



RESEARCH CURRENTS

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



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Photo by Lisa Pessin

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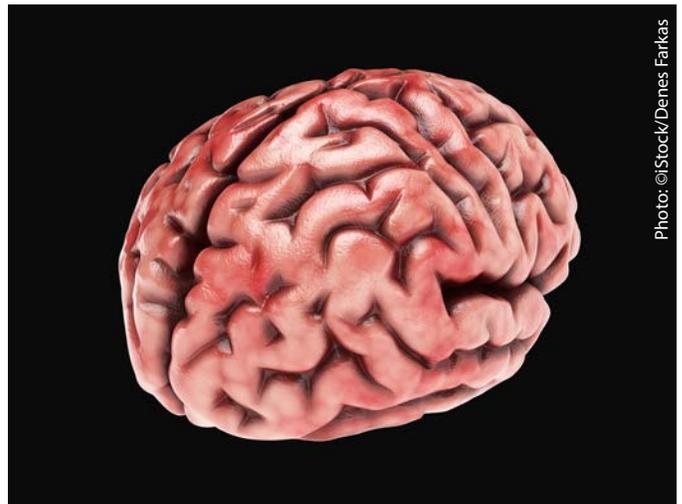


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Gene linked to thinner cortex in those with PTSD

Researchers at the VA Boston Healthcare System found evidence that gene variants are linked to reduced cortical thickness in people with PTSD. Past research has shown that PTSD is connected to reduced thickness in the cortex, the outer layer of the brain. By testing the genomes of 240 Veterans with PTSD, the researchers found that participants with specific variants of the gene PPM1F had reduced cortical thickness. The results suggest that people with these gene variants may be susceptible to greater PTSD severity from changes in brain structure, say the researchers. (*Journal of Affective Disorders*, Dec. 1 2019)



Cover photo: Dr. Mary Rhee, a physician-researcher with the Atlanta VA and Emory University, discusses the use of an insulin pen with VA patient Joseph Fields. Rhee's research has suggested a more accurate way to diagnose diabetes. Read more on page 3. (Photo by Lisa Pessin)

The print edition of
VA Research Currents
 is published quarterly by:
VA Research Communications
U.S. Department of Veterans Affairs
 31 Hopkins Plaza, Ste. 102
 Baltimore, MD 21201
 443-759-3456
 varesearchcurrents@va.gov

Read the expanded online edition of
 VA Research Currents at www.research.va.gov

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VA



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Study suggests a more accurate approach to diabetes diagnosis

Using HbA1c levels alone can lead to both over- and under-diagnosis of diabetes, according to Atlanta VA researchers and colleagues. HbA1c blood tests determine glucose levels over the previous two to three months. It is the most common test to diagnose diabetes and assess how well patients are controlling their blood sugar. However, for some people the HbA1c test is inaccurate. Some may have higher or lower HbA1c readings than would be expected based on actual glucose levels. The researchers gave participants with diabetes oral glucose tolerance tests, which compare fasting glucose levels with levels after the person is given oral glucose. They found that using

HbA1c alone led to under-diagnosis of diabetes for people who had lower HbA1c mismatches, and over-diagnoses for people with mismatches in the other direction. The results suggest oral glucose tests should be used along with HbA1c to ensure a proper diagnosis, say the researchers. (*Diabetic Medicine*, Nov. 13, 2019)



Tinnitus rates going up in active duty service members

Tinnitus rates in active duty service members have increased significantly in recent years, according to a study by South Texas VA Health Care System and University of Texas at San Antonio researchers. They studied the health records of more than 85,000 active duty service members. Between 2001 and 2015, the rate of tinnitus more than tripled. Tinnitus refers to a ringing or buzzing in the ears. It is often caused by blast exposure. This was the first study to assess tinnitus rates in active duty rather than in Veterans. Further studies are needed on how hearing damage impacts active duty service members, say the researchers. (*American Journal of Audiology*, Dec. 16, 2019)



Veterans with diabetes find peer mentors valuable

Veterans with diabetes found value in a peer mentor program aimed at improving self-care. Veterans at the Corporal Michael J. Crescenz VA Medical Center who had trouble controlling their diabetes were paired with other Veterans who had gotten their blood sugar under control. Mentors called mentees daily to offer encouragement and advice. The researchers interviewed both groups after a six-month period. Participants described several benefits of the program, including accessible support, improved self-confidence,

and increased accountability. Some participants faced barriers to the experience, such as scheduling problems and interpersonal conflicts. The more successful mentees said they had a strong connection to their mentor. The study shows that a low-cost peer mentor program can offer support to patients with diabetes that may improve their self-care. (*Diabetes Educator*, December 2019)



Dietary oils could help with diabetic nerve damage

A rat study has shown that dietary oils could be an effective treatment for nerve damage caused by diabetes. Researchers from the VA Iowa City Health Care System and University of Iowa simulated diabetes by giving rats a high-fat diet. They then replaced the fat in the rats' diets (from lard) with unsaturated fats from several dietary oils. Rats given fish oil and flaxseed oil showed improvement in peripheral nerve damage. Enriched fish oil also led to the greatest improvements in vascular dysfunction and cognitive activity. The other dietary oils tested—olive

oil, safflower oil, and evening primrose oil—provided no or only small improvements. The results show that dietary fat modification, especially with fish oil, could be a useful treatment for vascular and nerve problems caused by diabetes, say the researchers. (*Journal of Diabetes Research*, Aug. 7, 2019)



Smoking linked to higher prostate cancer mortality

Smoking is linked to a higher risk of dying from prostate cancer, found a VA San Diego Health Care System study. Researchers looked at more than 73,000 VA patients diagnosed with prostate cancer. The rate of death from prostate cancer was 5.2% for current smokers within 10 years of their diagnosis. Past smokers had a 4.8% mortality rate, while those who never smoked had a rate of 4.5%. The study shows that prostate cancer diagnosis may be an important opportunity to discuss quitting smoking. (*Prostate Cancer and Prostate Diseases*, Oct. 17, 2019)



E-cigarettes may impair body's infection-fighting ability

Electronic cigarettes may weaken the body's ability to fight infection by affecting immune cells called neutrophils, found a study by VA San Diego and University of California San Diego researchers. Neutrophils are white blood cells that help control infections. Researchers exposed human cells to e-cigarette vapor in a lab. Exposure to the vapor interfered with neutrophils' ability to respond to the presence of bacteria. The vapor hindered the neutrophils' ability both to move to the site of bacteria and to produce infection-fighting substances. The neutrophils were affected even when nicotine was not present in the vapor, meaning that e-cigarette

ingredients other than nicotine may be harmful. The researchers also found that mice exposed to e-cigarette vapor were less able to fight off bacterial infections than control mice. The results suggest that using e-cigarettes could change the immune response and make people more susceptible to infections, according to the researchers. (*American Journal of Physiology—Cell Physiology*, Jan. 1, 2020)



Army Veteran Joe Montanari suffered a TBI in Iraq. He currently works as the military coordinator for LIMBIC and is a study participant himself.

