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VA RESEARCH CURRENTS

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WHAT'S INSIDE

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Studies look at recent Veterans' linkage to VA care

About 48 percent of Army Veterans who served on active duty in Iraq or Afghanistan enrolled in and used VA care within one year of separation from the military, reported VA researchers and colleagues. The study included more than 151,000 active-duty members who had deployed and then separated from the Army between 2008 and 2012.


Sgt. Michael J. MacLeod/USA

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

Study finds gaps in VA care for hepatitis B

A study of national VA care for patients infected with the hepatitis B virus found significant gaps in testing and follow-up care. The results are similar to those from studies of non-VA care for those with the virus.


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

Long-term survival data support original results of landmark COURAGE study

Back in 2007, U.S. and Canadian researchers made headlines when they shared the results of a major study of patients with chest pain during physical exertion, due to blocked arteries.

The trial, known by its acronym COURAGE, found that relieving artery blockage by percutaneous coronary intervention (PCI)—typically, the use of balloon angioplasty plus stenting—did little to improve outcomes for 2,287 patients with stable coronary artery disease who also received optimal drug ther-

apy and underwent lifestyle changes. New long-term survival data on a subset of patients from the original study appear to support the original conclusions: There was no advantage to PCI over optimal medical therapy, at least in terms of staying alive.

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

Study at one VAMC finds high rate of sexual dysfunction among new Veterans

In a study of 247 Veterans who had served recently in Iraq or Afghanistan, almost 18 percent screened positive for sexual functioning difficulties. Factors that were linked with self-reported sexual dysfunction included depression, posttraumatic stress disorder, female sex, and a higher service connection rating.

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

Study finds scant evidence of TBI as trigger for mental health problems

Mild traumatic brain injury, by itself, may not lead to mental health problems such as PTSD or mood or anxiety disorders. That is the key finding from a VA study of 107 Iraq and Afghanistan Veterans.

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

Latest study from BrainGate team shows new advances in direct cortical control of computer

In the latest report on BrainGate, an investigational device that allows people with paralysis to control computer cursors just by thinking about the movement of their own hand, researchers describe the best performance yet by study volunteers using the system.

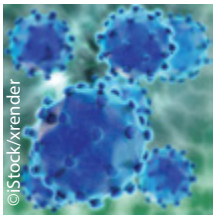
Read more at www.research.va.gov/currents

Study ties restless legs syndrome to heart, kidney problems

Imagine trying to lie down and rest but feeling an uncontrollable urge to keep moving your legs. That, in a nutshell, is the ongoing ordeal facing people with restless legs syndrome. A database study of Veterans found that those with restless legs syndrome are at higher risk for stroke, heart and kidney disease, and earlier death. Studies in the past had suggested such links, but the new research provides the strongest evidence yet of the connection.

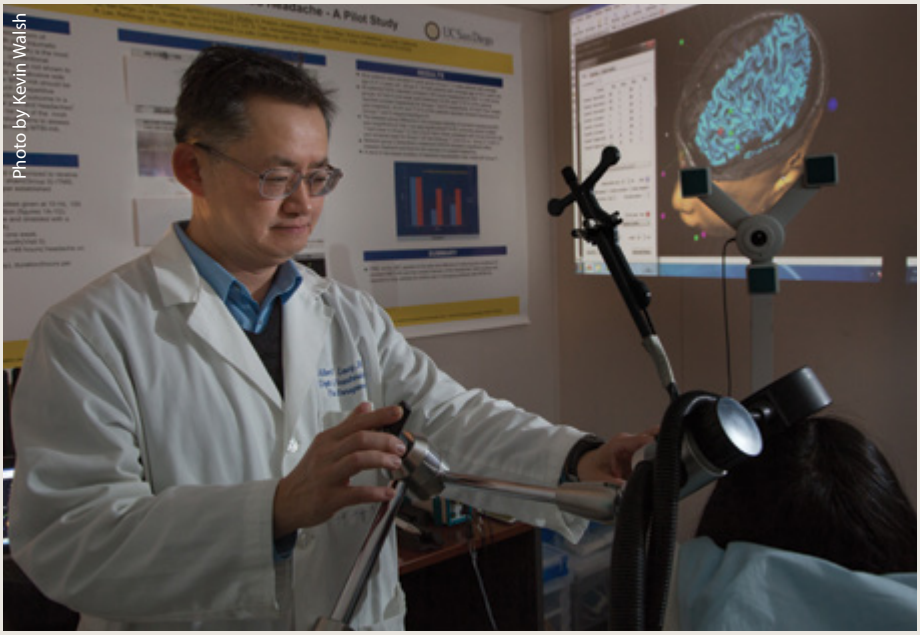
Read more at www.research.va.gov/currents

Study may temper expectations for new hepatitis C drug



VA researchers found that the cure rates for a new hepatitis C drug, as used in the "real world" VA population, did indeed beat those of older regimens—but they fell short of the successes seen in clinical trials for the drug.

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



Dr. Albert Leung's team fed volunteers' MRI images into software that enabled them to visualize the magnetic field and the participant's brain in real time and focus the energy into the target region.

Can magnetic stimulation help TBI headaches?

A small study involving Veterans with headaches related to mild traumatic brain injury found positive results from a treatment called repetitive transcranial magnetic stimulation.

The results appeared online Nov. 10, 2015, in the journal *Neuromodulation*.

In transcranial magnetic stimulation, or TMS, clinicians take an electromagnetic coil—essentially a wire wrapped around a solid core—charge it with electricity, and apply it to specific points on the skull. The result is a targeted magnetic field that can affect brain cells in a specific area.

