers interviewed 25 female and 25 male Veterans, all of whom had recently attempted suicide, about their suicidal thoughts. From a study led by Dr. Lauren Denneson of the VA Portland Health Care System. Infographic by VA Research Communications. Photos for illustrative purposes only: iStock/mladenbalinovac.

Study offers insight on how PTSD affects response to depression treatment

An analysis based on a large VA study on depression showed that patients with or without PTSD had similar relative responses to medication changes.

The original trial, the VA Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D) study, measured response in switching or augmenting treatment for patients not responding to antidepressants.

The new secondary analysis of this study group showed that participants who also had PTSD had generally worse rates of medication response, depression remission, and relapse than those without PTSD. However, different treatment changes yielded similar relative improvements in both groups.

'Better results than others'

VA researcher Dr. Somaia Mohamed, co-chair of the original VAST-D study and first author of the new analysis, notes that "VAST-D was the first study to show one treatment to have better results than others in the next step treatment of depression. The present secondary analysis extends these findings to show these differences in treatment benefits persisted when depression occurs with a specific psychiatric comorbidity."

The results appeared June 23, 2020, in the *Journal of Clinical Psychiatry*.

PTSD and major depressive disorder frequently occur together, especially among Veterans. Previous research has shown that Veterans with both conditions have worse mental health outcomes than those with only one condition. But how PTSD influences the effectiveness of next-step medication for depression has not been widely studied.

To investigate this relationship, researchers from multiple VA health care systems performed a secondary analysis of VAST-D.



Photo: ©iStock/junce

VA researchers studied how PTSD affects response to depression treatment.

Original study involved 35 VA medical centers

The VAST-D trial included more than 1,500 Veterans with non-psychotic major depressive disorder from 35 VA medical centers. At the time of enrollment, the participants were taking one of three common types of antidepressants: selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), or mirtazapine. For all participants, their current medication was not treating their depression effectively.

Participants were given one of three next-step treatments. Some were switched from their current medication to bupropion. Others had their current treatment augmented with bupropion. Bupropion is an antidepressant sold under several different names, such as Wellbutrin and Zyban. It can be taken on its own, but is also often used as a supplement to other antidepressants. A third group had the antipsychotic aripiprazole added to their existing treatment. Aripiprazole, sold under the brand name Abilify, is primarily used to treat schizophrenia and bipolar disorder.

[Read more at \[www.research.va.gov/currents\]\(http://www.research.va.gov/currents\)](http://www.research.va.gov/currents) ★

Researchers strive to improve kidney disease detection in VA



Photo by Edgardo Caballero.

Drs. Michelle Estrella and Michael Shlipak of the San Francisco VA work with a machine that measures two different kidney function tests: the cystatin C test and the creatinine test.

More than 15 years ago, Dr. Michael Shlipak began studying a test he believed to be much more accurate in detecting kidney disease than the one in standard practice for decades.

Shlipak, then the chief of general internal medicine at the San Francisco VA Health Care System, compared the relatively unknown cystatin C test, which Swedish scientists created in 1985, to the long-used creatinine test. Cystatin C is a protein that lives in all cells in the body; creatinine is a chemical byproduct of muscle activity. Both are filtered through the kidneys and are measured via a blood test, so the blood level reflects the speed of the filtering. Low filtration rates indicate a kidney problem.

His first big paper on cystatin C appeared in the *New England Journal of Medicine* in 2005. Shlipak and his team found that elevated blood levels of cystatin C accurately predict higher risks of heart disease, stroke, and death among elderly people with no known kidney problems. The creatinine test misses those risks almost entirely, according to the researchers.

Fast forward to today, and the creatinine test is still the predominant choice among nephrologists, who treat kidney disease. The question is why.

“That study put cystatin C on the map as saying, ‘Wait a minute. This may be a marker that could be useful,’ Shlipak says. “Cystatin C is clearly superior to creatinine because it overcomes the major weakness of creatinine’s inaccuracy in people with reduced muscle or limited activity. The obvious mystery is why after 15 years we’re still not using it very

much. I can't explain why the medical field is content to continue using creatinine when we have a better alternative. Unfortunately, some areas of medicine, like kidney testing, are very slow-moving."