New consortium probing mysteries of traumatic brain injury

LIMBIC, funded by VA and Defense, is the world's largest cohort of current and former military members that is dedicated to the study of mild traumatic brain injury.

A rmy Veteran Joseph Montanari is battling the aftereffects of concussions he experienced in the military—one in Iraq in 2004 and the other one in Kosovo in 1999. He struggles with balance issues and constant headaches. “It took a while to adapt once I got back from deployment,” he says.

Montanari is in an ambitious new project that is seeking answers. He’s participating in the Long-term Impact of Military Relevant Brain Injury Consortium (LIMBIC). It’s the world’s largest research cohort of Veterans and Service members that is dedicated to the study of mild traumatic brain injury (TBI), also known as a concussion.

LIMBIC is funded by VA and the Department of Defense. The acronym is a reference to the brain’s limbic system, which is involved in emotion, learning, memory, and motivation. All can be affected in TBI.

The five-year program centers on two elements. One is a long-term study of 3,000 to 5,000 Veterans and Service members from all eras, 80% of whom will have had at least one mild TBI. The other 20% of the participant will also be combat Vets, but without a TBI history. They will serve as a control group for the research.

The other core element is an epidemiological database of military and VA health records, disability assessments,

and all other administrative information on more than 2 million Vets and Service members.

Team includes more than 50 researchers

Dr. David Cifu, a leading TBI expert, heads LIMBIC. He is with Hunter Holmes McGuire VA Medical Center in Richmond and with nearby Virginia Commonwealth University.

The research team consists of more than 50 researchers from VA medical centers, universities, and military treatment facilities, including five Defense and Veterans Brain Injury Center sites.

"Over the next five years, we will work to deliberately unlock the mysteries of military concussion," says Cifu.

LIMBIC continues work of earlier consortium

VA and DOD funded LIMBIC in October 2019 to continue the work of the Chronic Effects of Neurotrauma Consortium (CENC). That six-year VA-DOD project focused on understanding the lifetime impacts of military service and mild TBI with respect to brain disorders like PTSD and neurodegenerative diseases, including dementia, Parkinson's, and amyotrophic lateral sclerosis.

Only one of the original seven CENC studies, a long-term analysis of more than 1,700 Veterans and Service members from Iraq and Afghanistan who incurred at least one mild TBI in combat, is continuing under LIMBIC. In addition to increasing the number of participants to as many as 5,000, the researchers will explore new ways to treat symptoms and prevent future ones through randomized controlled clinical trials. (The 1,700-participant CENC study included a similar control group.)

The epidemiological database, which is also a continuation of work under CENC, involves 2 million Veterans and Service members who have been treated in VA or the U.S. military health system. The LIMBIC research team recently added about 100,000 names

"Over the next five years, we will work to deliberately unlock the mysteries of military concussion."



Photo by Robert Lisak

Joe Montanari undergoes a blood draw with researcher Dr. William Walker in 2017, when Montanari was part of the Chronic Effects of Neurotrauma Consortium.

to the database, most of whom are Veterans, and new information from 2015 to 2018.

In early CENC findings from the database, researchers documented possible links between combat concussions and dementia, Parkinson's disease, chronic pain, opioid use, and suicide risk. To study how the brain recovers from injury, they also developed specialized diagnostic tests for Service members and Veterans using questionnaires, physical exams, brain imaging, fluid biomarkers, and electrophysiology.

As important as the epidemiological research is, the expansion from 1,700 to more than 3,000 participants in the long-term study is the highlight for LIMBIC. By at least doubling the number of participants and by recruiting Veterans and Service members from all U.S. conflicts and wars dating back to World War II, Cifu says, the researchers will be better able to explore the link between mild TBI and the potential development of neurodegenerative diseases. The participants will be followed with annual checkups for

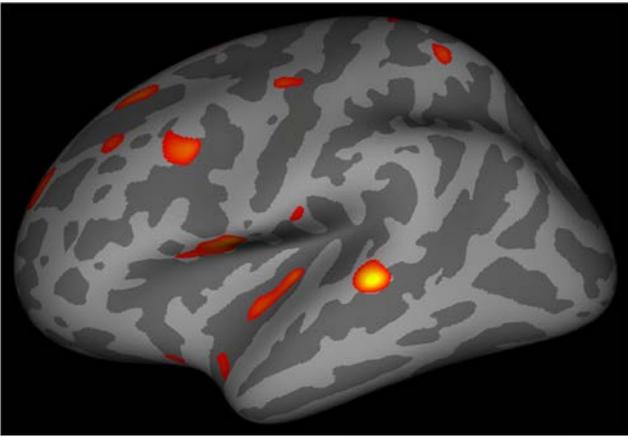


Image courtesy of CENC

This computerized image from a 2019 CENC study is based on MRI scans of participants. The colored regions indicate reduced thickness in the cortex among those with TBIs, compared to non-TBI controls.

the rest of their lives.

In addition to being a LIMBIC participant himself, Joseph Montanari works for the program. He helps get others involved in the research and supports them in a variety of ways.

“I really enjoy being a part of it,” he says. “It’s just great to know that you’re doing something to possibly help out our brothers and sisters in the military. I’ve pretty much been through everything and had a lot of close calls out there. Now that I’m back in the states, it’s great to be able to help wherever possible.”

