

VA

RESEARCH CURRENTS

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



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Photo courtesy of Matt Landis

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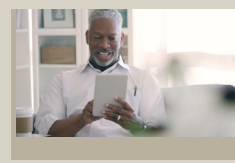
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Prolonged exposure therapy, medication show equal effects in PTSD study

PTSD treatment with prolonged exposure therapy and with the anti-anxiety drug sertraline (sold as Zoloft) showed similar effectiveness, in a study including several VA researchers. Researchers treated 223 Veterans with PTSD with one of three treatments: prolonged exposure therapy plus a placebo, prolonged exposure therapy plus sertraline, or sertraline plus a medication management program. After 24 weeks, patients in all three groups had significantly decreased PTSD symptoms. No significant symptom differences existed between groups. Prolonged exposure therapy, a type of psychotherapy, is a preferred PTSD treatment within VA. The researchers expected that therapy and sertraline together would prove the most effective. The results suggest that adding medication to prolonged exposure therapy does not further improve PTSD symptoms, although the researchers say more study is necessary. (*JAMA Psychiatry*, Dec. 5, 2018)



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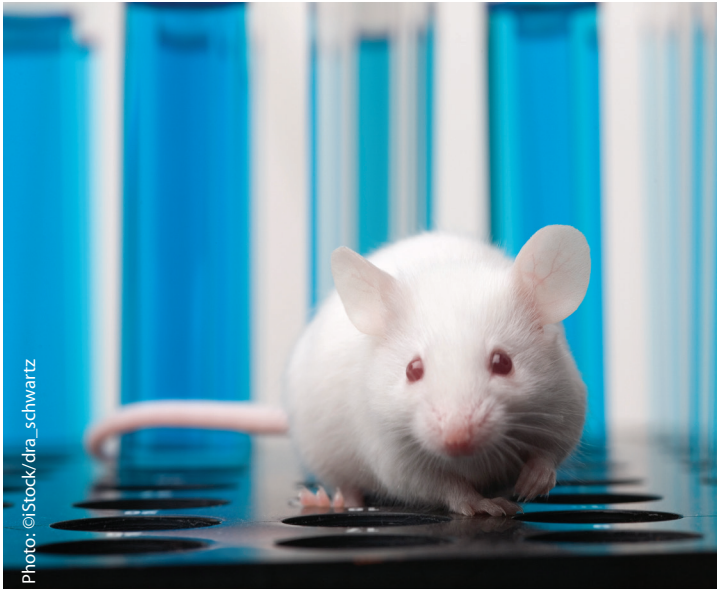


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Lab study suggests heart benefits from widely used diabetes drug

An international lab study that included a VA San Diego Healthcare System researcher showed that congenital heart disease (CHD) and obesity can lead to heart failure, but treatment with metformin, a widely used diabetes drug, can prevent the condition. CHD is the most frequent birth defect worldwide. Researchers found that the combination of CHD and a high-fat diet in mice led to heart failure. Giving mice the drug metformin prevented this heart dysfunction. Early treatment with metformin may prevent or delay the onset of heart failure in patients with CHD, say the researchers. (*Molecular Metabolism*, Nov. 15, 2018)

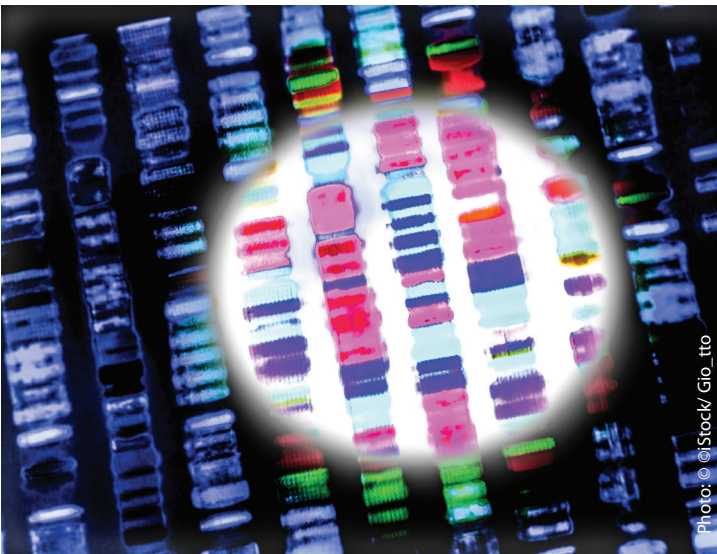


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Two DNA sites linked to PTSD risk

A team including a VA San Diego Healthcare System researcher identified two genome sites that may influence a person's risk for PTSD. While trauma exposure often leads to PTSD, not everyone who experiences trauma develops PTSD. To explore why that is, researchers looked at the genomes of trauma-exposed people with and without PTSD. They found that those with PTSD had more methylation at two specific genome sites: *NRG1* and *NGS*. Methylation is when a chemical compound (methyl) attaches to the DNA molecule. It can change how the DNA segment acts. Future research should focus on whether this DNA activity existed prior to trauma, making it a risk factor for PTSD, or whether PTSD causes the activity, say the researchers. (*Epigenomics*, Nov. 20, 2018)



Photo: iStock/Nerthuz

Cisplatin superior to cetuximab for cancer treatment

The drug cisplatin was superior to cetuximab in treating head and neck cancer along with radiation therapy, in a study by VA researchers in Philadelphia and the Bronx. Both cisplatin and cetuximab are commonly given along with radiation therapy to treat head and neck squamous cell carcinoma. The researchers looked at 4,520 cancer patients over a period of three years. They found that those on cetuximab had significantly inferior overall survival, compared with patients taking cisplatin. The results suggest that cisplatin is the most appropriate drug partner for radiation therapy, say the researchers. (*Cancer*, Oct. 20, 2018)