The treatment is FDA-approved for major depression that doesn't respond to other treatments. Over the past few years, researchers have been studying it for an array of other conditions involving the brain. A portable device that uses TMS was approved by the FDA in 2013 to treat certain types of migraines. But to date, only limited research has looked at the potential of TMS for treating other types of headaches.

Study volunteers had persistent daily headaches

The new study involved 24 Veterans, mostly men, at the VA San Diego Healthcare System. All had persistent daily headaches, the result of head trauma.

Half were randomized to a real TMS treatment, while the others received a sham version that looked and felt like the real thing.

Lead researcher Dr. Albert Leung and his team used MRI to pinpoint treatment with the magnetic coil on a precise area of the brain: the left motor cortex. Past research has shown this area may be involved in headache pain.

The MRI images were fed into special software that enabled the team to visualize the magnetic field and the participant's brain in real time and focus the energy as a cone-shaped beam into the target region. This helped ensure that the same exact brain area was targeted in exactly the same manner in each individual volunteer, across all treatment sessions.

The Veterans received three real or sham treatments within a week. In assessments one week later, about 58 percent of the real-treatment group showed at least a 50-percent reduction in headache intensity, versus only 17 percent in the sham group. In assessments after four weeks, the real-treatment group continued to show greater improvements than the sham group.

The authors concluded that the protocol "appears to be a clinically feasible and effective treatment option." They plan further tests of the treatment, along with imaging studies to better understand exactly how it works.

Using a mouse model of Gulf War Illness, researchers dig deep for potential treatments

About a quarter of the 700,000 men and women who served in the Persian Gulf during operations Desert Shield and Desert Storm in 1990 – 1991 continue to cope with troubling health symptoms well over two decades later. Meanwhile, researchers continue to work on understanding the causes and developing treatments.

At the Society for Neuroscience meeting held in October 2015 in Chicago, a team of VA and Roskamp Institute researchers presented their latest findings based on a mouse model of Gulf War Illness (GWI) that they developed.

Lead author on the study was Dr. Laila Abdullah, part of the GWI Research Program headed by Dr. Fiona Crawford at Roskamp. Both are also with the James A. Haley VA Hospital in Tampa, Fla.

The team tested the long-term adverse effects on the brain following exposure to two chemicals implicated in GWI. One is a pesticide called permethrin. The other is pyridostigmine bromide (PB), an anti-nerve gas agent that was given preventively to troops in the form of a pill.

To mimic the experience of affected Veterans—acute exposure, with chronic effects—the team gave the mice the chemicals over 10 days and then examined changes in the brain 16 months later. The scientists found disturbances in lipids, or fats, that are important for brain function.

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

Photo: ©iStock/dra_schwartz

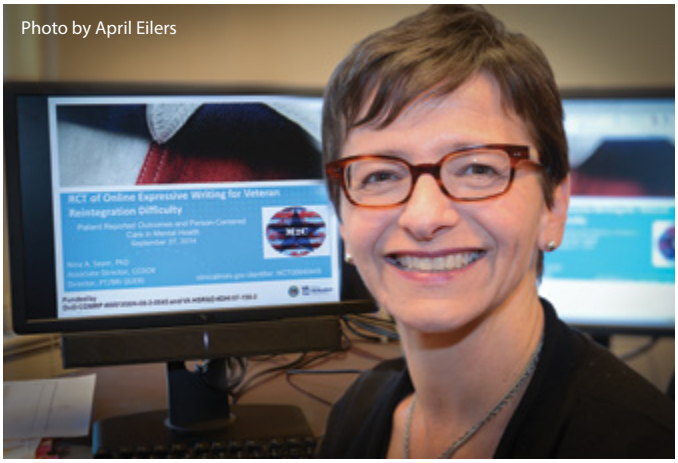


Photo by April Eilers

Dr. Nina Sayer and colleagues tested the benefits of expressive writing for returning Veterans.

Expressive writing shows some benefits for returning Vets

In a study of nearly 1,300 returning Veterans reporting reintegration problems, those who completed online expressive-writing sessions showed more improvements than peers who had not written at all or who had engaged only in factual writing.

The effects of the intervention, which involved four 20-minute writing sessions, were small. But the researchers say it nonetheless could be a worthwhile step in helping returning Veterans, given its low cost and high accessibility. They say it could be used as a stand-alone therapy or as an add-on to formal treatment.

The study appeared in the October 2015 issue of the *Journal of Traumatic Stress*.

"Online expressive writing, a simple, resource-efficient intervention that can be implemented online without clinician involvement, may be a promising strategy for improving symptoms and functioning among combat Veterans who experience reintegration difficulty," write the authors.

Study leader Dr. Nina Sayer points out that the low-tech activity is easily accessed by Veterans from all backgrounds.