But Shlipak is trying to pick up the pace. He is teaming up with the chief of nephrology at the San Francisco VA, Dr. Michelle Estrella, to improve kidney care for Veterans, in part, by making the cystatin C test available across the VA system. The two are co-leading a VA-funded study that will implement the test at the VA hospitals in San Diego and Houston, before it is accepted nationwide. They have also spoken to VA decision-makers about the test, including Dr. Michael Icardi, VA's national director of pathology and laboratory medicine services, and Dr. Susan Crowley, VA's national program director for kidney disease and analysis.

Icardi is "very enthusiastic" about incorporating the cystatin C test in VA. The procedure, he notes, does not have the limitations that come with the creatinine test, which is much less expensive per examination. But "with the advent of new measurement techniques, the financial advantage to creatinine testing is diminished," he adds.

Crowley wants the cystatin C test made available through each of VA's 22 VISNs (Veteran Integrated Service Networks). "Working with the VHA National Kidney Program and the VHA Pathology and Laboratory Medicine Service, Dr. Shlipak has been championing greater adoption of cystatin C measurement by VA providers," she says. "Leveraging VA data, he and

others have also been studying the use of cystatin C as a risk prediction marker for death among Veterans."

'You need to know how the kidney is functioning'

Shlipak knows of only two VA hospitals that do in-house blood sampling for cystatin C: the San Francisco VA and the James A. Haley Veterans' Hospital in Tampa, Florida. Some VA facilities that offer cystatin C measurement outsource the test to an external lab, but doing so is far less effective, he notes.

"When you have a hospitalized patient, you're making decisions hourly or at least twice daily," says

Estrella, who, like Shlipak, is affiliated with the University of California, San Francisco. "When you send a test out that comes back in two or three days, the information arrives too late. You may be dosing blood thinners, antibiotics, and chemotherapy drugs. You need to know how the kidney is functioning, so you don't prescribe too much or too little."

Kidneys perform life-sustaining functions that keep the rest of the body in balance, including by removing waste products and excess fluids. They also maintain a safe level of blood chemicals and control blood pressure. But a gradual loss of their ability to filter blood properly can lead to kidney disease, which can progress to kidney failure. The latter requires a kidney transplant or dialysis, which rids the body of waste products and excess fluids.

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

"We think patients need the cystatin C test for everyday decision-making, and using it may lead to earlier detection of kidney disease and fewer adverse events from kidney disease."