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

Photo: Staff Sgt. William Tremblay/USA



Traumatic brain injury is considered the signature injury from the post-9-11 conflicts. The Defense and Veterans Brain Injury Center reported more than 408,000 TBIs among U.S. Service members between 2000 and early 2019. The majority were classified as mild in severity.

Million Veteran Program study sheds light on genetic basis of anxiety

In the largest genetic study on anxiety to date, VA researchers found new evidence on the underlying biological causes of the disorder. The study used VA Million Veteran Program (MVP) data to identify regions on the human genome related to anxiety risk. This could lead to new understanding and treatment of the condition, which affects one in 10 Americans. According to Dr. Dan Levey of the VA Connecticut Healthcare Center and Yale University, one of the lead authors on the study, the findings are “an important step forward” in the understanding of anxiety disorders and how genes contribute to mental conditions.

The results appeared Jan. 7, 2020, in the *American Journal of Psychiatry*.

Working toward ‘precision medicine’ for anxiety disorders

Anxiety refers to anticipation of perceived future threats. In anxiety disorders, these concerns are out of proportion to the actual anticipated event, leading to distress and disability. Anxiety disorders often occur alongside other mental health disorders like depression.

Only a third of those with anxiety disorders receive treatment. Some forms of psychotherapy, such as cognitive behavioral therapy, have proved effective, as have medications such as selective serotonin reuptake inhibitors. In other fields of medicine, genetic studies have led to precision medicine approaches—tailoring drug treatment to patients’ individual genetic and biochemical profiles—for a number of diseases. The researchers hope more genetic insight will lead to similar approaches for anxiety.

The researchers compared the genomes of nearly 200,000 MVP participants. They identified five



Photo by Robert Lisak

Numerous genetic studies are now underway using data from VA’s landmark Million Veteran Program, which currently has upwards of 800,000 participants.

locations on the human genome related to anxiety in Americans of European descent, and one in African Americans. Gene variants at these genome locations could increase anxiety risk, say the scientists.

Findings on African American participants ‘especially important’

The findings for the African American participants are especially important, says Levey. “Minorities are underrepresented in genetic studies,” he explains “and the diversity of the Million Veteran Program was essential for this part of the project. The genetic variant we identified occurs only in individuals of African ancestry, and would have been completely missed in less diverse cohorts.”

The study produced the first genome-wide significant findings on anxiety in African ancestry, notes Levey. About 18% of MVP participants are African American.

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



Dr. Bruce Montgomery meets with Navy Veteran Allen Petchnick, whose prostate cancer has been effectively treated to date with targeted therapy.

VA, Prostate Cancer Foundation seek solutions for aggressive prostate cancer

A partnership between VA and the Prostate Cancer Foundation is speeding the development of treatments and cures for Veterans with aggressive prostate cancer through precision oncology.

While in treatment for an aggressive form of prostate cancer at the VA Puget Sound Health Care System in Seattle, Navy Veteran Allen Petchnick faced a daunting situation. His PSA blood test, the main screening tool for cancer of the prostate, had risen to 13, which for him was dangerously high. Plus, his cancer had spread to other parts of his body.

“He was looking at very tough outcomes,” says Dr. Bruce Montgomery, an oncologist at VA Puget Sound. “He was passing out because his tumor had metastasized to lymph nodes in his neck, which was pressing against one of his arteries.”

Montgomery led a medical team that performed next-generation sequencing, an innovative way to sequence the human genome at high speed and low cost, on tissue in Petchnick’s lymph nodes. They spotted mismatch repair (MMR)

deficient cells, which usually have many genetic mutations—the changing of the structure of a gene—that may lead to cancer. Knowing if a tumor is MMR-deficient may help clinicians plan treatment or predict how the tumor will respond to treatment. This is an example of precision oncology.

Petchnick received immunotherapy, a form of precision oncology in which organisms in the body's immune system are used to fight cancer. Now age 79, he's been on immunotherapy drugs for nearly two years, during which time his PSA (prostate specific antigen) level has become undetectable and the tumor continues to shrink, Montgomery notes.

“He went from basically being unable to get out of a chair to going shopping with his granddaughter in just one cycle of therapy,” Montgomery says. “He may be cured. But we'll only know that when we stop his therapy, which is likely to happen soon. Right now, he's very close to a complete response after looking like he was going to be in very difficult straits.”

Petchnick is one of several major success stories that have surfaced from an advanced level of medical care made possible by a partnership between VA and the Prostate Cancer Foundation (PCF), a philanthropic group that funds research to prevent and cure prostate cancer. The partnership is centered on speeding the development of treatment and cures for Veterans with aggressive—or metastatic—prostate cancer through precision oncology.

The procedure involves the molecular profiling of tumors to identify targetable genetic mutations through means such as immunotherapy, chemotherapy, and targeted therapy, all of which are used to kill aggressive cancers that have spread in the body. Targeted therapy, which works by targeting the genes, proteins, or tissue that contribute to cancer growth and survival, can be immunotherapy or chemother-

apy, as long as it's being used because of a specific marker or target that makes it more likely to work.

Precision oncology is fast developing and has entered the mainstream

of clinical practice, with application to a myriad of cancers. Each cancer patient may have different mutations in play, and researchers are learning how to leverage this genetic information to improve outcomes.

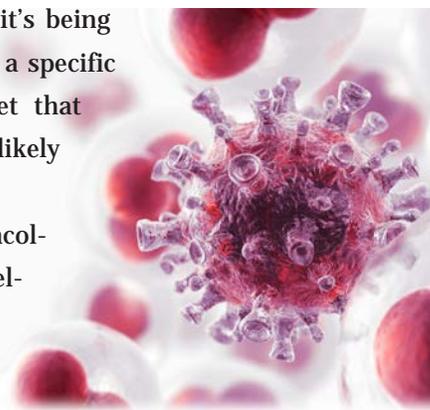


Photo: ©iStock/BlackJack3D

"He went from basically being unable to get out of a chair to going shopping with his granddaughter in just one cycle of therapy."