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

Telemedicine helps get diabetes under control

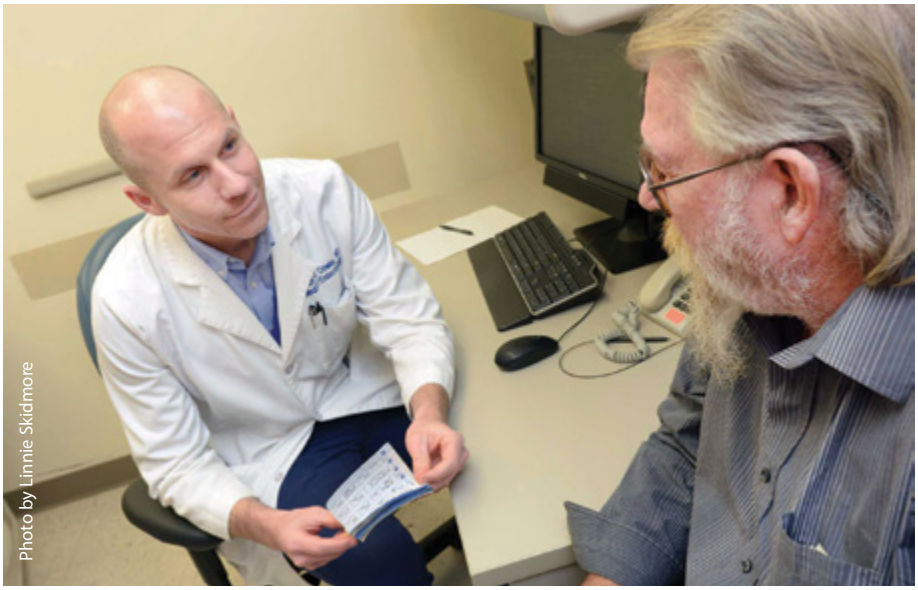


Photo by Linnie Skidmore

Dr. Matthew Crowley meets with diabetes patient Jon Morris at the Durham VA. Crowley's team is studying how to use telehealth to boost care for Veterans with diabetes whose condition has not responded to standard clinic-based care

A new telehealth program developed at the Durham VA Medical Center may be sweet news for Veterans whose diabetes has not responded to standard care.

The program is called ACDC—short for Advanced Comprehensive Diabetes Care. Tested in a pilot study of 50 Veterans with persistently poor diabetes control, the approach beat standard clinic-based care for nudging blood sugar levels toward normal. The pilot study results went online Nov. 5, 2015, in the journal *Telemedicine and e-Health*.

Half the Veterans in the study got "usual care," without any special interventions. They also got an education packet.

The other half took part in the telehealth program. It combined four key elements:

- The telehealth patients were asked to check their blood sugar before each meal and at bedtime. Upon receiving a daily automated reminder call, they used an interactive voice system to transmit their readings to the clinic.
- Every two weeks, a nurse checked in with the patient by phone, with the conversation lasting about 30 minutes. During most calls, the nurse delivered an education module. The topics included, for example, the fine points of checking blood sugar, how to know when blood sugar is dropping too low, and warning signs of diabetes complications.
- Doctors reviewed patients' cases every two weeks to see if any medication tweaks were needed, based on data forwarded by the study nurses.
- The study team checked for depression—which often foils self-care—and quickly called in a psychiatrist for in-person evaluations when needed.

The researchers compared several outcomes across the two study groups. The main measure was HbA1c, which shows average blood sugar levels over the past two to three months.

After six months, the usual-care group showed a slight reduction: from 10.5 to 10.2. The drop was sharper in the ACDC group: 10.5 to 9.2. That may not sound like a lot, but the researchers say that over time such an improvement in blood sugar could significantly cut the risk of heart attack or other complications, and death.

"You need to consider the population we're working with—these are patients for whom nothing else has worked. A 1 percent change is actually a pretty big deal in this population," says lead researcher Dr. Matthew Crowley.

The reduction in blood sugar, not surprisingly, was greater for those ACDC participants who took part in more phone encounters. For patients who completed more than 6 of the scheduled 12 encounters, the average A1c improvement was nearly 2 percent.

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

Dr. Alexander B. Niculescu, with VA and Indiana University, is studying blood biomarkers and questionnaires that can accurately predict suicide attempts.

Researchers report biomarkers and apps that predict suicide risk

Researchers with VA and Indiana University School of Medicine have developed blood tests and questionnaires that can predict with more than 90 percent accuracy which mental health patients will begin thinking of suicide, or attempt it.

The findings appeared in the November 2015 issue of the journal *Molecular Psychiatry*.

"We believe that widespread adoption of risk-prediction tests based on these findings during health care assessments will enable clinicians to intervene with lifestyle changes or treatments that can save lives," said Dr. Alexander B. Niculescu III, professor of psychiatry and medical neuroscience at the IU School of Medicine, and attending psychiatrist and research and development investigator at the Richard L. Roudebush VA Medical Center.

Using RNA biomarkers from blood samples along with newly developed questionnaires in the form of an app, the researchers were able to predict which individuals in a group of patients being seen for a variety of psychiatric illnesses would experience significant suicidal ideation with approximately 92 percent accuracy. Among patients with bipolar disorder, the accuracy reached 98 percent, Niculescu said. The combination of biomarkers and app was also accurate in predicting which of the patients would be hospitalized for suicidality in the year following testing (71 percent across all diagnoses, 94 percent for bipolar disorder).

The questionnaires by themselves, implemented as apps on tablets, were able to predict the onset of significant suicidal thoughts with more than 80 percent accuracy.

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

Promising results seen from deep brain stimulation in combat Veteran with treatment-resistant PTSD

VA doctors in Los Angeles have performed the first-ever trial of deep brain stimulation to treat PTSD. The patient is a Gulf War Veteran whose traumatic nightmares and other PTSD symptoms had failed to respond adequately to standard treatments, including medications and psychotherapy.

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

Photo by Cpl. Artur Shvartsberg/USMC

What good can come of trauma? **Researchers probe posttraumatic growth**

'Posttraumatic growth' may not be a household term like posttraumatic stress disorder. But thanks in part to recent VA studies, the idea is becoming more familiar—both in the research world and among Veterans who have been through traumas.

Navy corpsmen tend to a Marine wounded in a firefight in Afghanistan in 2009. VA researchers are studying the after-effects of trauma—not only the negative ones, but the "posttraumatic growth" that often occurs as well.