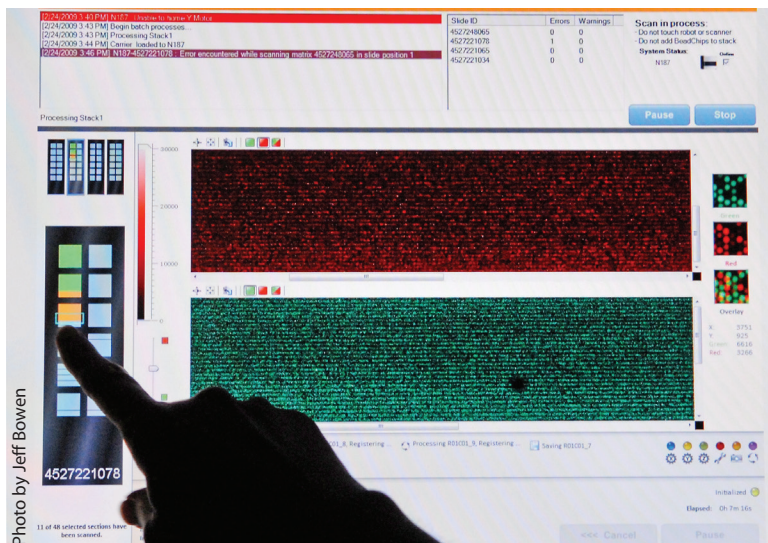
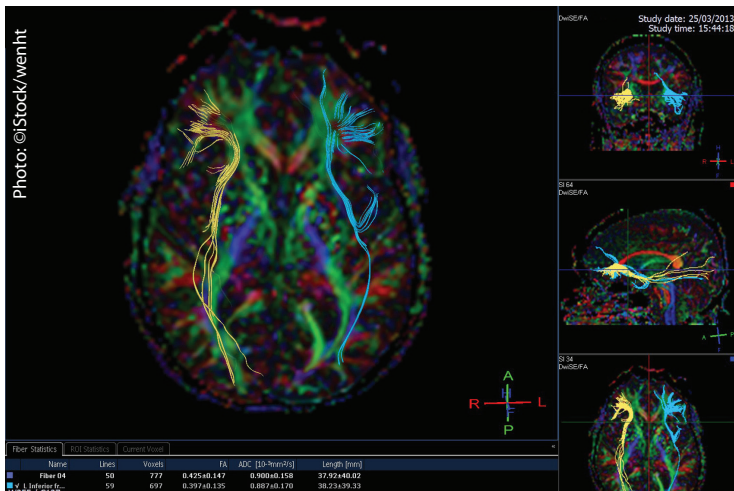


Photo by Jeff Bowen

Large genome study leads to better understanding of high blood pressure

A large international genetic study that included several VA researchers has identified more than 500 new gene locations that affect blood pressure. The project is the largest genetic study of blood pressure to date, involving more than 1 million participants. It included data from VA's Million Veteran Program. By comparing participants' genetic data, researchers identified 535 new locations on the human genome that influence blood pressure. The researchers calculate that the new findings increase the knowledge of inheritable blood pressure traits by 27 percent. They call the

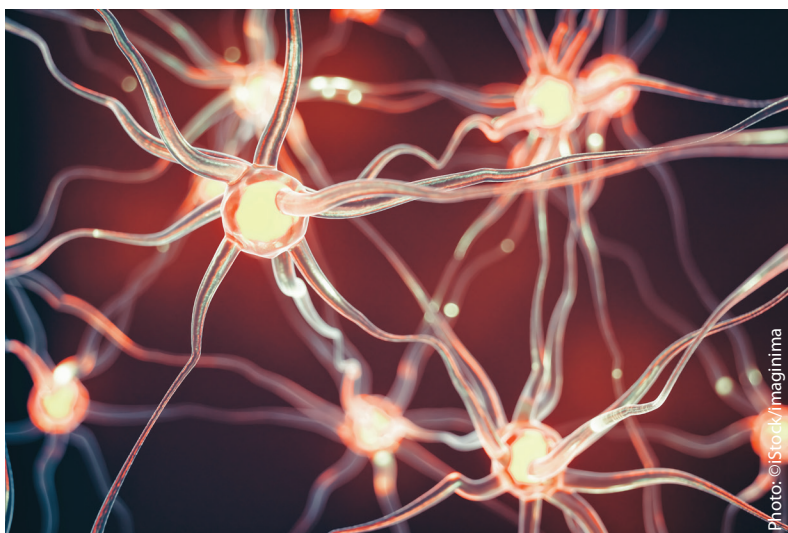
findings "an important step forward" in understanding how genes affect blood pressure. (*Nature Genetics*, October 2018)



White matter damage could explain chronic headaches after TBI

Researchers with the VA San Diego Healthcare System have identified white matter abnormalities in the brains of patients with mild traumatic brain injury that may help explain their chronic headaches. The study used brain imaging data from 12 patients with TBI and chronic headache, compared with healthy controls. The TBI patients had abnormalities of the white matter in two brain tracts: the left superior longitudinal fasciculus, and the right anterior thalamic radiation. These tracts

link different parts of the brain. This disruption of communication within the brain could be partly responsible for chronic headaches often experienced by patients with TBI, say the researchers. (*Molecular Pain*, Jan.–Dec. 2018)



Study explains gene mutation's link to ALS

Researchers at the VA Lexington Medical Center and University of Kentucky have shown how a gene mutation may contribute to the development of amyotrophic lateral sclerosis (ALS). Mutation to a gene called fused in sarcoma (FUS) are known to contribute to some cases of inherited ALS. The researchers showed that this mutation can suppress protein translation and interfere with how RNA functions in the body. The mutated proteins generated by the FUS gene disrupt an RNA quality-control pathway, which

damages neuronal maintenance and function. Because this mutation suppresses how proteins are translated within cells and disrupts how RNA regulates cell activity, it likely contributes to the motor cell death seen in ALS. According to the researchers, the results will add to the understanding of both how this specific mutation can lead to inherited ALS, and more generally how ALS develops. (*Proceedings of the National Academy of Sciences*, Nov. 19, 2018)



Is alcohol healthy?

A new study finds that consuming alcoholic beverages daily—even at low levels that meet U.S. guidelines for safe drinking—can be “detrimental” to your health. The findings are similar to those of other recent research.

A new study finds that consuming alcoholic beverages daily—even at low levels that meet U.S. guidelines for safe drinking—appears to be “detrimental” to your health.

The researchers found that downing one to two drinks at least four days per week was linked to a 20 percent increase in the risk of premature death, compared with drinking three times a week or less. The finding was consistent across the group of more than 400,000 people studied. They ranged in age from 18 to 85, and many were Veterans.

Dr. Sarah Hartz, a psychiatrist at the VA Eastern Kansas Health Care System, led the study. It appeared in November 2018 in the journal *Alcoholism: Clinical & Experimental Research*. She’s not too surprised by the findings, noting that two large international studies published in 2018 in the British journal *The Lancet* reached similar conclusions about the dangers of alcohol.

“There has been mounting evidence that finds light drinking isn’t good for your health,” says Hartz, who is also an assistant professor at Washington University in St. Louis.

Hartz and her coauthors note that their results don't necessarily prove cause and effect. In other words, people who tend to drink more may indeed have shorter lives—but not necessarily as a result of more alcohol consumption. It could be, for example, that those people have harder lives all around, with more stress, which takes a toll on health and longevity. But the researchers did adjust for a range of demographic factors and health diagnoses to try and tease out the direct effects of alcohol.

Another limitation of the study is that it relied on in-person self-reports of alcohol use, which research has shown may lead to under-reporting, compared with anonymous surveys.

The study had many strengths, however. Hartz explains that two major factors separate her study from papers that found light-to-moderate drinking to have health benefits. For one, the researchers studied a much larger population so they could distinguish between groups of drinkers when looking, for instance, at quantity and frequency of alcohol consumption.

"We're seeing things that we didn't before because we have access to such large data sets," she says. "In the past, we couldn't distinguish between these drinking amounts. To have any statistical power, to be able to reach conclusions that are statistically significant, the larger the data set the more power you have and the easier it is to make conclusions."