Partnership 'opens new doors' for prostate cancer research

VA and PCF signed the agreement in 2016 and put it into action early this year. It comes at a time when more than 16,000 Veterans

are diagnosed each year with prostate cancer, making it the most common solid tumor cancer among Veterans.

“Our goal is to increase our scientific understanding of prostate cancer among Veterans and to kick-start the development of precision medicine treatments for them, as well as the general population,” Dr. Jonathan Simons, president and CEO of the Prostate Cancer Foundation, said in a video produced by PCF. “This agreement will open new doors for the research community to work with Veterans facing a life-threatening disease and ultimately reduce the disease burden on America's Veterans.”

Prostate cancer, the second-leading cause of cancer deaths among men, is most common in men age 65 and older. The disease is usually found in its early stages, typically due to PSA screenings, and often grows slowly. It may take many years for a tumor to become large enough to be detectable and even longer to spread beyond the prostate, the walnut-size gland

Continued on next page



Dr. Bruce Montgomery is an oncologist at the VA Puget Sound Healthcare System.

that sits just outside the rectum and bladder and forms part of the male reproductive system. Most men who have the cancer live with it for decades without symptoms and die of other causes even without early

surgery. But a subset of men quickly develop more aggressive prostate cancer—the focus of the VA-PCF effort.

Currently, nearly 500,000 living Veterans have been diagnosed with prostate cancer. Of those, an estimated 3% have metastatic prostate cancer.

Getting more Vets enrolled in trials

PCF donated \$50 million to VA in the five-year partnership. It calls for increasing the number of VA facilities that are doing precision oncology and prostate cancer clinical trials, raising the number of VA researchers applying to PCF for funding, and getting more Veterans enrolled in studies. About half of the funding is aimed at building a network of VA sites that are doing precision oncology. The network now includes 10 sites: Washington; Philadelphia; Seattle; Los Angeles; Chicago; Ann Arbor, Michigan; Durham, North Carolina; Tampa, Florida; Bay Pines, Florida; and New York City, in Manhattan and the Bronx. The goal is to eventually have at least one network site in each of the 21 VISNs (Veteran Integrated Services Networks) into which the VA health care system is divided.

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

For an overview of the latest VA research on high-priority topics affecting Veterans' health, visit www.research.va.gov/topics.

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, assault, or disaster. While stress is common after a trauma, for those with PTSD symptoms such as ruminating an event in their mind 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. Military sexual assault or harassment can also lead to PTSD.
- The disorder can lead to distressing and persistent symptoms, including re-experiencing the trauma through flashbacks or nightmares, emotional numbness, insomnia, relationship problems, sudden anger, and drug and alcohol abuse. Recently, reckless and self-destructive behavior has been added as a PTSD symptom.

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 of large, subgroup Veterans, families, 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's **National Center for PTSD** (NCPD) 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's **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 disorders. Other brains are from healthy controls. The goal is to help 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**.

SELECTED MILESTONES AND MAJOR EVENTS

- 1989 - Created the **National Center for PTSD**.
- 2007 - **Confirmed** the value of prolonged exposure therapy.
- 2010 - Funded, along with the DoD, two **clinicals** to improve treatment for PTSD and mTBI.
- 2014 - **Found** that cognitive processing therapy by telemedicine is as effective for PTSD as in-person therapy.
- 2014 - **Found** that Veterans who sought and received care soon after their service had lower rates of PTSD than those who waited to get treatment.
- 2016 - **Announced the PTSD Pharmacogenetics Initiative** to foster work on identifying, testing, and confirming the most effective PTSD medications for Veterans.

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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 the protective 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 injured. 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 impair 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 treatments and learning the best ways to help family members cope with the effects of TBI and support their loved ones.
- VA's **TBI Model System (TBMS)** is a longitudinal multisite 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's **Translational Research Center for TBI and Stress Disorders (TRACTS)** conducts studies to understand the complex changes in the brain, thinking, and perception that 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.
- The **Chronic Effects of Neurotrauma Consortium (CENC)** serves as a comprehensive research network for DoD and VA that focuses on the long-term effects of combat and military-related TBI. The CENC is designed to conduct research that provides clinically relevant answers and interventions for service members and Veterans and to develop long-term solutions to the chronic effects of TBI.
- Established a **Brain Bank** to collect and study post-mortem human brain and spinal cord tissue to better understand the effects of trauma on the human nervous system.
- Discovered** chronic traumatic encephalopathy, a degenerative disease linked to repeated head trauma such as concussion, in the brains of four Veterans after their deaths.
- Funded, along with the DoD, two **clinicals** to improve treatment for PTSD and mild TBI as part of the **National Research Action Plan**.
- Learned** that Veterans who were near to bomb blasts in Iraq and Afghanistan appear to experience faster brain aging.

(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, 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 sensations, slurred speech, and 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 can also vary 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 very responsive 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 self-management programs, health services and the care delivery to evaluate and improve most
- and fatigue and telehealth interventions to improve access to care and symptom management, among others.
- VA's **Multisite Scientific Centers of Excellence (MSCoE)** 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. MSCoE East is located in Baltimore, and MSCoE 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 referrals within the VA health care system.

SELECTED MILESTONES AND MAJOR EVENTS

- 2005 - **Founded the National Scientific Centers of Excellence**.
- 2014 - **Discovered** that military deployment to the first Gulf War was not a risk factor for developing MS.
- 2017 - **Found** that high dosage of folic acid can significantly slow brain atrophy, reduce falls, and improve walking times in some MS patients.

(Continued on back)

Health ranks as top concern for Veterans immediately after military service

In the months after separating from military service, most Veterans are less satisfied with their health than with their work or social relationships, found a study by VA researchers. While the Veterans surveyed were mostly satisfied with their work and social well-being, a majority were dealing with chronic physical health conditions and a third reported chronic mental health conditions.

According to Dr. Dawne Vogt of the VA Boston Healthcare System and Boston University, lead author on the study, the results highlight the importance of addressing Veterans' health concerns early.

“What remains to be seen is whether those Veterans with health conditions—which were more commonly experienced by deployed Veterans—continue to maintain high levels of well-being in other life domains over time,” she says. “Given that it is well-established that health problems can erode functioning in other life domains, it may be that these individuals experience declines in their broader well-being over time.”