VA aims to validate effective COVID-19 treatments through new initiative

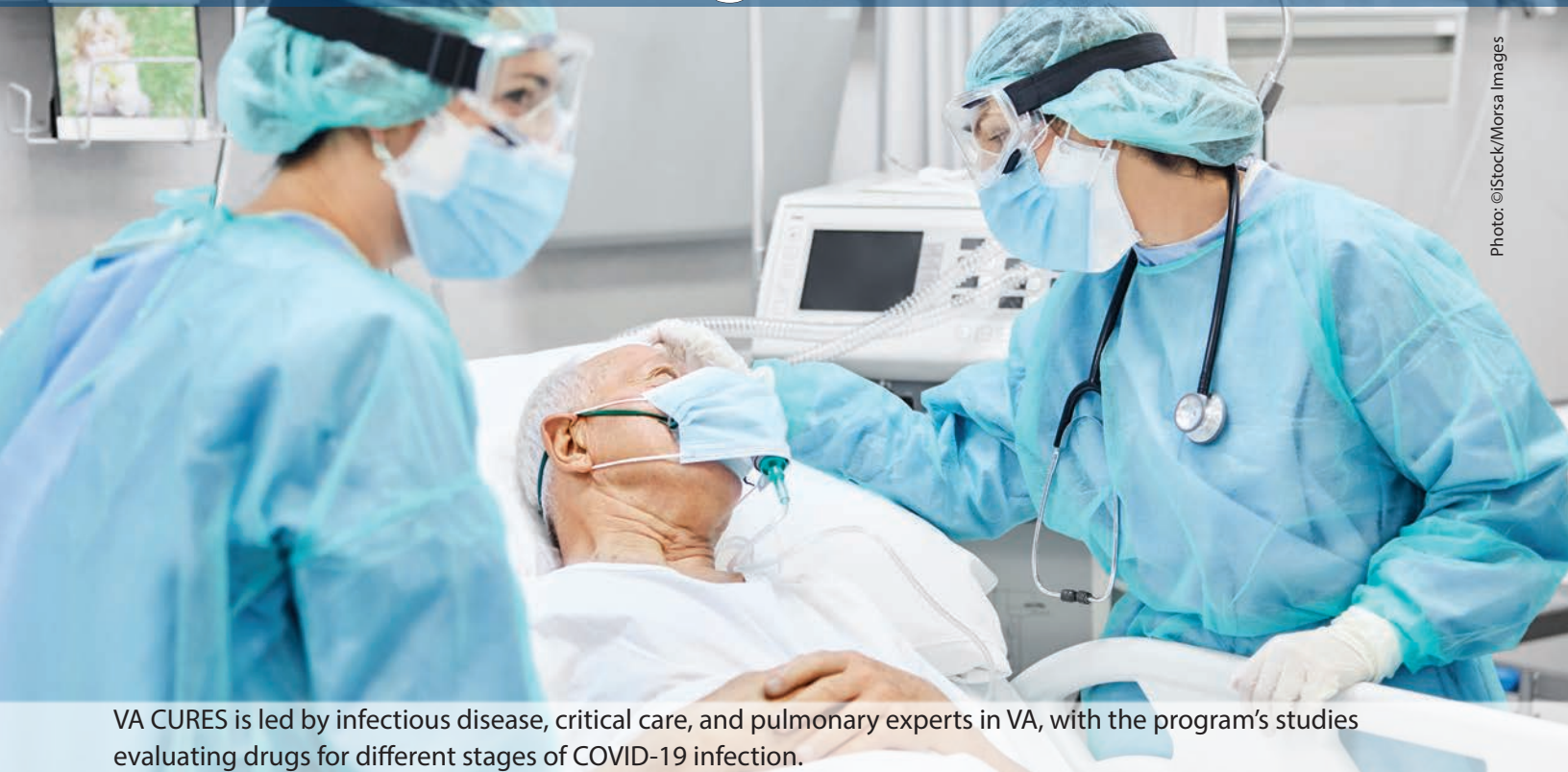


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VA CURES is led by infectious disease, critical care, and pulmonary experts in VA, with the program's studies evaluating drugs for different stages of COVID-19 infection.

VA is launching a new initiative aimed at giving Veterans faster access to potential COVID-19 treatments and confirming their effectiveness.

VA CURES—the “VA Coronavirus Research and Efficacy Studies”—is a master protocol. It offers a standardized framework for studies on many potential treatments for COVID-19, without the need for a new study design and protocol each time. Over the coming months, VA CURES studies will evaluate drugs for different stages of COVID-19 infection, from the prevention to outpatient and inpatient stages.

About 25 VA medical centers are participating in VA CURES. The program is led by infectious disease, critical care, and pulmonary experts in VA.

“This coordinated effort for controlled trials is very important so we can develop an infrastructure within VA to show what works with our patients,” says Dr. Edward Janoff, an infectious disease specialist at the VA Eastern Colorado Health Care System.

VA CURES studies will evaluate new treatments, such as antiviral agents and drugs that impact the immune system. Some trials may include outpatients with mild symptoms to prevent their progression to hospitalization. The VA CURES team also plans to prioritize preventive measures for Veterans who would be at high risk for illness should they become infected.

“We will begin by carefully evaluating treatments to study that we think have the best chance of bringing about an effective treatment not only for Veterans but also for other people,” says Dr. Sheldon Brown, an infectious disease

specialist at the James J. Peters VA Medical Center in the Bronx, New York. “That’s our immediate priority. The only thing we can rely on is good quality evidence. That’s exactly the purpose of having a program like VA CURES. We want to obtain the best quality evidence we possibly can so people are not misled about a benefit or the potential harm of a treatment when, in fact, it may be something that’s important to help them.”