"Posttraumatic growth" may not be a household term like posttraumatic stress disorder. But thanks in part to recent VA studies, the idea is becoming more familiar—both in the research world and among Veterans who have been through traumas.

"It's the general idea that after a trauma, not everything that happens to someone is necessarily bad," explains Dr. Jessica Keith, a psychologist who works with trauma survivors at the Bay Pines (Fla.) VA Healthcare System.

The literature on posttraumatic growth dates back to seminal work by University of North Carolina authors Drs. Lawrence Calhoun and Richard Tedeschi in the 1990s. They define it, in a nutshell, as positive psychological changes that result from struggling with traumatic events.

Those changes could bring a greater appreciation of life, more self-esteem and connectedness to others, a renewed sense of meaning and purpose. Psychologists believe such growth can counter and in some cases overcome the lingering negative impacts of traumas such as combat or sexual abuse.

What might seem like two opposing forces in the wake of crisis—positive changes, versus distressing symptoms—are not really opposing after all. They can and often do occur at the same time. And they can work hand in hand.

'A weird juxtaposition'

"A lot of people think of posttraumatic growth as something that develops later on, after the PTSD symptoms have subsided," says psychologist Dr. Jack Tsai, with Yale and VA's New England Mental Illness Research, Education, and Clinical Center, whose group has conducted long-term studies of trauma survivors. "But we've found that a lot of times there's this weird juxtaposition, in which people are experiencing the negative effects of trauma, but at the same time reporting some positive effects."

That's an important point to drive home to Veterans, says Tsai. "The approach is not, 'Hey, suck it up and get over it and then you'll be able to grow from it.' Rather, in many cases they are expressing a lot of pain at the same time."

Keith agrees. A recent study by her group, led by Dr. Alaa Hajizi, then a postdoctoral fellow at the Bay Pines VA, included 167 combat Veterans from different eras. "We looked at people pretreatment, and we found that some of them had levels of posttraumatic growth that were quite high, even though they'd yet to have any treatment and they had significant symptoms."

Keep in mind that those who go through bad events and remain fully intact psychologically may not be considered to have experienced posttraumatic growth at all. By definition, it involves going

through some mental struggles, perhaps intense at times—and emerging stronger for the ordeal.

"If someone is not affected by their trauma at all, they're not going to have much posttraumatic growth," says Tsai.

The role of treatment

Some researchers see posttraumatic growth as a form of emotional resilience. Others, like Keith, have a different take.

"Resilience means you went through a potentially traumatic event, such as combat, and you weren't affected," she says. "You didn't really experience emotional or mental health problems afterward. With posttraumatic growth, in general, you experienced some very difficult moments after the trauma, maybe some PTSD symptoms or full PTSD, and then in the working-through process, the healing process, you grappled with it and eventually got to the point where you experienced some growth."

"We need to challenge the old-school way of thinking that trauma is linked only to bad things."

For some Veterans, posttraumatic growth takes shape only after months or even years of treatment. But treatment is by no means a pre-requisite. In fact, some treatments, like sedating drugs, may thwart growth—even if the drugs are needed for a time to quell troubling symptoms and enable the person to function.

Keith: "We know some medications, like benzodiazepines, can interfere with PTSD psychotherapy, because you can't feel your emotions enough to actually work through them. So they could possibly interfere with posttraumatic growth as well, if they numb you so you don't need to grapple and struggle."

On the other hand, treatment, especially psychotherapy, can often spur growth. In fact, Keith believes that generally, "we're increasing posttraumatic growth by the end of treatment, to some degree, although there are still levels of it pre-treatment."

The main goal of talk therapy is a reduction in symptoms, but posttraumatic growth could be a positive byproduct. Keith cites cognitive processing therapy as a prime example. "This therapy, in particular, looks at how people see themselves, and how they see others and the world around them. It is specifically trying to form a new belief system."

'Cognitive flexibility' predicts growth

Keith, who specializes in working with women who've experienced military sexual trauma, tells of Veterans who would write, before their sessions began, about not being able to trust anyone. "Then if they process their trauma and look at their thoughts, they can come out the other side and realize that

'in this trauma there were some people who had my back, who I trusted a lot. And there are some people I can trust now.' So they get these more nuanced views, and there can be some growth through that. It's not an explicit goal of treatment, but I think it could be made more explicit."

The evolution in thinking that Keith describes is a result of cognitive flexibility, which has emerged in research as one of the traits that predict posttraumatic growth.

"In two papers we found a very strong relationship between cognitive flexibility and posttraumatic growth," says Keith. She describes cognitive flexibility as "the ability to see shades of gray, to see things from different perspectives, to change your viewpoint on certain things." She adds, "You can understand why that would be important for posttraumatic growth."

Can someone learn to be more cognitively flexible, or is it something you're born with? Keith says it's both. She acknowledges that some people will come into therapy with more of this trait, and perhaps treatment will be smoother for them because of it. But at the same time, "it can be learned to some degree. In fact, a lot of the psychotherapies being used for PTSD do speak to cognitive flexibility." Again, she cites cognitive processing therapy in particular: "It's all about helping people challenge their unhelpful thinking, seeing things in more shades of gray. That's part of these treatments, and we know they work."

The balance between PTSD and growth

Surprisingly—or perhaps not—the presence of PTSD symptoms is another factor shown in studies to enhance posttraumatic growth. But the balance between PTSD symptoms and posttraumatic growth is a delicate one. A moderate level of symptoms can spur growth. Stronger symptoms can thwart it.