The results appeared Jan. 2, 2019, in the *American Journal of Preventive Medicine*.

Pain, poor sleep among top problems

More than 200,000 U.S. service members transition out of military service each year. Researchers have pointed to the early transition period as a critical time to address challenges Veterans may face in readjusting to civilian life.

To investigate which of these challenges are most pressing to newly separated Veterans, researchers from the VA National Center for PTSD and colleagues surveyed almost 10,000 Veterans from a roster of all separating service members. All participants left the



military in the fall of 2016. Veterans were surveyed about three months after their separation, and then six months after that.

The researchers found that the biggest concern was health. At both three and nine months after leaving the military, 53% of participants said they had chronic physical health conditions. About 33% reported chronic mental health conditions at both time points.

The most commonly reported health conditions were chronic pain, sleep problems, anxiety, and depression. Slightly more than half of participants said they had reduced satisfaction with their health between when they first left the military and a few months later. Health satisfaction did not change much between three and nine months after separation.

Veterans report high work and social well-being

While physical and mental health was a concern for many Veterans, most reported high vocational and social well-being. The majority of participants said they were satisfied with their work and social relationships and that they were functioning well in these areas. According to Vogt, the fact that most participants had high work and social satisfaction “highlights the resilience of the Veteran population, and should provide some reassurance to those concerned about the well-being of newly separated Veterans.”

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



Dr. Daniel Hall (left), seen here in a VA Pittsburgh Healthcare System operating suite with OR technician Mark Yost, is leading efforts to spread preoperative frailty screening in VA.

Study raises new warnings about frail surgery patients

A VA study underscores the value of preoperative frailty screenings.

A VA-funded study has shown that frail surgery patients may be at higher risk than previously thought. Mortality rates were high for frail patients even after surgeries normally considered low-risk. This led the researchers to conclude that “there are no ‘low-risk’ procedures among frail patients.”

The findings appeared in the Nov. 13, 2019, issue of *JAMA Surgery*.

Dr. Myrick C. Shinall, Jr. of the Vanderbilt University Medical Center, first author on the paper, explains that the findings change the view of which surgeries are considered dangerous. “We certainly found it surprising that surgeries usually considered low-stress and low-risk had such high risk of mortality for frail patients,” he said. “We think other surgeons will also be surprised by the results.”

Frailty refers to overall physical weakness. It is common in older adults. Frail patients have lowered resilience, energy, and ability to cope with stress. They show physical signs such as weakness and slowed activity.

Study included data on more than 400,000 Veterans

While frailty is a well-known surgery concern, most research on frail patients has focused on high-risk surgeries. A surgery is usually considered high-risk when the post-surgery mortality rate is above 1%.

To test frailty's impact on surgeries generally considered less risky, the researchers looked at data on more than 400,000 Veterans who had non-cardiac surgeries within the VA health care system. Out of this group, 8.5% were considered frail and 2.1% were very frail, based on a measure called the Risk Analysis Index (RAI).

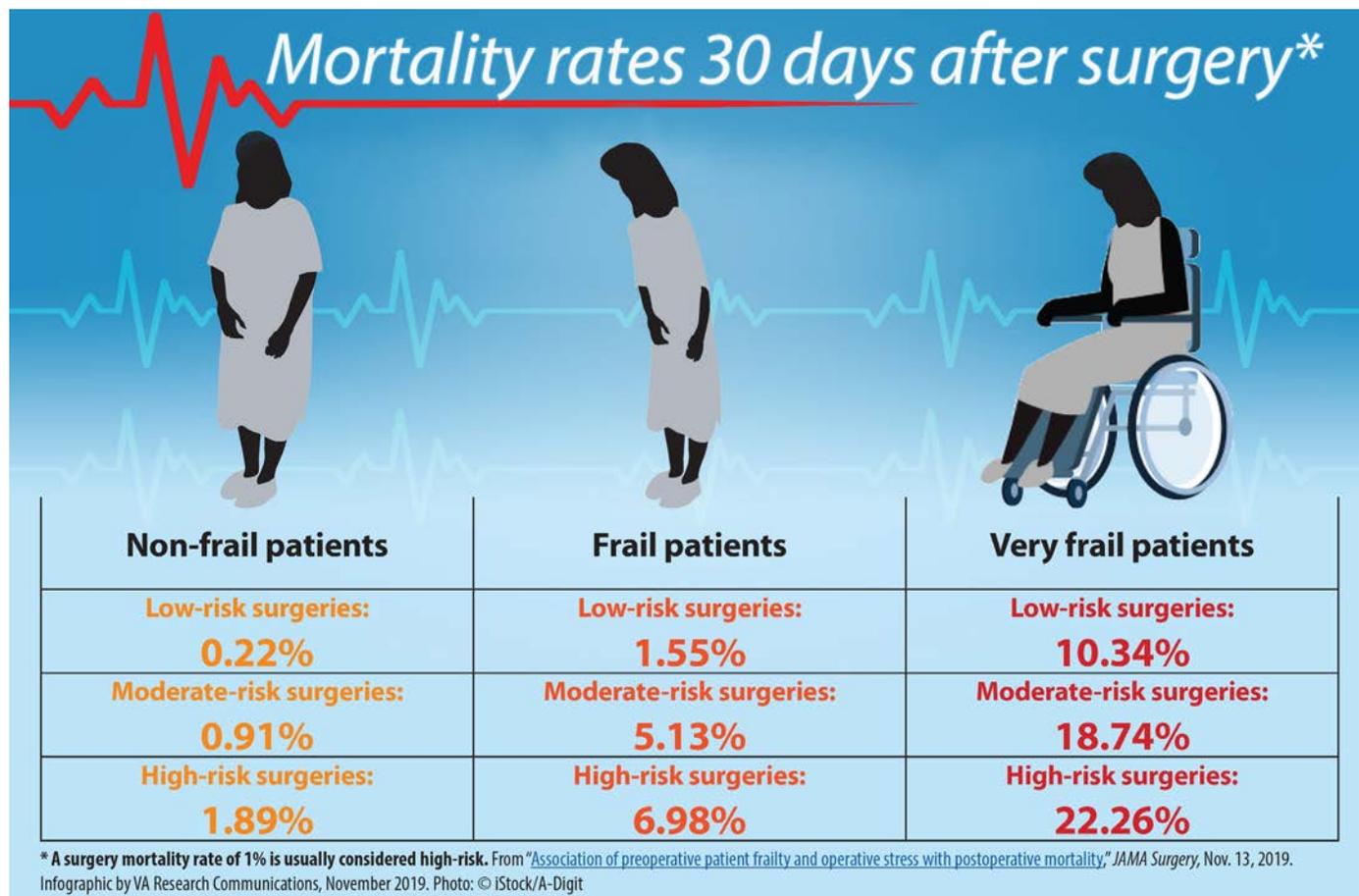
Patients were grouped based on what type of surgery they had. Low-risk surgeries included hernia surgery, appendectomy, and cyst removal. Surgeries such as amputation; arterial plaque removal; and knee, shoulder, or hip replacement were considered moderate-risk. High-risk procedures were mostly open surgeries on the aorta, lungs, liver or pancreas.