First trial to focus on convalescent plasma

In the first VA CURES clinical trial, researchers are studying convalescent plasma for treating seriously ill COVID-19 patients. Convalescent plasma is the liquid part of the blood that contains antibodies, which are proteins the body makes to fight infections, such as COVID-19. It is donated by people who have recovered from COVID-19.

Some 700 Veteran volunteers with COVID-19 who are hospitalized at VA medical centers are being enrolled in the trial, which Janoff and Brown are leading. The study team is randomizing half of the patients to receive convalescent plasma. The others are receiving a saline placebo. Both the study team and patients are blinded to the form of treatment.

The study will determine whether convalescent plasma donated by Veterans and others can help COVID-19 patients recover when it’s infused into their blood. The key outcome measurement is how many patients experience respiratory failure or die from any cause by day 28. A secondary outcome is time to recovery within the 28-day period.

"This coordinated effort for controlled trials is very important so we can develop an infrastructure within VA to show what works with our patients."

Earlier this year, the U.S. Food and Drug Administration (FDA) authorized use of convalescent plasma as an investigational treatment for COVID-19 through the FDA’s expanded access program. That program was used widely throughout the nation, including about 80 VA sites, as an approach for seriously ill patients who have few, if any, options left. It ended last month. The FDA has now authorized emergency use of the therapy, based on the available scientific evidence to date. That means not only can researchers use convalescent plasma for investigational purposes, but health care providers can also use it for hospitalized patients with COVID-19.

“This trial will go a long way toward helping in the fight against COVID-19,” VA Secretary Robert Wilkie said in a press release. “VA CURES will provide valuable information that will benefit our Veterans who are battling COVID-19, as well as other patients and the medical community in general.”

'Well-validated treatments to improve the health of Veterans'

Each VA CURES study, Janoff explains, will build on the preceding trials and involve patients with different levels of disease severity. “These clinical trials are carefully designed studies to prove what does and what doesn’t work for optimal care of patients with COVID-19,” he says. “Convalescent plasma is the first of a number of studies. We will verify what the outcomes are before we move on to another study.”

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

Vets have good experiences with VA and VA-purchased community care



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Veterans have a generally favorable view of their care at VA facilities and in the community, according to survey data from more than 1 million former service members.

“**H**ow was your experience?” That question, or some version of it, is increasingly being asked of consumers—including in health care. Visit a medical practice nowadays and you’re likely to get a follow-up email asking you to rate the experience.

VA is no different. VA medical centers send surveys to random samples of outpatients every month asking how their visits went.

These data are part of a newly published study. Researchers compared survey responses from 2016 and 2017 from VA-enrolled Veterans who either received outpatient care in VA or went outside VA for primary, mental health, or other specialty care in their local communities. In all, survey responses from over 1 million Veterans are included in the analysis.

The new study, published in the August 2020 issue of *Health Affairs*, found that overall Veterans had a generally favorable view of their care at both VA facilities and in the community. However, VA care scored better than community care in three of the four categories covered in the surveys: overall provider rating, communication, and coordination.

In the fourth area, access to care, the results were more mixed, depending on the type of care. VA scored slightly lower on access to specialty care, such as cardiology or orthopedics. There were no differences in access to primary or mental health care.

For provider ratings, average scores in both settings were mainly between 8 and 9 on a scale on which 10 was the

highest possible score. For the other areas—communication, coordination, and access—average composite scores for both settings were mainly between 3 and 4, with 4 representing the most favorable rating.

“Overall, patient experiences were quite good in both VA and community care,” says study leader Dr. Megan Vanneman. She emphasizes that VA’s goal is to promote the best patient experiences and health outcomes regardless of where Veterans end up receiving their care. “We want to see Veterans having access to high-quality care,” she says.

Comparisons now ‘more important than ever’

Thanks to recent laws, eligible VA patients—mainly those who live far from VA clinics and hospitals, or those who need types of care not provided adequately or in a timely fashion in VA—are able to see non-VA healthcare providers in their community, with VA paying for this care. These options widened under the VA MISSION Act of 2018. Prior to that, the Veterans Choice Program offered similar access to outside care, albeit on a less extensive scale.