Secondly, Hartz and her colleagues compared drinkers to drinkers.

"Traditionally, the reference group has been people who don't drink," she says. "People who don't drink are different in many, many ways than people who do drink. People who never drink are different culturally from people who drink. For example, I would not have been able to grow up in my culture without ever having a full drink. There are a lot of lifestyle things that go along with your culture—both healthy and unhealthy—which are very hard to tease apart."

"There has been mounting evidence that finds light drinking isn't good for your health."

The researchers reviewed two data sets of self-reported alcohol use and mortality follow-up. One set included more than 340,000 people from the National Health Interview Survey (NHIS), a source of information for monitoring the health of U.S. citizens; the other set listed nearly 94,000 Veterans from VA outpatient medical records. The health and survival of the people was tracked between seven and 10 years.

According to the findings, people who drank four or more times a week, even when limiting it to only a drink or two, had about a 20 percent greater risk of dying during the study period. Among those who consumed one to two drinks at a time, the minimum risk level for premature death was drinking 3.2 times a week in the NHIS data and two to three times a week in the VA data. The VA sample had a higher mortality rate based on deaths per 1,000 person-years—13 versus 5—and more people with medical co-conditions.

The findings were consistent in analyses of men, women, and non-smokers.

Hartz's team also evaluated deaths due to heart disease and cancer. For heart disease, they found a benefit to drinking, specifically that one to two drinks per day about four days a week seemed to protect against death from heart disease. But drinking *every day* eliminated those benefits. In terms of death from cancer, any drinking was "detrimental," she says.

Safe alcohol consumption guidelines vary widely across the globe, according to a study that analyzed recommended levels in 37 countries. Dietary guidelines issued by the U.S. Centers for Disease Control and Prevention (CDC) call for alcohol to be used "in moderation—up to two drinks a day for men and up to one drink a day for women." A standard drink in the U.S. contains about 14 grams of pure alcohol, meaning men can consume up to 196 grams per week and women 98 and stay within safe guidelines.

The CDC also says one type of an alcoholic drink isn't necessarily safer than another type. For instance,

one 12-ounce beer has about the same amount of alcohol as one 5-ounce glass of wine or 1.5-ounce shot of liquor. The CDC guidelines don't recommend that people who do not drink should start doing so for any reason.

In contrast, the U.S. safe drinking guidelines are way above the limits in Sweden and Germany. Britain suggests low-risk limits for men almost half that of those in the United States. In France, the recommended limits are more in line with those in the United States: 140 grams (10 drinks) per week for women and 210 grams (15 drinks) per week for men.

The 'French Paradox'

In the past, some studies have found positive health effects from low-level alcohol consumption. Case in point: One study examined alcohol consumption and the risk of heart attack among men over a 12-year period. Drinking was linked to a lower risk of heart attack, regardless of the type of alcohol. Men who reported drinking up to seven days a week had a lower risk than those who drank less than once a week.

Another study linked light-to-moderate drinking to a lower risk of multiple heart-related outcomes.

Then there's the "French paradox." It's the belief that while the French and American people both maintain a diet high in saturated fats, which can raise the risk of heart disease and stroke, the French have much lower rates of heart disease because they drink a lot of red wine.

More recently, however, studies have challenged the theory that alcohol has health benefits. In one of the studies in *The Lancet*, researchers reviewed data from dozens of studies on drinking patterns and health outcomes among nearly 600,000 people in 19 advanced countries.

The study team found that drinking more than 100 grams of alcohol per week, the equivalent of about seven drinks, could lead to death, with life expectancy starting to drop at age 40. The per-week figure was in the range in Hartz's study in which alcohol can cause serious health problems. Drinking was also tied to a greater risk of stroke, coronary artery disease, and various forms of heart failure. The people in the study had no prior heart disease.

Interestingly, increased consumption was linked to a slightly lower risk of non-fatal heart attack. But that trend must be balanced against the higher risk associated with other serious and potentially fatal types of heart disease, according to the study's lead author, Dr. Angela Wood of Cambridge University in England.

In Wood's view, her research and that of Hartz both reached the same conclusion: There are no apparent long-term health benefits from moderate or even light drinking. "Whether low-to-moderate drinking improves social well-being is a different question," she says.

One way or the other, if you think it's fine to consume a glass of wine or a beer every evening while winding down at home or in a bar—you may want to think again. ★



Researchers explore Vet preferences for receiving results from genetic tests

In recent years, VA has become quite active in studying genomics, the structure, function, editing, and mapping of genes. The agency is now funding more than 100 studies on genetics and its relation to health and diseases.

One of VA's most ambitious genomic endeavors is the Million Veteran Program (MVP). Vets enrolled in the program provide blood samples to allow for analysis of their genes and give access to their medical records—all so scientists can pinpoint the role genes play in diseases and health. Genetic data of the more than 700,000 Veterans enrolled in MVP has been used to study such medical issues affecting Veterans as mental illness, heart disease, PTSD, and Gulf War illness.

What if that information can be applied in a different way? What if Veterans can see their results and share them with a provider who may suggest a treatment for an illness linked to the genetic information?

Dr. Sara Knight of the VA Salt Lake City Health Care System is exploring those questions. She's leading a study that aims to find out if Vets want their results returned, why they'd want them returned, and what details they'd want to see and under what circumstances. The findings will help guide VA executives in how to disclose to Veterans the results of whole genome sequencing, the process of learning the complete DNA sequence of a person's set of genes at one time, and other genome-based tests, she says.

Currently, MVP does not return genetic results to enrollees, for several reasons.

"There's an urgent need to know this information, but we just don't understand what Veterans want," says Knight, who is also a professor at the University of Utah. "That's what this study will find out about and document. With that evidence, we can go to VA policymakers and say, 'We have great interest among Veterans, but they need some things to occur when they get the results back. They need to be able to talk to someone who has knowledge of genetics and can



Dr. Sara Knight studies genomics and personalized medicine, among other areas, at the VA Salt Lake City Health Care System and the University of Utah.

help them understand the results.' This study starts to define what the Veterans want and under what conditions they want it."

To MVP Director Dr. Sumitra Muralidhar, knowing Veterans' thoughts on the return of their research results is very important, as is allowing Vets to choose whether to receive that information.

She points out that the topic has been discussed since MVP was launched in 2011.

Currently, VA is planning pilot studies in the areas of prostate cancer and high cholesterol in families to better understand the questions tied to giving back that information, she says.

"In our ad-hoc discussions with Veterans on this subject, we've had some that are very interested in getting their genetic results, especially if it has a bearing on their health," Muralidhar says. "Other Veterans don't want to know their genetic results, and still others worry that their VA benefits may be affected if they have positive results for certain illnesses."

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



Dr. Marco Zenati is chief of thoracic and cardiovascular surgery at the VA Boston Healthcare System.