Mortality rates for frail and very frail patients were "alarmingly high" across all levels of surgery, compared to stronger patients. Thirty days after a low-risk surgery, 1.6% of frail patients and 10.3% of very frail patients had died. Non-frail patients had a 0.22% mortality rate after low-risk surgery.

For moderate-risk surgeries, 5.1% of frail patients and 18.7% of very frail patients died within 30 days. Mortality continued to rise for frail patients as time went on. The highest mortality rate recorded in the study was for very frail patients 180 days after moderate-risk surgery. About 43% of those patients had died.

Surgeons often do not consider whether patients can endure the stress of surgery for low-risk procedures, according to the researchers. Based on the results, the researchers recommend that patients be assessed using the RAI before any type of surgical procedure. If frailty is shown to be a risk, they say, surgeons could focus on pre-operative interventions to address it.

Study coauthor Dr. Daniel Hall, with the VA Pittsburgh Healthcare System and the University of Pittsburgh, is leading efforts to spread preoperative frailty screening in VA. The practice has been implemented in several VA medical centers already.





Navy Veteran Natale Stella (left), seen here with Dr. Lauren Beste, has lived with hepatitis B for two decades but has never experienced any symptoms.

Combat a possible risk factor for hepatitis B

A new study finds Veteran prevalence of hepatitis B to be greatest among those with traditional risk factors, but also suggests that combat exposure can be a risk factor on its own.

The hepatitis B virus causes a liver infection that, if not treated properly, can lead to serious health consequences, such as cirrhosis—a deterioration of the liver—liver cancer, or even death.

Now, a new study finds Veteran prevalence of hepatitis B to be greatest among those with traditional risk factors, such as drug-use or high-risk sexual practices, but also suggests that combat exposure can be a risk factor on its own. Hepatitis B can be acquired, for example, by being wounded or making contact with infected blood when a fellow service member is wounded.

Dr. Lauren Beste, an internist at the VA Puget Sound Health Care System in Seattle and a senior official in VA's HIV, Hepatitis, and Related Conditions Program Office, led the research. She believes the study, which appeared in the journal *Clinical Gastroenterology and Hepatology* in August 2019, is the first to gauge the prevalence of hepatitis B in relation to combat.

Her study included 1,146 Veterans who received VA care from 1998 to 2000. Estimates of hepatitis B among VA users before the 21st century were based on laboratory results and administrative data from the less than 30% of patients tested for

the virus in the course of standard medical care.

Beste and her team found that evidence of hep B exposure was highest among Veterans with traditional risk factors, such as drug use or high-risk sexual practices. Of these people, 60% reported a history of combat exposure. After adjustment for demographic and traditional risk factors, the researchers determined that service in a combat zone and being wounded in combat were independently associated with exposure to hepatitis B.

The study team concluded that more research is needed to determine whether Veterans who were in combat prior to the era of universal vaccination should be screened for exposure to hepatitis B. The military began vaccinating all service members for the disease after 2000. Vets who have served in the 21st century are presumed to be vaccinated and thus protected from the virus.

“The hepatitis B virus has effective treatments and can be identified with a simple blood test, but military service is not one of the risk factors that is traditionally used to prompt screening,” says Beste, who is also an assistant professor at the University of Washington. “There are many important reasons to study whether military exposures are linked to hepatitis B. One is to make sure we offer screening to Veterans who could be at risk. Another is to give Veterans a chance to apply for VA compensation if their hepatitis B is related to military service.”

“There are many important reasons to study whether military exposures are linked to hepatitis B.”

Preventing long-term consequences

It’s important to note that the study does not show cause and effect, only an association between combat and hepatitis B. The researchers can’t prove definitively that any case of hep B came about because of a combat wound or contact with infected blood in a combat setting.

The hepatitis B virus is transmitted when people come in contact with the blood or bodily fluids of someone else who has the virus. This most often happens through sexual contact or the sharing of needles, syringes, or other drug-injection equipment; or from mother to baby at birth.

Hepatitis B can be either acute, generally meaning the virus will leave a person’s body within the first six months, or chronic, in which case it never goes away even if treated. “It’s important to identify the people at risk in order to treat them and hopefully prevent the long-term consequences of the disease,” Beste says.

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

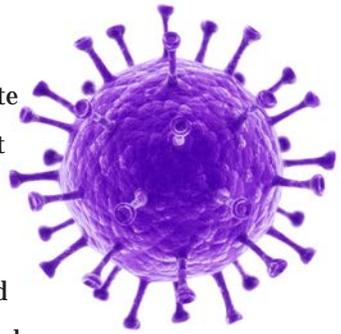


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Photo by John Liston

Capt. Israel Orengo is evaluated by physical therapist Tyler Snow at Madigan Army Medical Center. Snow was part of an Army study that looked at incorporating alternative methods into pain management. A new study based on VA records suggests long-term benefits from service members' non-drug pain treatment.

Study backs long-term benefits of non-drug therapies for pain

A new study finds that non-drug therapies given to service members with chronic pain may reduce the risk of long-term adverse outcomes such as alcohol and drug disorders and suicide attempts.