Given the expanded options for Veterans to seek care outside VA, comparing the two sectors “is more important than ever,” says Vanneman. Her group’s study is the first to compare the experiences of VA-enrolled Veterans in the two different care settings.

Vanneman is a health services researcher at the VA Salt Lake City Health Care System and the University of Utah. She is part of the VA Informatics, Decision-Enhancement and Analytic Sciences (IDEAS) Center. Researchers at two other VA centers contributed to the study: the Center for Healthcare Organization and Implementation Research (CHOIR), in the Boston area; and the Health Economics Resource Center

(HERC), in Menlo Park, California.

The researchers also worked with staff from VA’s Office of Community Care, which oversees VA-purchased care; and the Office of Reporting, Analytics, Performance Improvement and Deployment (RAPID), which oversees VA patient surveys and other quality measures. The patient questionnaire is called the Survey of Healthcare Experiences of Patients, or SHEP. It’s based closely on the Consumer Assessment of Healthcare Providers and Systems surveys developed by the Agency for Healthcare Research and Quality and considered the industry standard.

‘Experience’ versus ‘satisfaction’

Vanneman notes that the focus of the research was patient experience, not satisfaction. The two are related, but experience is seen as a more objective measure. For instance, the SHEP asks patients if they had to wait more than 15 minutes past their appointment time. That’s considered a reasonable standard for medical practices to meet, regardless of whether a patient objects after waiting only five minutes, or enjoys watching TV and browsing magazines and doesn’t mind waiting 30 minutes to be seen.

While patient experience is an important health care measure, it’s not the only one health systems take into account. “I think of patient experience as one type of quality metric,” says Vanneman. “There are other quality metrics that relate to care processes—for example, whether or not follow-up care occurred. And others that relate to positive or negative health outcomes—for example, complication rates of surgeries.” She notes that VA also looks at these and other metrics, in addition to patient experience.

[Read more at \[www.research.va.gov/currents\]\(http://www.research.va.gov/currents\)](http://www.research.va.gov/currents) ★

Researchers study effects of smoking on therapeutic stem cells



Photo by Adan Pulido

Dr. Alex Chan and Dr. Ngan Huang are studying a rodent model of peripheral artery disease to learn whether nicotine will block the creation of new blood vessels in response to therapeutic stem cells.

Many in the research community believe there is huge potential for stem cell therapy to treat a broad range of diseases. Stem cells, special human cells that can develop into many different cell types, essentially serve as a repair system for the body.

Currently, more than 5,000 clinical trials worldwide are based on therapeutic stem cells, including some at VA hospitals for illnesses ranging from cardiovascular disease to cancer.

But gaps remain in the transition of stem cell application from the research stage to patients.

“One of these gaps is how a patient’s lifestyle choices and underlying health conditions may negatively affect stem cell therapy,” says Dr. Ngan Huang, a biomedical engineer at the VA Palo Alto Health Care System in California. “Given the prevalence of cigarette use and rise of electronic cigarettes, we believe this subject is an important aspect of stem cell application that remains unexplored. Not much is known about nicotine and its direct effect on therapeutic stem cells.”

Huang and Dr. Alex Chan, a postdoctoral research fellow at VA Palo Alto, are studying the effects of nicotine, a highly addictive tobacco stimulant normally inhaled with cigarettes, on therapeutic stem cells. The two co-authored a review article on the effects of nicotine on stem cell therapy that appeared online earlier this year in the journal *Regenerative Medicine*. Both scientists are also affiliated with Stanford University.

Researchers to treat disease that obstructs blood vessels

There are two arms to their study. In one, Huang and Chan are injecting cells into mice that have been exposed to nicotine, as well as those that haven't, with the intention of treating peripheral artery disease, which obstructs blood vessels in the arms and legs. In the other arm, the researchers will compare stem cells in smokers and non-smokers. They will see if the groups differ at producing cells that are effective at making new blood vessels.

Veterans and service members are more likely to use tobacco products than civilians, according to the U.S. Centers for Disease Control and Prevention (CDC). CDC statistics show that about 30% of Veterans used some form of a tobacco from 2010 to 2015. Tobacco use was higher among Veterans than non-Veterans for males and females across all age groups, except men ages 50 and older.