Tsai's group, which has analyzed data on thousands of Veterans from the National Health and Resilience in Veterans Study, describes

Photo by Crystal Ettridge

When growth happens later in life

For some war Veterans, posttraumatic growth can happen decades after the trauma.

A team with the Stress, Health, and Aging Research Program at the Boston VA has looked at aging Veterans who grapple with their war traumas only later in life. The group, funded by VA's National Center for PTSD, came up with a concept they call "later-adulthood trauma reengagement," or LATR.

In a recent article in The Gerontologist, they write: "We suggest that later in life many combat Veterans confront and rework their wartime memories in an effort to find meaning and build coherence. Through reminiscence, life review, and wrestling with issues such as integrity versus despair, they intentionally reengage with experiences they avoided or managed successfully earlier in life, perhaps without resolution or integration."

The research is not focused on those for whom PTSD has been an ongoing struggle. Among men who served in Vietnam, for example, about 11 percent are estimated to still have full-blown PTSD, more than four decades after the war, according to the National Vietnam Veterans Longitudinal Study. The figure is 7 percent for women.

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

the statistical relationship between PTSD and posttraumatic growth as "curvilinear." Picture an upside-down U shape. There's a mid-range of PTSD symptomatology that's conducive to growth. "But when it's just too much," says Tsai, "and the symptoms are too debilitating, it's hard to develop posttraumatic growth from that."

In the title of one of their reports on the findings, Tsai's team used the phrase "what doesn't kill you makes you stronger," based on the old adage, but also playing off the lyric from the 2011 hit "Stronger" by singer-songwriter Kelly Clarkson.

But Tsai himself is quick to point out that for some trauma survivors, this is not the case. Not everyone ultimately benefits from trauma.

Keith says she would amend the catch-phrase: "What doesn't kill you could make you stronger."

Another growth predictor that emerged in the study by Keith's group was a sense of moral wrong-doing—having hurt others, having gone against one's own moral principles. Psychologists call this "moral injury."

Keith says: "This might be because the trauma caused more pain, and they had to grapple with it more. They were forced to work at making some meaning out of it, and as a result they experienced growth."

The altruism factor

Tsai's research has identified other factors that appear to be associated with posttraumatic growth, although it's hard to tease out whether they are pre-existing traits that spur growth, or the products of it. They include qualities like altruism, religiosity, a sense of purpose in life, and an "active reading lifestyle," in which the person seeks out new knowledge and enlightenment.

"It seems a lot of these factors relate to people doing things outside themselves, whether it's worshiping or volunteering or connecting with others in other ways," reflects Tsai. "Being involved with the greater world seems to bring on growth. When you give you receive."

Whatever the drivers of posttraumatic growth, both Keith and Tsai say it's good news that the topic is increasingly on researchers' radar.

"It's great it's being studied at all, so people know it exists," says Keith. "We need to challenge the old-school way of thinking that trauma is linked only to bad things. We cannot assume the person will have growth, but we know they can. Even with the very difficult aspects of trauma, it's often talking about them, feeling them, being devastated by them for a while, that can lead to growth." ★

How common is posttraumatic growth?

In a study by Dr. Jack Tsai's group, based on survey results from a nationally representative sample of more than 3,000 Veterans, 50 percent of all Veterans reported "moderate" posttraumatic growth. Among those who screened positive for PTSD, 72 percent reported moderate posttraumatic growth.

Among those with PTSD, those reporting posttraumatic growth also reported better mental functioning and general health than those without posttraumatic growth.

The researchers concluded: "[Posttraumatic growth] is prevalent among U.S. Veterans, particularly among those who screen positive for PTSD. These results suggest that there may be a 'positive legacy' of trauma that has functional significance for Veterans."

Photo by Robert Turtil

Nowadays, women make up more than 15 percent of the U.S. military, and at least 1 in 5 new recruits is a woman.

The trend, of course, translates into Veteran statistics. Women now account for more than 9 percent of the 21.6 million Veterans in the U.S, and nearly 7 percent of VA health care users.

In response, VA researchers have been working in recent years to include more women in VA studies and to sharpen the focus on their health needs. One milestone was the creation in 2010 of the Women's Health Research Network. The network, funded by VA Health Services Research and Development, has two parts:

- The Women's Health Research Consortium boosts training for women's health researchers. It also helps them network and promotes partnerships with VA managers and frontline providers, so research findings can be applied toward improving care.
- The Women's Health Practice-Based Research Network (PBRN) builds infrastructure and a national community of frontline clinicians, researchers, and managers. By linking research programs at dozens of sites, the PBRN makes

▲ These investigators were among the participants at the 2014 VA Women Veterans Health Services Research Conference.

it easier for VA researchers to do large, multisite studies involving women Veterans. It helps researchers tackle the challenge of doing women's studies in a health care system that is still predominantly male.

The PBRN was the topic of an article in the September-October 2015 *Journal of the American Board of Family Medicine (JABFM)*. The authors discuss lessons learned from the first study conducted through the PBRN. The study, launched in 2012 and published earlier this year, explored women Veterans' preferences for mental health care. It also sought to refine PBRN operations.

VA Research Currents interviewed three of the authors on the inaugural study and the recent *JABFM* article, all of them among the leaders in VA women's health research, to learn more about the progress of the PBRN and its impact on women Veterans.

The interview included Drs. Susan M. Frayne, Rachel Kimerling, and Elizabeth Yano. Frayne and Kimerling are based at the VA Palo Alto Health Care System and Stanford University. Yano is with the VA Greater Los Angeles Health Care System and UCLA.