A new study finds that non-drug therapies given to service members with chronic pain may reduce the risk of long-term adverse outcomes, such as alcohol and drug disorder and self-induced injuries, including suicide attempts. The findings appeared in October 2019 in the *Journal of General Internal Medicine*.

The researchers concluded that service members with chronic pain who received non-drug therapies while in the military, such as massage or acupuncture, had a “significantly lower” risk in VA of new onset alcohol or drug disorder; poisoning with opioids and related narcotics, barbiturates, or sedatives; and suicidal thoughts and attempts. The research team did not study death by suicide.

Dr. Esther Meerwijk, a statistician and suicide researcher at the VA Palo Alto Health Care System in California, was the lead author. Her team reviewed the VA health records of more than 140,000 Army soldiers who reported chronic pain following their deployment to Iraq or Afghanistan from 2008 to 2014. The most common types of chronic pain were joint

discomfort, back and neck issues, and other problems involving muscles or bones.

“Chronic pain is associated with adverse outcomes, such as substance use and suicidal thoughts and behavior,” Meerwijk says. “It made sense that if non-drug treatments are good at managing pain, their effect would go beyond only pain relief. However, I was surprised that the results of our analyses held, despite our attempts to prove them wrong. Often enough in research, significant results disappear once you start controlling for variables that can possibly affect the outcome of the study.”

The researchers controlled for length of a service member’s care in VA, whether the Veteran had been exposed to non-drug therapies in VA, and the number of days a VA patient received opioids. They also tested to see if service members who received non-drug treatments were healthier to begin with and if more Veterans who received non-drug therapies died before any of the adverse outcomes occurred.

Research part of large observational study

It’s possible, Meerwijk explains, that soldiers who received non-drug therapies didn’t have to rely on opioids as much for their chronic pain and are therefore at lower risk for adverse outcomes. “We may also be seeing a genuine effect of non-drug therapies that occurs regardless of whether soldiers use opioids or not,” she says. “If non-drug treatments make chronic pain more bearable, people may be more likely to have positive experiences in life. That makes them less likely to have thoughts of suicide or to turn to drugs.”

Meerwijk’s research is part of the Substance Use and Psychological Injury Combat Study (SUPIC), the largest and longest observational study to date of

"It made sense that if non-drug treatments are good at managing pain, their effect would go beyond only pain relief."



Photo: ©iStock/Wavebreakmedia

Massage was among the alternative pain treatments that some of the Veterans in the study had received while in the service.

pain management and behavioral health conditions in Army service members returning from Iraq and Afghanistan. VA has participated in the study, which is led by Dr. Mary Jo Larson of Brandeis University in

Massachusetts. Meerwijk became part of the study in 2016.

Chronic pain is often managed with prescription opioids. Especially at higher doses and longer length of use, opioids have been linked to a greater risk of substance use disorder and self-inflicted injuries, such as opioid overdose and suicide attempts.

While in the service, the soldiers included in the study had received non-drug therapies that included acupuncture, dry needling, biofeedback, chiropractic care, massage, exercise therapy, cold laser therapy, osteopathic spinal manipulation, electrical nerve stimulation, ultrasonography, superficial heat treatment, traction, and lumbar supports.

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



Dr. Paul King with his children.

VA Researchers Who Served: Dr. Paul King

Dr. Paul King, an Army Veteran, is a clinical research psychologist at the VA Center for Integrated Healthcare (CIH), a VA Center of Excellence located at the VA Western New York Healthcare System. He's also the associate director of the CIH Postdoctoral Fellowship Program. The center's mission is to enhance Veterans' health care by improving the integration of mental health services into primary care. In addition to mental health, King focuses on post-deployment health issues and health care use by combat Veterans, cognitive and emotional impacts of deployment on combat Veterans, and the assessment and management of traumatic brain injury, persistent post-concussion symptoms, and PTSD. He has authored more than 25 peer-reviewed papers and is an adjunct assistant professor at the State University of New York at Buffalo.

What motivated you to join the military?

I started considering military service when I was in high school. Service to others was a value that was instilled in me, and I found that the opportunity to serve my country was a very personally meaningful way of living out that value. Plus, it offered a very real opportunity to challenge myself and an added benefit of financially supporting my education.

What inspired your research career?

I can't say there was just one inspiration but multiple experiences that became self-reinforcing. Critical thinking was something that was emphasized throughout my education. But in studying social sciences as an undergraduate, I had a number of wonderful professors who relayed the value of actually going out to gather, and then trying to make sense of, real-world data. As I progressed in my graduate training and current position, the inspiration became more about learning

to use research data to improve Veterans' everyday lives in meaningful ways.

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

I've been fortunate to have had many positive influences in my life and career, though my family and a few influential instructors and colleagues deserve special mention. My mother and grandmother were always huge advocates for my education and role models for hard work and humility. My wife, Jill, like many military partners, maintained steadfast support for me during my deployment and does to this day. Of course, I'd be remiss without honoring my undergraduate advisor, Dr. Lisa Brooks; my graduate school mentor, Dr. Jim Donnelly; and my career development award mentorship team, Drs. Laura Wray, Greg Beehler, Kerry Donnelly, and Jen Funderburk, for their ongoing support and the way they challenge me as I continue to grow in my profession. As for military influences, my friends and mates from my engineer squad who I worked with on a daily basis drive me to succeed in my work

Describe your military experience.

I enlisted as a combat engineer in the New York Army National Guard while I was in college at the State University of New York at Buffalo and attending Army Reserve Officers' Training Corps (ROTC) classes. My plan at the time was to enlist, complete college and my ROTC courses, and ultimately pursue a commission as an Army officer either on active duty or in the National Guard.

Upon enlisting, I took advantage of a program known as the Split Training Option, or Split-Op, which allowed me to complete Army basic training one summer and advanced individual training the next so I could continue attending college classes in the interim. Following the attacks on the World Trade Center in 2001, my National Guard unit was activated twice: for a brief time for state active duty, and then to federal active duty from 2003 to 2005 in support of Operation Iraqi Freedom.