Huang and Chan are hoping to bring more awareness about the effects of smoking on stem cells to the Veteran community, as well as other types of nicotine exposure that may impact the effectiveness of stem cell therapy, such as electronic cigarettes.

E-cigarettes, also known as "vapes," are battery-operated devices that people use to inhale an aerosol, which typically contains nicotine, flavorings, and other chemicals that are known to harm one's respiratory system.

The effects of lifestyle and co-occurring health conditions on stem cells have been "largely neglected," Chan explains. "Preclinical studies of stem cell therapies have mainly been conducted in healthy animal models. This does not reflect the settings in the clinics where patients requiring stem cell therapy may have underlying diseases, such as diabetes, high blood pressure, and lifestyle choices like smoking and diet."

The lab study calls for exposing 10 mice to nicotine for a month, before they and another 10 mice that have not been exposed to nicotine are injected with

stem cells. The researchers are then simulating a case of peripheral artery disease in each animal, before severing and removing one of the main arteries that supplies blood to the leg—the femoral artery. That will create a condition called critical limb ischemia, a blockage of the arteries that reduces blood flow to the hands, feet, and legs.

'The main highway being clogged or obstructed'

Huang and Chan believe the nicotine will prevent the ischemia leg from using the stem cells to create new blood vessels.

"We're using this peripheral arterial disease model to mimic a real scenario where people who are prior or current smokers have peripheral artery disease," Huang says. "We're injecting stem cells into the ischemia leg to see if they are able to create new blood vessels. That's something these therapeutic cells should normally be able to do."

There are two main types of stem cells: pluripotent stem cells and adult stem cells. The research team is using endothelial cells that are generated from a form of pluripotent stem cells called induced pluripotent stem cells. Those cells are collected from a human donor

and are altered to have elements like those of embryonic stem cells but do not trigger the same ethical concerns. They are often derived from skin cells or white blood cells but can also be generated from other kinds of cells. Once they are isolated from the donor, they go through genetic modification steps to turn them into induced pluripotent stem cells, which are being studied as a potential tool for drug development, disease modeling, and cell therapy.

Endothelial cells make up the inner layer of all blood vessels in the body.

"Those cells interact with blood all the time," Huang says. "They are also the cells that are the first responders in terms of making new blood vessels. Whenever we have a disease or an injury where we

"But with many unknowns, it will be years before stem cells therapies become the gold standard treatment for certain diseases."

need to create new blood vessels, the endothelial cells become activated and make the beginnings of new blood vessels.

“Capillaries, blood vessels that contain just the endothelial cells, are the most rudimentary blood vessels,” she adds. “That’s why endothelial cells are critical for making new blood vessels. In the case of peripheral artery disease and obstructed blood flow, the idea is to create new blood vessels that may be able to bypass the area of obstruction to allow the blood to flow through the leg. Think of peripheral artery disease as the main highway being clogged or obstructed. The endothelial cells are trying to create side streets and other kinds of detours to allow blood to flow through the leg.”

More research needed to validate findings

Huang’s lab also works with adult stem cells called mesenchymal stem cells, which live in bone marrow and fat tissue.

Generally, Chan says, nicotine reacts similarly in different types of stem cells because it’s known to interact through one type of receptor on the cells. “There are some studies suggesting that induced pluripotent stem cells are more resistant to cigarette smoke exposure compared to mesenchymal stem cells,” he notes. “However, these studies are quite narrow in their scope and more research is needed to validate such findings.”

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

SMOKING AND THERAPEUTIC STEM CELLS

VA researchers want to learn if smoking can potentially affect the outcome of stem cell therapy. In an ongoing study, they are injecting stem cells into 10 mice that have been exposed to nicotine, as well as 10 that haven't, with the intention of treating peripheral artery disease, which obstructs blood vessels in the arms and legs. The researchers believe the nicotine will prevent the leg with reduced blood flow from using the stem cells to create new blood vessels.