VA Research Currents: *How many studies been completed through the PBRN, aside from the inaugural project gauging women's preferences for mental health care?*

SF: The saying goes, "If you build it, they will come." When Dr. Yano and I first started the PBRN, we didn't know whether that would prove to be true. So you can imagine our delight that so many investigators have approached us about using the PBRN! We have already had more than 30 funded research studies or program evaluations or quality-improvement projects in the PBRN, and we continue to be approached about new studies.

Could you provide a few examples of the studies now being conducted?

SF: One of our current studies is led by Dr. Kristin Mattocks at the VA Central Western Massachusetts. Her team is eliciting the perspectives of pregnant women regarding their experiences with maternity care coordination in VA. To achieve a good representation of women from diverse racial and ethnic backgrounds and to recruit enough women, that

study is using 13 PBRN sites. Another major initiative that has just recently launched is the EMPOWER QUERI [Quality Enhancement Research Initiative], led by Dr. Alison Hamilton, which will be using multiple PBRN sites. Yet another hallmark suite of studies currently using the PBRN is the Women's Health CREATE, led by Dr. Yano.

Dr. Yano, could you tell us more about that effort, and how it's been helped by the PBRN?

EY: The Women's Health CREATE is a collection of five studies that together are working to accelerate implementation of comprehensive care for women Veterans. These five studies are working with a large number of PBRN sites. I can say that having a PBRN site lead "on the ground" who can help with local logistics and provide warm handoffs to local leadership or providers is huge.

One of the CREATE studies is also working directly with local quality-improvement teams. The PBRN site leads were either the right people to begin with or got us to the right people within days, and then helped us get to the right leaders quickly and easily. This saved us so much time and headache!

For the site leads who are also clinicians, many of them are also directly involved in the intervention, so we are able to really engage and support them in making local evidence-based quality-improvement changes to tailor PACT [Patient-Aligned Care Team, VA's primary care model] to meet women Veterans' needs. It has been so gratifying to work in these partnerships with site leads!

How many sites are currently taking part in the PBRN?

SF: This summer we expanded from 37 sites to 60 sites nationally. These sites span the country. Some are at big hospitals in major metropolitan areas, whereas others are serving women in remote rural communities. We have an amazing and dedicated group of PBRN site leads who represent diverse clinical and research backgrounds. A number of

An attendee at the 2012 15th anniversary commemoration event at the Women in Military Service to American Memorial in Washington, D.C.

A Naval Academy midshipman crawls through the mud during "Sea Trials" at the U.S. Naval Academy in 2006. Women now account for more than 9 percent of U.S. Veterans and nearly 7 percent of VA health care users.

them are Veterans themselves. The PBRN now represents 200,000 women Veterans nationally, which is more than half of the women Veterans who use VHA services.

What have you learned about women Veterans' preferences for mental health care?

RK: One of the most robust findings in the inaugural PBRN study was that women with strong preferences for designated mental health services for women also preferred to receive those services within their primary care setting. These included services that focused on mood, PTSD, and coping with chronic health conditions. One of the newly established QUERI programs, the EMPOWER QUERI, will build on what this study has learned, and on what the Women's Health Research Network has learned about engaging women Veterans, to derive effective strategies for implementing gender-tailored services for these conditions into VA primary care. And of course, the PBRN will provide important infrastructure for this program.

How is VA's Central Institutional Review Board (IRB) important to the PBRN?

SF: The Central IRB is a very helpful innovation for those of us who are involved in multisite research. Because we have a Central IRB, the principal investigator can complete an overarching protocol describing how participants will be protected in the study, and then each site can just adapt templated paperwork and consent forms for their local site. This works better than having a large number of separate IRBs, each with its own forms and regulations. It certainly streamlines processes for us, especially when a study has a lot of sites.

In your article, you talk a lot about integrating seamlessly with the clinical side. Why is that so important?

SF: At the heart of the PBRN are the strong clinician-researcher collaborations at the local level, and the cross-site partnership at the national level. The idea of PBRNs is that researchers don't "helicopter in" to the clinic setting, recruit patients, and then leave. Instead, we are committed to building long-term relationships and finding opportunities for mutual benefit.

For example, clinicians have contributed to various phases of the research process for a number of projects—from elements of the design or methods, to interpretation of findings. That is expected to result in research findings that can be more readily applied at the bedside. Through our national network we can also get results back to clinicians more easily, to help reduce the risk of delay in putting research findings into practice.

With regard to effectively recruiting and enrolling women Veterans, the JABFM *article mentions that some participants are intimidated by HIPAA*

language, and you offer recommendations to address that. Could you talk a bit about that?

RK: The research information we present to any Veteran must be clear, concise, and accessible. Required language may vary depending on the level of risk and other characteristics of the study, but we certainly found it helpful to take steps such as assessing the reading level of any wording developed by the study team and including a plain-language study information sheet. I really also have to give credit to our dedicated and skilled site coordinators, who did not see these forms as perfunctory. They took the time to talk with women. They made sure that the women understood the content and that their concerns were addressed.

The PBRN now represents 200,000 women Veterans nationally, which is more than half of the women Veterans who use VHA services.

Are there any other insights you'd like to share concerning connecting with women Veterans and promoting their participation in research?

EY: For one of our studies, we worked with PBRN site leads to identify the best local person to send out endorsement letters for a patient survey. It had to be someone that women Veterans would know and that they could talk to about the survey or study if they wanted to. So every site's contacts with women Veterans is customized.

We also have a Women Veterans Council in which we talk about what in our study findings is important to them. In addition, we briefed VA's Advisory Committee on Women Veterans, and it just so happened that a couple of members had been research participants, and they reminded us how critical it was to always circle back to women Veterans who have participated and share study results. So we are doing that on every level now.