Trial confirms safety of vein-removal technique used in open-heart surgery

A VA Cooperative Studies Program trial has found that a form of vein removal used in heart bypass surgery—endoscopic vein harvesting—is just as safe as “open” vein harvesting when it’s performed by surgeons with ample expertise in the technique.

A new study finds that a form of vein removal used in heart bypass surgery—endoscopic vein harvesting—is just as safe as open vein harvesting when it’s performed by experts in vein removal. The findings appeared in *The New England Journal of Medicine* on Nov. 11, 2018.

In a randomized trial of more than 1,100 patients, researchers with VA’s Cooperative Studies Program found no major difference in the rates of the two leg vein removal techniques to prevent cardiac events. The combined rate of all-cause death, heart attacks, and repeat vascularization, a procedure that creates a new or additional blood supply to a body part or organ, was 14 percent for endoscopic removal and 16 percent for open removal over nearly three years.

The VA study also confirmed what is already known about endoscopic vein removal: Its rates of post-surgical leg

infections are lower than those of open vein removal.

Dr. Marco Zenati, the chief of thoracic and cardiovascular surgery at the VA Boston Healthcare System, led the study, which is known as the REGROUP trial. He says the findings in a sense “redeemed” endoscopic vein removal, the safety of which has been called into question by clinicians in the past.

The difference this time around is that the REGROUP trial “crucially only included expert vein harvesters,” says Zenati, who is also a professor of surgery at Harvard University.

Endoscopic vein removal ‘is the way to go’

“My conclusion is that endoscopic is the way to go when it’s in the hands of experienced medical personnel,” he says. “Endoscopic vein removal has a steep learning curve, and inexperienced harvesters may damage the conduit, leading to early graft failure and heart problems. If the harvester is inexperienced, open harvesting is likely to be preferred.”

The REGROUP trial included harvesters with at least 100 cases of endoscopic vein removal and less than a five percent use of open harvesting over the previous two years. That’s an excellent level of experience, Zenati says. Vein harvesters are essentially heart surgeons.

Both endoscopic and open vein harvesting call for removal of the greater saphenous vein in the leg for use in coronary artery bypass grafting, the most common type of open-heart surgery. The saphenous vein is the conduit most often used in heart bypass surgery because of its ease of access.

Endoscopic vein removal requires greater skills and is much more complex than the open vein approach. It’s also used in more than 90 percent of cases because it reduces the rate of leg infections following surgery. That’s because the procedure requires only one small incision at the knee to insert a lighted, flexible instrument called an endoscope, before the saphenous vein is removed. In open vein removal, doctors make one

long incision, or many small ones, to remove the vein, increasing the risk of infection, as well as pain, numbness, bleeding, and other complications.

However, evidence of the long-term cardiac safety of endoscopic vein removal has been limited by small trials with short follow-up.

Cardiovascular disease, the No. 1 killer of Americans, is the leading cause of hospitalization in VA. The disease is associated with ailments that often affect Veterans, including diabetes, PTSD, and spinal cord injuries.

One of the most common forms of heart disease, coronary artery disease is a blockage of the vessels that supply blood to the heart. It’s a key reason people have bypass surgery in hopes of avoiding a heart attack or death. In heart bypass surgery, grafts using the saphenous vein route the blood around an artery lesion to restore blood flow and oxygen to the heart. But those

grafts may develop atherosclerosis, a hardening and narrowing of the arteries, which then necessitates a repeat procedure, or revascularization.

Study is ‘likely definitive’

The REGROUP trial came nearly a decade after a large study led by Duke University investigators called the PREVENT IV trial questioned the safety of endoscopic vein removal. The 2009 study, which appeared in the *New England Journal of Medicine*, found over three years that a group of patients who underwent endoscopic vein removal had higher rates of death, heart attack, or repeat revascularization than an open vein group.

Zenati and his colleagues assume the vein harvesters in PREVENT IV were inexperienced because he says the study leaders set no threshold for minimum experience.

Zenati’s study included 1,150 patients undergoing heart-bypass surgery at 16 VA medical centers. The patients were randomized evenly into two groups, one

“My conclusion is that endoscopic is the way to go when it’s in the hands of experienced medical personnel.”

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Open vs. endoscopic vein harvesting for heart bypass surgery

In heart bypass surgery, surgeons usually harvest a vein from the leg to graft onto the coronary artery, to reroute blood flow to the heart. Endoscopic vein removal requires greater skills and is far more complex than the open approach. But it's used in most cases because it reduces the rate of leg infections after surgery. It requires only one small incision at the knee to insert a lighted, flexible instrument called an endoscope, before the saphenous vein is removed. In open vein removal, doctors make one long incision, or many small ones, to remove the vein, increasing the risk of infection, as well as pain, numbness, bleeding, and other complications.

Photos depict scarring a few days after open (left) or endoscopic (right) vein harvesting.



Infographic by VA Research Communications, November 2018. Photo: © iStock/kirisa99.

that had endoscopic vein removal and the other open vein removal. In addition to cardiac events, the scientists looked at the rate of leg infections.

- Cardiac events*: 89 in the open group (15.5 percent); 80 in the endoscopic group (13.9 percent).
- All-cause death*: 46 patients in the open group (8 percent); 37 in the endoscopic group (6.4 percent).
- Heart attacks*: 34 patients in the open group (5.9 percent); 27 in the endoscopic group (4.7 percent).
- Repeat revascularization*: 35 patients in the open group (6.1 percent); 31 in the endoscopic group (5.4 percent).
- Leg infections*: 18 patients in the open group (3.1 percent); eight in the endoscopic group (1.4 percent).

Zenati says the results increase the likelihood that endoscopic vein removal will continue to be used in more than 90 percent of heart bypass surgeries in the United States. The study may also influence a change in practice in Europe, where endoscopic removal is used in less than 20 percent of heart bypass procedures, he notes.

“Open and endoscopic harvesting are the same in terms of safety,” he says. “But fewer leg-wound complications tip the scale toward endoscopic.”

In Zenati's view, it's unlikely there will be more randomized trials to better understand the long-term safety of endoscopic removal.

“That's because our study is likely definitive,” he says. ★

Study: In-person, but not online, social contact may protect against psychiatric disorders

In-person social contact seems to offer some protection against depression and PTSD symptoms, but the same is not true of contact on Facebook, suggests a study by VA Portland Health Care System and Oregon Health and Science University researchers. The results are in the Jan. 15, 2019, issue of the *Journal of Affective Disorders*.