No exposure to nicotine

exposed to nicotine

Based on work by Drs. Ngan Huang and Alex Chan at the VA Palo Alto Health Care System. Infographic by VA Research Communications, August 2020. Photo: ©iStock/Nastco, Dr_Microbe, Pakhnyuschchy.

Insomnia in Post-9/11 Veterans

In a study of 5,552 post-9/11 Veterans using VA health care:

57%
had insomnia

Veterans with other conditions had higher rates of insomnia:

93%

Posttraumatic Stress Disorder

78%

Traumatic Brain Injury

70%

Chronic Pain

Conclusion: "The findings suggest alarmingly high rates of insomnia disorder in this population. Examining and treating insomnia disorder, especially in the context of co-occurring disorders (e.g., PTSD) will be a necessity in the future."

From "Prevalence rates and correlates of insomnia disorder in post-9/11 Veterans enrolling in VA healthcare." *Sleep*. 2020 June 12. Infographic by VA Research Communications. Photo © iStock/demaerrev.

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www.research.va.gov/pubs/infographs

The high burden of 'subthreshold' PTSD

- Those with subthreshold PTSD have some PTSD symptoms but not enough to meet the criteria for a PTSD diagnosis.
- The findings below are based on data from the National Health and Resilience in Veterans Study.

Subthreshold PTSD	Probable PTSD (meets full diagnostic criteria)
Lifetime (any time during life)	Lifetime (any time during life)
22.1%	8.0%
Past month	Past month
13.3%	5.3%

Conclusion: "The results of this study suggest that a strikingly high proportion of U.S. veterans - approximately one in three (subthreshold plus full diagnosed PTSD) - experience clinically significant PTSD symptoms in their lifetime."

Source: "High burden of subthreshold PTSD: Sleep, trauma, and disability in VA military veterans." *World Psychiatry*, June 2016. Infographic by VA Research Communications, January 2018. Photo for illustrative purposes only. Photos © iStock/MTMCOMS

Individual Placement and Support for Veterans with PTSD

- Individual placement and support helps Veterans with PTSD find employment through job coaching based on their interests and backgrounds, rather than traditional one-size-fits-all vocational rehabilitation and transitional work placements.
- The results below are from the Veterans Individual Placement and Support Towards Advancing Recovery (VIP-STAR) study of 541 Veterans.

	Transitional Work	Individual Placement and Support
Found steady work	23%	39%
Found competitive jobs	57%	69%
Average income for study period	\$10,989	\$14,642

Conclusion: "Individual placement and support is more successful than transitional work at helping unemployed Veterans with PTSD obtain and sustain competitive employment."

Source: "Effects of Evidence Based Supported Employment on Achieving Steady Work among Veterans with Posttraumatic Stress Disorder: A Randomized Controlled Trial." *PTSD Psychiatry*, Feb. 28, 2018. Infographic by VA Research Communications, February 2018. Photo for illustrative purposes only. © iStock/Steve Grijpman 9411117

Firearm training among U.S. adults

Findings from a study by VA researchers and colleagues

- The percentage of U.S. firearm owners who reported receiving formal firearm training showed little change between 1994 (56-58%) and 2015 (61%).
- The most commonly reported combination of training topics was safe handling, safe storage, and accident prevention.
- Only 15% of owners said their training covered suicide prevention.
- Conclusion: The proportion of U.S. firearm owners with formal fire arm training has not meaningfully changed in two decades. Training programs vary widely. Efforts are needed to standardize and evaluate the effectiveness of training.

Source: "Standardizing and evaluating the effectiveness of firearm training." *Firearm Injury Prevention*, July 2017. Photo for illustrative purposes only. © iStock/Steve Grijpman 9411117



Dr. Bertrand Huber is the director of the PTSD Brain Bank at the VA Boston Healthcare System.

VA Researchers Who Served: Dr. Bertrand Huber

Dr. Bertrand Huber, an Army Veteran, is the director of the PTSD Brain Bank at the VA Boston Healthcare System. His research focuses on the relationship between traumatic brain injury and neurodegenerative diseases, with a primary interest in how the brain clears damaged proteins after injury. Much of his current work centers on repetitive brain trauma and preventing the accumulation of tau, a critical protein that can choke off or disable neural pathways that control memory, judgement, and other areas of the thought process. He is also an assistant professor of neurology at Boston University. He served in the U.S. Army from 1989 to 1992 and received the Army Service Ribbon, the National Defense Service Medal, and the Overseas Service Ribbon, among other honors.