Meanwhile, another of the things we are very excited about is that Dr. Alison Hamilton is leading a new component of our Women's Health Research Network grant that focuses specifically on multi-level engagement. By that we mean engagement of women Veterans, clinicians, VA leaders, and researchers. She is conducting qualitative interviews with all these groups, and we expect to learn a lot about what does and does not inspire people to get involved in research about women Veterans, and what all of us in the research community can do better.

RK: We would also really like to thank the women Veterans for taking the time to share their experiences and preferences with us, so women's voices are heard in the design and development of VA services. ★

Unleashing the power of the grape: Researchers revisit resveratrol

Dr. Nihal Ahmad's lab at the Madison VA Medical Center and the University of Wisconsin studies natural compounds that may fight cancer. Resveratrol, found mainly in red grapes, shows great potential—provided scientists can figure out how to get the body to absorb it more effectively.

Photo: ©iStock/anna1311

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

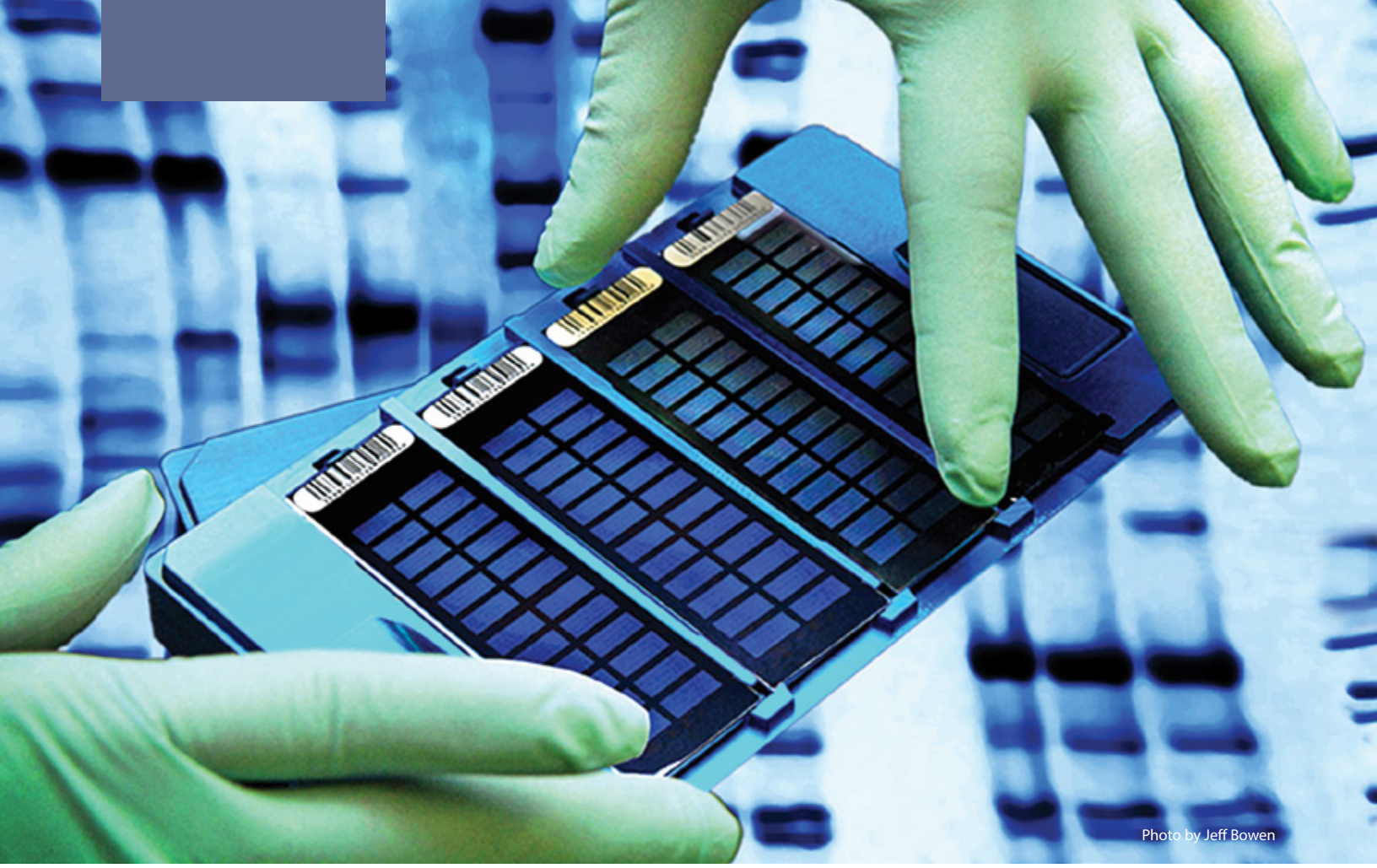


Photo by Jeff Bowen

Genomic medicine: Tackling the next frontiers in VA

Dr. Ronald Przygodzki is VA's director of genomic translation research. As the Million Veteran Program moves steadily toward its goal of enrolling 1 million volunteers, Przygodzki's team is figuring out how VA can best use the resulting data and research findings to improve Veterans' care.

In August 2015, a VA patient in Dallas became the 400,000th enrollee in VA's Million Veteran Program (MVP).

Within the next few years, the program is expected to reach its goal and have DNA and health data from 1 million Veterans. Then what?

How will the Veterans Health Administration (VHA) use the information? How will VHA apply the research based on MVP data? Will this large-scale genomics effort truly change the health care Veterans receive?

Perhaps no one is pondering those questions more deeply than Dr. Ronald Przygodzki.