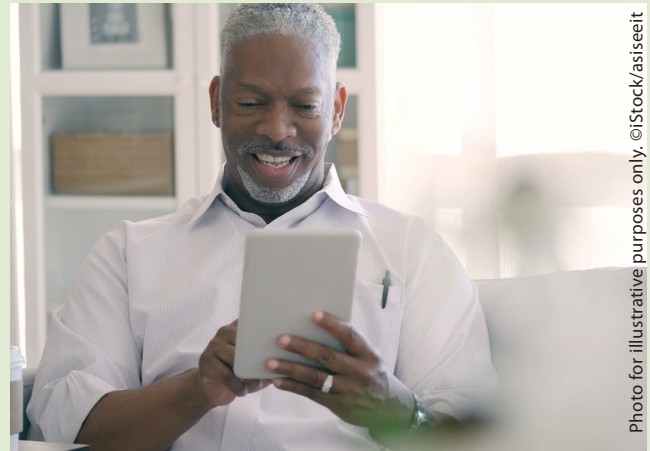
Dr. Alan Teo, lead author on the paper, summed up the findings this way: “When we look at a head-to-head comparison of time spent socializing on Facebook vs. face-to-face, it is the time spent in-person with our friends and family that probably matters most to reducing symptoms of depression and PTSD in Veterans.”

Past research has shown that social isolation is closely linked with negative mental health outcomes. Social support may act as a buffer against stressors that worsen depression, anxiety, or other emotional problems. While in-person social contact is known to lead to better health, little research exists on whether this connection also applies to social media interaction on the internet.

Researchers surveyed 587 Vets

To find out, the researchers gave an online survey to 587 Veterans who had served since September 2001. Participants were recruited through Facebook ads, meaning that everyone in the study was a Facebook user. The survey asked participants how often they had social contact with family and friends in person and on Facebook. Each participant was also screened for major depression, PTSD, alcohol use disorder, and suicidality.

The results showed that participants who had in-person contact at least a few times per week had



New VA research suggests that while keeping in touch with friends and family on social media has clear benefits, there is no replacement for in-person social contact for promoting good mental health.

about 50 percent lower odds for both major depression and PTSD symptoms, compared with participants who saw friends and family infrequently. The researchers caution that the results cannot prove a direct cause and effect between social contact and better health. While this and other research suggests that social relationships may directly affect health, it may also be that mental health conditions lead to more social isolation.

The frequency of social contact through Facebook did not affect risk for depression or PTSD. Neither in-person nor Facebook interaction frequency affected risk for alcohol use disorder or suicidality for the study group.

The findings line up with previous research. A 2015 study headed by Teo found that in-person social contact lowered the risk of developing depression, but contact via phone, writing, or email did not.

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



Dr. Leonardo Tonelli (right) and research assistant Brent Stewart are conducting mouse studies to learn about the role of the immune system in mental health.

Tackling trauma, depression via the immune system

A VA research team hopes to show how the immune system can be harnessed to treat depression and PTSD.

If you cut your finger or stub your toe, or a virus enters your body, your immune system responds. A fierce army of white blood cells mounts an attack.

How about when emotional trauma or depression strikes? We may not think of the immune system as part of the healing process.

But that thinking is outdated. Just ask experts like Dr. Leonardo Tonelli, of the Baltimore VA Medical Center and the University of Maryland. A psychoneuroimmunologist, he studies the link between the nervous system—mainly the brain—and the immune system.

Tonelli believes the immune system may be a potent tool for treating depression and post-traumatic anxiety, or even full-blown PTSD, in Veterans. He is conducting experiments in mice that he hopes will spawn new therapies—such as rebuilding or reshaping a patient’s reservoir of T cells, which are subsets of white blood cells. The “T” is for the thymus gland, where the cells mature.

“Perhaps it will require a stepwise approach of getting rid of the ‘bad’ T cells and rebuilding the ‘good’ T-cell population,” speculates Tonelli.

One approach, he says, could be using a patient's own stem cells to grow new T cells, and then injecting those into the body. A less invasive approach might be using a "super probiotic" to jump start a healthier T cell population.

"All these options are on the table," Tonelli says.

Glowing T cells offer window into immune system

His newest VA-funded mouse study is a deep dive into how exactly stress affects the immune system—and whether manipulating T cells can alter behavior. If behavior can be normalized in mice, the hope is that the effect can one day be translated into humans.

The focus is on two types of T cells. One is CD4+ cells. They are known as "helper" cells because one of their main jobs is to send signals to activate other immune cells. The other is CD8+ killer cells, which earn their fearsome moniker because they knock off cancerous, infected, and other damaged cells.

Tonelli's lab uses genetically altered fluorescent T cells. Their green glow allows them to be tracked microscopically as they migrate into different tissues—including the brain.

The team injects these cells into genetically engineered mice that lack T cells. This way, the researchers can carefully follow what the cells do and where they go.

Another phase of the work involves administering antibodies that neutralize CD4+ and CD8+ cells. The mice are then assessed for anxiety, despair, and startle response.

Mice can't fill out questionnaires. So how can scientists test their symptoms? One way is a "social interaction box." A mouse is placed into a two-compartment box, open at the top. In one of the compartments is another mouse, in a small enclosure. If the mouse being tested shows signs of trauma—analogue to PTSD—she will tend to avoid the other mouse. A mouse that is emotionally intact will be more social.

"We now know the immune system and the brain have everything to do with each other."

Yet another phase of the study involves blocking certain proteins in the immune system to tease out their role in T-cell-mediated inflammation.

Taking account of emotional and physical trauma

Tonelli expects the results of these and other experiments to "provide proof of concept" that CD8+ T cells are the main culprit in the inflammation triggered by traumatic stress, and that "it is possible to reduce inflammation and improve emotional regulation by targeting these cells."

He hopes the work will eventually benefit many patients, but especially those with military PTSD. His group is in the forefront of exploring the immune system as a potential healing resource for this population.

The concept is drawing increasing interest from experts in the biology of PTSD.

"The link between PTSD and chronic illness has been established but the potential role of immune system markers in mediating this association is only beginning to be examined," wrote VA clinician-researchers Drs. Janine Flory and Rachel Yehuda in a special report in *Psychiatric Times* in April 2018.

Flory and Yehuda raised several intriguing questions that tie into Tonelli's work:

- If we can tamp down inflammation, will that ease PTSD symptoms?
- Does psychotherapy affect the immune system?
- Do certain antidepressants that help PTSD work, in part, through the immune system?
- Do other therapies or lifestyle changes that help PTSD—ranging from yoga and meditation to better diet—work, in part, by reducing inflammation?

In the same issue of *Psychiatric Times* Dr. Charles Raison, with the University of Wisconsin-Madison, offered further perspective on the topic. He wrote that his time in medical school in the 1980s was like the "dark ages," with respect to understanding the brain-immune connection.

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“We now know the immune system and the brain have everything to do with each other; really, they are best understood as part of one larger system with causal influences that move in both directions. Brain states that produce mental illness also tend to activate inflammation. And inflammation is equally capable of producing depression, anxiety, fatigue, and social withdrawal.”

He added that environmental insults—for example, toxic exposures—can hike inflammation and “likely increase the risk of mental illness through this mechanism.”

Tonelli shares that view. He points out that military PTSD may be different in its complexity than other forms of the disorder—for example, like that seen in cases of sexual or child abuse—because war can mean not only severe emotional trauma, but also bodily injury, exposure to extreme heat or cold, sleep deprivation, and other physical assaults on the human organism.