In terms of day-to-day activities as a combat engineer in Iraq, my tasks ranged widely. They included providing aid to Iraqi civilians; building infrastructure on our forward operating base or in the community; and conducting security operations, patrols, and recovery and demolition of weapons caches and explosive ordnance. I separated from the National Guard following my return from active duty.

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

My research program is focused on post-deployment health care, in particular primary care management of some of the major health concerns faced by combat Veterans, including concussions, PTSD, and depression. My current work involves development, modification, and testing of clinical strategies that can be delivered right in primary care clinics to improve the health and well-being of Veterans. The main idea behind this work is basically to address these very common concerns as soon as possible in a highly accessible treatment environment.

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



Dr. Paul King served in Iraq as a combat engineer with the New York Army National Guard.

VA Research by the Numbers

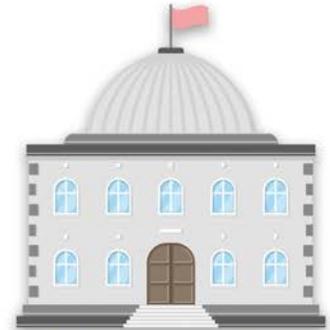
(For Fiscal 2019)



Active research sites nationwide
105



Published research articles authored or co-authored by VA investigators
11,279



Total congressional appropriation for VA medical and prosthetic research
\$729M



Active funded research projects (including VA funding and other sources)
7,372



Active funded principal investigators
3,611



Total research budget (including other VA and non-VA sources, such as NIH)
\$1.96B

Infographic by VA Research Communications, January 2020. Illustrations: © iStock/Olena Chernenka, Andrew_rybalko, all_is_magic, sesame, Misha Shutkevych.

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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
13.5%	4.5%

Conclusion: The results of this study suggest that a strikingly high proportion of U.S. veterans—approximately equal to those with full and plus full diagnosed PTSD—experience clinically significant PTSD symptoms in their lifetime.

Source: "High burden of subthreshold PTSD: Service members' stress disorder in U.S. military veterans." *World Psychiatry*, June 2019. Infographic by VA Research Communications, January 2019. Photo for illustrative purposes only. Photo © iStock/MITCANY.

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-SAR) 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." *VA Psychol*, Feb. 20, 2018. Infographic by VA Research Communications, February 2018. Photo for illustrative purposes only. © iStock/Sean-Phillip WALKER.

Firearm training among U.S. adults

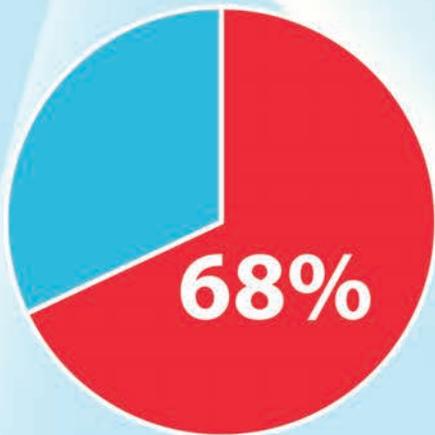
Findings from a study by VA researchers and colleagues

- The percentage of U.S. firearm owners who reported receiving formal firearm training showed little change between 1994 (54 – 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 firearm training has not meaningfully changed in two decades. Training programs vary widely. Efforts are needed to standardize and evaluate the effectiveness of training.

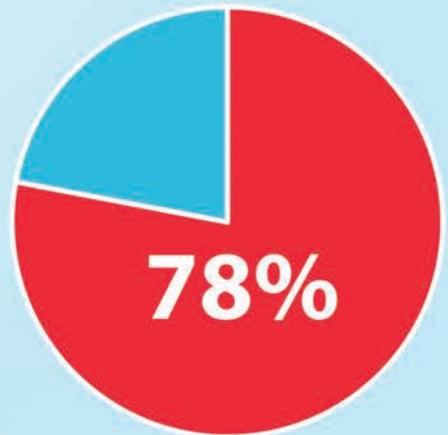
Source: "Improving understanding of firearm training among U.S. adults." *VA Research Communications*, November 2017. Photo for illustrative purposes only. © iStock/Sean-Phillip WALKER.

Vets with TBIs have higher suicide risk

Those with moderate/severe traumatic brain injury are **2.45x** more likely to die by suicide versus those with no TBI



Percentage of all suicides in sample that involved a firearm



Percentage of moderate/severe TBI suicides that involved a firearm

Based on a review of the records of more than 1.4 million VA patients. From "Suicide and Traumatic Brain Injury Among Individuals Seeking Veterans Health Administration Services Between Fiscal Years 2006 and 2015," *Journal of Head Trauma Rehabilitation*, Sept./Oct. 2019. Infographic by VA Research Communications, September 2019. Photo: © iStock/laremenko, ieang.



RESEARCH CURRENTS

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

Gleason score for prostate cancer

In the 1960s, VA researcher and Army Medical Corps Veteran Dr. Donald Gleason and his colleagues at the Minneapolis VA Hospital developed a grading system to classify the stage and prognosis of prostate cancer. Today, the Gleason score is almost universally used to rate prostate cancer. It is considered the most reliable measure of prostate cancer's chances of growing and spreading. To find a Gleason score, doctors take a biopsy of a patient's prostate and look at the cells under a microscope. Lower scores mean areas of cancer cells are small and closely packed, resembling a normal prostate. Higher scores mean cancer cells are more widespread. Today, doctors complement the Gleason score with other tools to ensure the most accurate diagnosis and appropriate treatment plan.

For more examples of VA research innovations being translated into everyday care, visit

www.research.va.gov/research_in_action.



Photo courtesy of University of Minnesota

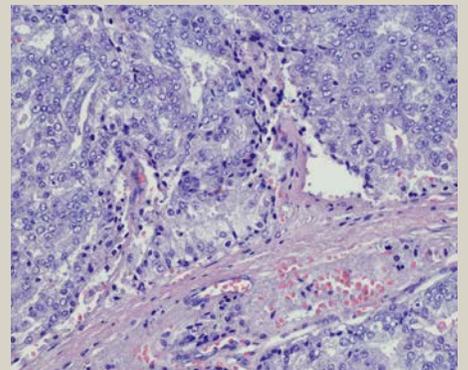


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