What motivated you to join the military?

Two main factors influenced my decision to join the military. The first was that I grew up during the Cold War, and it truly felt like nuclear war could happen at any time. I felt that joining the military was something I had to do to defend the country. Even though a person is inconsequential during a nuclear exchange, I felt that serving the country is an important act. I also joined the military because the United States opened its doors to my family after World War II. My great grandfather was killed in the Nazi concentration camps. While it's not clear if it was because of his heritage or his refusal to work for the German war machine, he was eliminated. After the war, my grandmother immigrated to America. From an early age, I knew that I would join the military to do my part to prevent what happened in Germany from ever

happening again. I felt that I would never be able to pay back what I had gained by being an American, but that I might at least be able to pay it forward to the next generation.

What inspired your research career?

When I was in the Army stationed at Fort Stewart in Georgia, I met a soldier after the first Gulf War who had a strange new sickness. We now know this disease as Gulf War illness. I met him while we were both processing out of the Army. We became friends. This chance encounter started me thinking about what kind of career I wanted. At the time, it was just a seed of an idea. But as I studied at the University of California, Santa Cruz, medicine became the focus of my academic work, eventually leading me to a doctorate in biophysics at the University of California, San Francisco, and later a medical degree from the Health Sciences & Technology program at Harvard University.

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

Many mentors have inspired me during my career, but it is exceedingly difficult to pick one above another. When I was in the military in basic training, my drill sergeant was very inspiring. He was a champion kickboxer who had served in the military for many years and had an attitude toward life that anything is possible if you set your mind to it. His way of thinking made me realize that most limitations are self-imposed, which paved my way for graduate school and medical school. I now work with Dr. Ann McKee, one of the top experts in the country on the neurodegenerative disease chronic traumatic encephalopathy, at the PTSD Brain Bank. She has mentored me while I have been in Boston. Her stories and insights about science are a constant source of inspiration to me. Her work is an example of how you can make a difference through scientific research. I have also worked with Dr. Matthew Friedman, who was the leader of the National Center for PTSD for years and was responsible for the creation of the PTSD Brain Bank. His ability to lead and find consensus is inspiring.

Describe your military experience.

I entered the military in 1989. I did my basic training at Fort Bliss in Texas. I signed up for the Army



Bertrand Huber served in the Army from 1989 to 1992 and was stationed in Germany at a frontline NATO air base during the Cold War.

College Fund, which limited me to a small number of combat arms jobs. But I did have the opportunity to pick my duty station. I picked Germany and was stationed at Bitburg Air Base, which was a frontline NATO base during the Cold War. I was part of an anti-aircraft group that was deployed to protect the base from Soviet attack. My time in the military coincided with the removal of the Berlin Wall. It was an amazing time to be in the military, especially in Germany, because it was the end of the Cold War.

However, almost as soon as the Soviet Union fell, the first Gulf War started. I recall the anxiety as we prepared for war. The base was locked down as we prepared for deployment. At that time, I had the rank of specialist and was responsible for targeting and firing our anti-aircraft system. Our training took on a different feel as we drilled for combat. For those old enough to remember, the war was over in five days, and my unit was not deployed to the Persian Gulf. I have many fond memories of Europe.

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



RESEARCH CURRENTS

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

Potential new migraine medication developed

An international team including an Iowa City VA researcher has developed a potential new nasal migraine medication. Previous research has established that the peptide (a string of amino acids) CGRP is involved in migraine development. The researchers prepared a compound that blocks the receptors in the brain that bind to CGRP. Using a mouse model, they found that the compound significantly reduced CGRP's ability to activate the receptors, compared to other compounds. The compound can be formulated into a dry powder without degrading, meaning it potentially could be used nasally to treat migraines, according to the researchers. (*Journal of Pharmacy and Pharmacology*, June 25, 2020)



Photo: ©iStock/NickyLloyd



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