“We need to incorporate physical trauma to the pathophysiology of PTSD,” he says. “Getting hurt physically in any way is an important mechanistic process leading to PTSD in which the immune system and inflammation play crucial roles.” ★



Photo by Mitch Mirkin

A device called a “social interaction box” is used to test whether a mouse is exhibiting signs of trauma such as social avoidance and withdrawal.

When it comes to using birth control, intention *and* attitude matter

A new VA study adds to the evidence that women's intentions around becoming pregnant don't fully explain whether and how they use contraception. Rather, their *attitudes* toward becoming pregnant also play a role.

For example, women who don't plan on getting pregnant, but who nonetheless say it would be fine if it happened, or even that they would be happy about it, may be less likely to use birth control at all, or to use effective methods, than those who aren't planning a pregnancy but say they would be upset if it occurred.

The finding, reported in the Nov. – Dec. 2018 edition of *Women's Health Issues*, doesn't seem surprising. Some past research has indicated as much. But the new evidence will help round out counselors' understanding of what drives women's decisions to use or not use contraception. It may also bolster efforts in VA to improve reproductive health services for women Veterans.

Dr. Sonya Borrero, who led the research, says the finding offers a window into the complexity of women's behaviors around planning or preventing pregnancies.

"Pregnancy intention and attitudes toward a hypothetical pregnancy are not always aligned," says Borrero, who is with the University of Pittsburgh and VA's Center for Health Equity Research and Promotion. "Counselors need to be aware of the range of thoughts and attitudes that may be shaping a woman's behavior when it comes to using contraception." And, Borrero points out, intentions and attitudes may be relatively fluid, changing over the course of a few months based on factors like relationship status, financial situation,



Dr. Sonya Borrero is an associate professor of medicine and director of the Center for Women's Health Research and Promotion at the University of Pittsburgh. She is also a core faculty member at the VA Center for Health Equity Research and Promotion and a staff physician in the VA Pittsburgh's women's health clinic.

or social support. She says routine or frequent assessment is needed to help women make the best reproductive decisions.

Borrero's team conducted phone interviews with 858 women Veterans who had recently been VA primary care patients. The work was part of a larger study called Examining Contraceptive Use and Unmet Need among Women Veterans.

The new analysis was limited to women Veterans at risk for an unwanted pregnancy. They answered questions about whether they were currently trying to become pregnant or planning to do so in the next year or at any point in the future. "Not sure" was another option.

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



Uridine, a natural substance found in human breast milk and other foods and plants, has been studied for its possible effects on brain health and other areas. VA is studying its possible role in suicide prevention.

Can a natural compound subdue suicidal thoughts?

VA researchers are trying to learn whether uridine, a naturally occurring dietary supplement, has the potential to subdue suicidal thinking, or ideation.

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The compound, uridine, is an unproven treatment for suicidal ideation. Administered orally, it's found in human breast milk and commercial infant formula.

Based at the Salt Lake City VA Medical Center, Dr. Douglas Kondo is a psychiatrist with the Rocky Mountain MIRECC (Mental Illness Research Education and Clinical Center). He's leading a trial on uridine in relation to suicidal ideation. The project is part of the U.S. Food and Drug Administration's (FDA's) Investigational New Drug program. Currently, there's no FDA-approved oral drug for suicide prevention.

Kondo's main goal is to test the anti-suicidal ability of uridine. If the data are encouraging, they could set the stage for a larger multi-site study. He also hopes to identify, through neuroimaging, brain chemistry changes that occur when participants experience a reduction in suicidal thoughts while taking uridine.

Kondo, also an associate professor at the University of Utah, stresses that uridine is still considered "investigational."

“That means it’s not ready for prime time,” he says. ‘As with any drug in the early stages of development, no conclusions can be drawn right now.’”

‘We’re just playing a small role in this problem,’ he adds. ‘Suicide is a big problem not just for Veterans, but for everyone.’”

According to Kondo, uridine has never been studied for suicidal ideation in a non-VA setting. He’s now leading a separate trial to see if the compound reduces signs of depression in adolescents with bipolar disorder, a mental condition marked by alternating periods of sadness and elation. Bipolar disorder is one of the most common psychiatric illnesses linked to suicide.

The non-randomized pilot phase of the trial tied uridine to a drop in depressive symptoms in the seven adolescents who consumed the drug for six weeks. However, Kondo and his team cautioned that uridine should not enter clinical practice as a treatment for depressed adolescents with bipolar disorder until randomized controlled trials have been done to confirm its effectiveness.

‘Rapid onset of action may be a distinguishing feature of uridine,’ the researchers wrote. ‘Open-label studies are an initial step in testing a novel intervention, but these findings should be considered preliminary.’”

Uridine is FDA-approved for treating negative reactions to cancer chemotherapy, as well as a rare condition related to urine called hereditary orotic aciduria.

A ‘window of opportunity’ for oral drug

Kondo is testing uridine at the same time VA scientists are researching two other drugs that are believed

to possess anti-suicidal properties: ketamine and lithium. Ketamine has long been used as an anesthetic but has emerged in recent years as a possible antidepressant. Lithium has FDA approval for treating bipolar disorder, which could lead to suicidal thoughts.

Suicide prevention is VA’s highest clinical priority. An average of 20.6 Veterans and service members a day are killing themselves, a rate that has been holding steady in recent years. Studies have found that Veterans, both men and women, are more likely than non-Veterans to commit suicide.

Research has also shown that about a quarter of Veteran suicides occur within seven days of the person’s final VA visit, and that half occur within 30 days of their last appointment.

Those statistics, Kondo says, provide a ‘window of opportunity’ for an oral and rapid-acting treatment with mild side effects, such as uridine, to be an effective clinical tool for VA researchers. If uridine proves effective, he notes, its status as a natural compound in breast milk means it could be prescribed by primary care, emergency department, and women’s health professionals.

For the uridine trial, scientists are recruiting 90 Veterans who have suicidal ideation as defined by a diagnostic interview and two scales that help measure those at risk for suicide: the Beck Scale for Suicidal Ideation and the Columbia-Suicide Severity Rating Scale. The researchers will combine the scores from all three assessments to figure out if someone is eligible for the study. Eligibility is based on whether suicidal ideation has had a negative impact on one’s social life, family life, spiritual life, and recreation and hobbies.

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“There been an increase in evidence that GABA and glutamine may be where the action is, where the rubber hits the road, so to speak, when you’re talking about the neurobiology of suicidal behavior.”



Matt Landis is a computer engineer at the Human Engineering Research Laboratories, a joint project between the VA Pittsburgh Healthcare System and the University of Pittsburgh.

VA Researchers Who Served: Matt Landis

Matt Landis is a man with a passion for service. The Army Veteran is a computer engineer at the Human Engineering Research Laboratories (HERL), a joint project between the VA Pittsburgh Healthcare System and the University of Pittsburgh. He and the HERL staff work to create wheelchair technologies, advanced prostheses, and other innovative systems that improve the quality of life for people with disabilities like lost limbs and spinal injuries. He was originally recruited to participate in HERL's ELeVATE program, which is designed to re-integrate Veterans into college. He graduated from the University of Pittsburgh with a degree in electrical engineering in 2016, after which he became a full-time employee at HERL. He served two tours in Iraq as an Apache helicopter pilot and earned many honors, most notably the Army Commendation Medal. He's been featured in the video series "Living to Serve," which is produced by the internet search engine Google.

What motivated you to join the military?

I actually joined twice. The first time, the motivation was purely machismo. The captain of the rugby team I played for at the time was a former special forces medic. I wanted to be just that. I wanted to be as tough and able as he always seemed, and he encouraged me to pursue that path. Ultimately, I didn't follow in his footsteps and made my own way.

What inspired your research career?

It was purely because of my son. All three of my children are on the autism spectrum. But my middle child is severe and non-verbal at 15 years old. Ever since he was young, we've had to innovate to communicate with him. With my

technical background, I've been researching methods for facilitating communication and exploration with him since he was diagnosed. When I heard there was a specific field for this, termed rehabilitation science and technology, or rehab engineering, I immediately began searching for a program. The first name that came up was Dr. Rory Cooper, the director of HERL and my mentor. Once I saw the work he was doing, I knew where I needed to be.

Have you had mentors who you've looked up to in life, the military, or your research career?

Absolutely. I think everything I am is built on my ideas about and the study of certain people, both historical and contemporary. Chief among them are Robert Kennedy and Muhammad Ali. They're both fighters who spent their lives growing, changing, and becoming better people, all through the most difficult circumstances imaginable. I lost my parents and grandparents when I was young and had a brother murdered. So I've always looked at those men as models for how I can fight through and do good. In my military years, I always had at least one mentor that helped me grow and learn. Officers Dennis Yates and Kenneth Royar were two of the most impactful. I worked directly under each one and learned a leadership style from them that I try to emulate. They were patient, thoughtful men who embodied the essence of servant-leaders. They were the first real-life warrior poets I would meet. I've tried to walk in their steps ever since. In my research career, Dr. Cooper stands alone. He's a generational luminary, the kind of man that you can't stand next to without being better and doing better. He takes away every excuse you make for yourself in life just from the example he sets.

When and where did you serve in the military? Describe your military experience.

I joined the Army as a forward observer in 1999 and served with the 187th Infantry Regiment at Fort Campbell in Kentucky until 2002. Just before 9-11, I was selected for warrant officer candidate school (WOCS) and left in January 2002 for Fort Rucker in Alabama. There, I would complete WOCS and flight



An Army Veteran, Landis served two tours in Iraq as an Apache helicopter pilot

school, graduating as an AH-64D Apache Longbow pilot. I was assigned to the 11th Aviation Regiment in Illesheim, Germany in 2003. I joined that unit in Iraq in June 2003 as an Apache helicopter pilot and remained with it until February 2004. After a promotion to chief warrant officer and a transfer to the 3d Armored Cavalry Regiment, I was sent to Fort Hood in Texas in 2006. I served the rest of my career in that unit, deploying to Iraq from 2007 to 2009 as part of the Iraq war surge efforts at the time. I left the military shortly after redeployment in July 2009

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

We develop technologies at HERL that improve the quality of life and independence for those with disabilities. Much of the lab's early work focused on wheelchair technologies and adaptive sports technologies. While we continue to lead academic exploration in those areas, we also have projects dedicated to advanced prostheses, robotics, and adaptive communications. We also are working on projects that may advance detection and treatment of PTSD-driven episodes in real time.

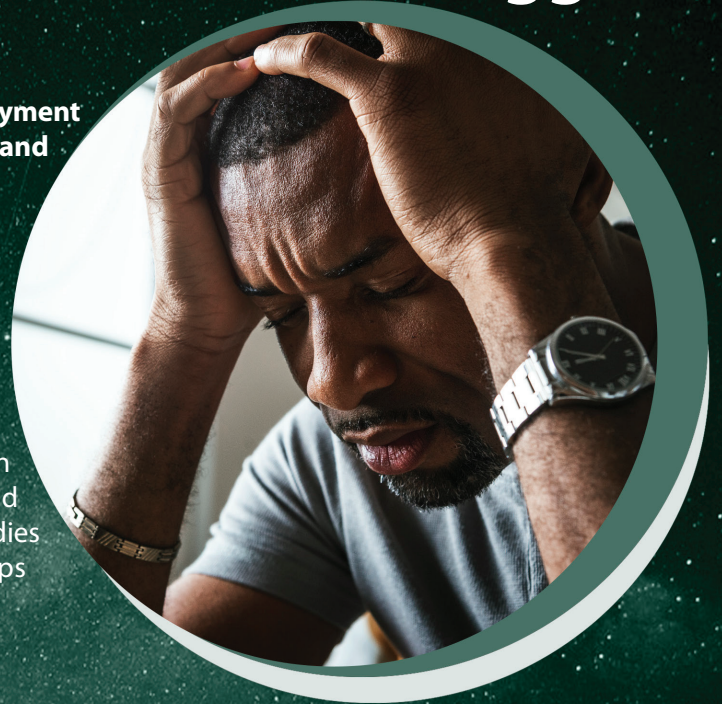
To read more profiles of "VA Researchers Who Served," visit www.research.va.gov. ★

Pre-deployment insomnia linked to post-deployment mental health struggles

VA and university researchers analyzed data from **4,645 Army soldiers** who completed surveys before **deployment to Afghanistan** and then **upon their return** and at **three and nine months later**.

In one statistical model, **pre deployment insomnia** was associated with about a **threefold-higher risk** of **post-deployment PTSD** and **suicidal thinking**.

Conclusion: "Pre-deployment insomnia contributed to prediction of post deployment PTSD and suicidal ideation in Army soldiers, suggesting that **detection** of insomnia could facilitate targeting of risk-mitigation programs. Future studies should investigate whether **treatment of insomnia** helps **prevent PTSD and suicidal ideation** among deployed servicemembers."



From "Pre-deployment Insomnia is Associated with Post-deployment PTSD and Suicidal Ideation in US Army Soldiers," online Dec. 3, 2018, in *Sleep*. Infographic by VA Research Communications, December 2018. Photo for illustrative purposes only. © iStock/Rawpixel.

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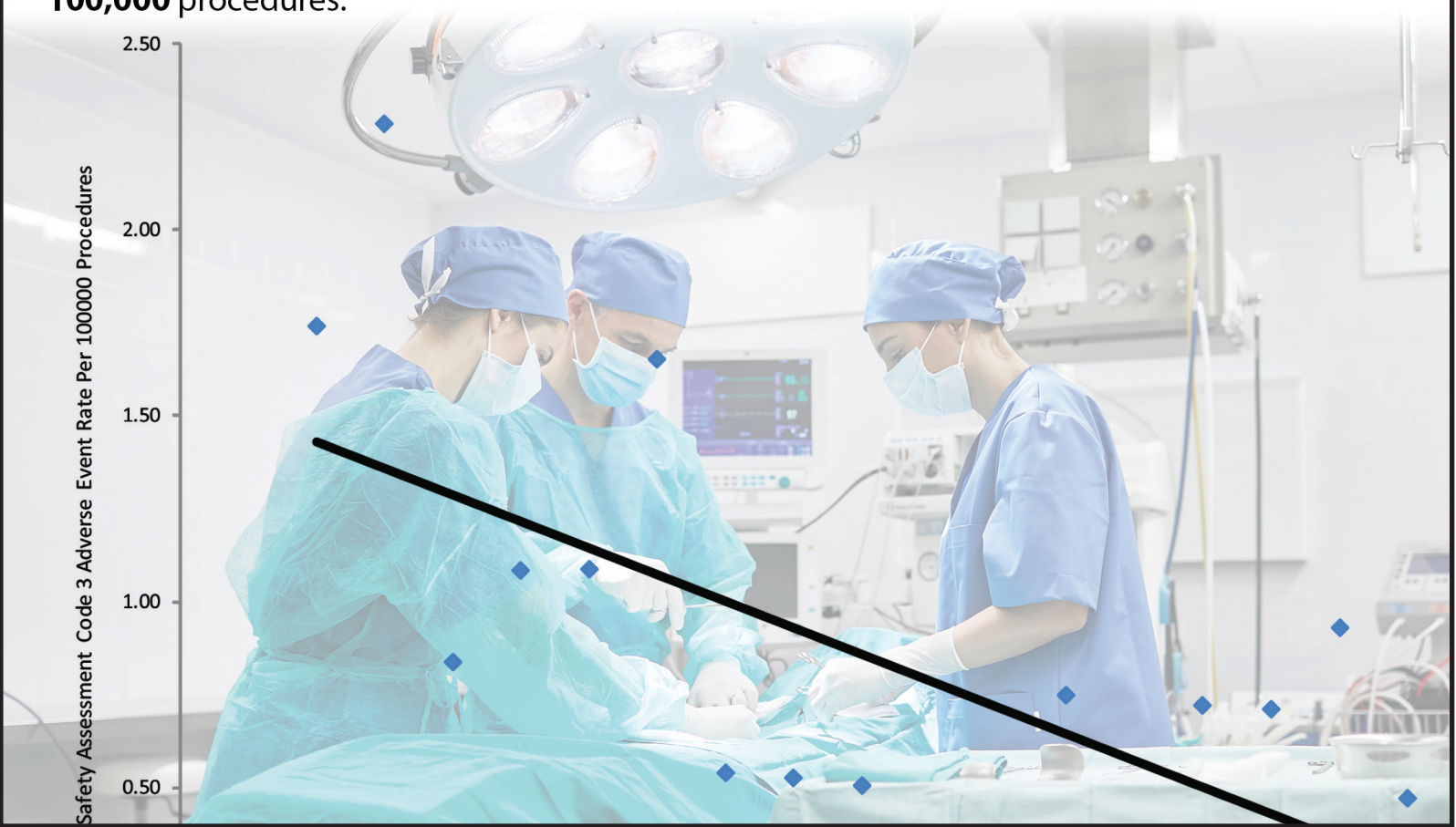
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Steady drop in incorrect surgical procedures

VA researchers tracked the rates of wrong-site surgery and other incorrect surgical procedures in VA between **2010 and 2017**. They compared the results with those of similar studies dating back to 2001. The overall trend was a **steady decline**. The rate of reported adverse events in operating rooms dropped from **1.74 per 100,000 procedures** to **0.47 per 100,000 procedures**.



Check out more VA Research infographics at:
www.research.va.gov/pubs/infographics

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.

PTSD Category	Prevalence
Subthreshold PTSD	22.1%
Probable PTSD	8.0%

Conclusion: The results of this study suggest that a relatively high percentage of VA veterans experience enough PTSD symptoms to be classified as having subthreshold PTSD, but not enough to be classified as having PTSD.

Source: https://www.research.va.gov/publications/PTSD/PDF/PTSD_Subthreshold.pdf, 2016. PTSD prevalence among VA veterans. VA Research Communications, January 2016. PTSD prevalence among VA veterans. VA Research Communications, January 2016.

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 (VIPS) Advancing Recovery (IPSWAR) 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: "Effect of Evidence-Based Supported Employment on Achieving Steady Work among Veterans with Posttraumatic Stress Disorder: A Randomized Controlled Trial." https://www.research.va.gov/publications/PTSD/PDF/PTSD_IPSWAR.pdf, 2016. Infographic by VA Research Communications, January 2016. PTSD prevalence among VA veterans. VA Research Communications, January 2016.

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 (24-34%) and 2011 (21%).
- The most commonly reported combination of training topics was safe handling, safe storage, and accident prevention.
- Only 1% of owners said their training covered suicide prevention.
- Conclusion: The preparation of U.S. firearm owners with formal firearm training has not meaningfully changed in two decades. Training programs using widely efforts are needed to standardize and improve the effectiveness of training.

Source: https://www.research.va.gov/publications/PTSD/PDF/PTSD_Firearm_Training.pdf, 2016. PTSD prevalence among VA veterans. VA Research Communications, January 2016.



RESEARCH CURRENTS

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

Mouse study: Aspirin may slow multiple sclerosis

Low-dose aspirin could suppress multiple sclerosis symptoms and slow the disease, according to a mouse study by Jesse Brown VA Medical Center researchers. Mice with a condition similar to MS were given small doses of aspirin orally. Mice given aspirin show reduced symptoms for both relapsing-remitting and chronic forms of the disease. The aspirin also seems to have prevented destruction to the myelin sheath in the spinal cord caused by destructive T-cells. The researchers found that aspirin reversed the depletion of regulatory T-cells that occurs in MS, which may have helped stop other T-cells from attacking nerve fibers. While more study is needed, the results suggest that low-dose aspirin regimens could help patients with MS, say the researchers. (*Science Signaling*, Nov. 27, 2018)

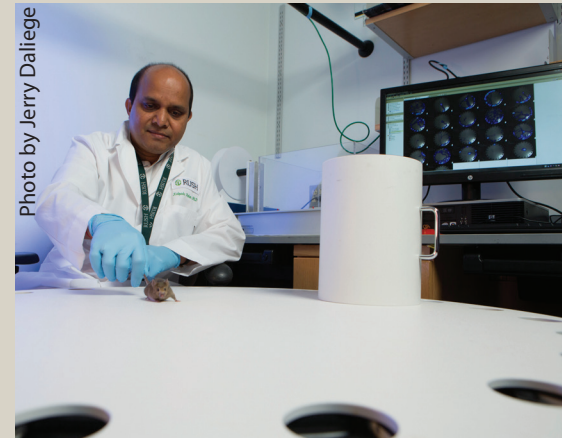


Photo by Jerry Daliege



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