Przygodzki, a pathologist and genetics expert, has served in leadership positions in VA's Office of Research and Development since 2007. His newest title captures the thrust of his mission nowadays: director of genomic translation research.

"We're trying to use genomic research to find new solutions and move those into Veterans' care," says Przygodzki.

Among other applications, he envisions using genomic data to help ward off illness and disability

◀ A VA technician handles a tray containing bar-coded DNA from research volunteers, along with more than a million micron-sized beads of lab-supplied DNA, each bead containing a different genetic variant. A special scanner is used to detect matches between the sets of DNA, thus determining which variants a patient or research volunteer has.

among returning Veterans. Agent Orange, Gulf War Illness, burn pits—past wars led to medical mysteries that have lingered on for years, in some cases decades. Przygodzki says genomics may be one tool for preventing similar scenarios in the future.

"We can use genomics to help find out what is going on with them as various conditions appear. One outcome might be advising the Department of Defense on health issues they might be able to address, to better protect troops and have them return home more intact."

Gene-based treatment already standard in some cancers

Begun in 2011, MVP has become the largest database of its kind in the nation. The effort is now part of President Obama's Precision Medicine Initiative, announced last year. The idea is to scale up the push nationwide to use patients' genetic information to tailor their medical care.

The approach is already in use in medicine to a certain extent—particularly with cancer. Genetic testing is even considered standard care—and covered by insurance—for a few cancers, such as non-small cell lung cancer, since there are proven therapies that target mutations known to drive those cancers.

The idea now—fueled by MVP and the White House's wider initiative—is to expand the approach across a much wider scope of health problems. One example is depression.

Przygodzki and colleagues are in the early planning stages of a pilot study, based on MVP data, that would look at how genetics can predict response to antidepressants. Genetic variants known generally as "pharma markers" reveal if a person is a slow or fast metabolizer of a drug. Emerging findings are increasingly catching the eye of psychiatrists and others who prescribe the drugs.

"Some people can take a pill once a day and get a dose that's adequate," says Przygodzki. "Others don't metabolize it until the drug starts accumulating in their system. Others, you give the drug, and it just passes through in a few hours—there's no drug left."

What might be the right antidepressant dose for one patient might send another into psychosis, due to an overdose.

Addressing providers' skepticism

Przygodzki says few mental health providers, in or outside VA, are taking advantage of the promise of genomics to boost outcomes for those on depression drugs. Part of the problem is providers' skepticism. They are used to adjusting dosage by trial and error—not by ordering DNA tests for their patients.

"The information is limited but available. But we in VA are not doing this on a large scale, nor is anyone

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"We're trying to use genomic research to find new solutions and move those into Veterans' care."

else at this point," says Przygodzki. "They wonder if it's useful."

He describes the pilot he envisions:

"We have these people in MVP. We can find out if they have major depressive disorder, whether they've had any injury through drug, or failure of drug. We can get that data. We can set up a pilot with clinicians and see what they do. Do they use the information? Does it affect prescribing? Will it help in the therapy of these patients long-term? It would be a start."


Photo by Robert Turtil

Dr. Ronald Przygodzki is VA's director of genomic translation research. His team is looking at how to use MVP data to advance research and improve Veterans' health care.

Przygodzki stresses that genomics doesn't replace more conventional ways of diagnosing illness or deciding on treatment—it's just another tool.

By way of analogy, he says: "You can take a patient and squeeze his skin to see if he's well-hydrated—or you can go and do blood tests. Whichever one is appropriate. It all depends."

And even with a full panel of genomic information, or brain scans or any other newer tools, the skill and insight of the clinician remain vital, says Przygodzki.

"The genotype [a person's gene profile] is important, but it's not going to be the sole determinant of the diagnosis, or of treatment. You always have to have a clinician. Medicine is, as it always was, an art. It requires experience and judgment."

Making genomic medicine cost-effective

Also, sending blood samples out to a lab for genotyping comes at a cost. But there are ways to offset that cost, suggests Przygodzki.

One would be doing a one-time overall genetic analysis of a Veteran, ideally when he or she first enrolls in VA care. That way, the information could be available in a database as needed for different providers, regardless of what condition is being treated.

This would likely involve "exome sequencing." This is similar to whole-genome sequencing, in which the entirety of a person's DNA is described—every gene, every mutation. That process is dramatically cheaper today than it was even five years ago, and it's likely to get even cheaper in the next few years. But as of now, it' still upwards of $1,000 per person.

The exome represents only a small portion of the genome—less than 2 percent. But it's the part that codes for proteins, which, in rough terms, is DNA's business end. Of the genetic mutations known to cause disease, for example, more than 8 in 10 are found in the exome.

Sequencing the exome, instead of the whole genome, is cheaper and more cost-effective. MVP has already sent out some 25,000 DNA samples for whole exome sequencing. Przygodzki envisions this aspect of MVP being ramped up going forward.

"Doing individual lab tests costs money," he says. "That's part of the quandary. On the other hand, if we were to do exomes on all these people, and have that record ready, it's done once. And now we have a reference we can go back to."

Another cost-saver for VHA, says Przygodzki, would be having core genomics labs to service wide regions, or even the entire VA health system. A few such facilities already exist—in Little Rock and San Antonio, for example.

"With mental health, for example, if we set up a lab at one VA medical center, why would we need a

second, or a third, or a ninth, or a 50th? It would be too costly to have this at every VA, and there would be too few tests of any given kind at one site." Rather, he says, "let's have it at only one or two sites, and have them be the experts in doing this. They can live and breathe it. They would be the VA center for it."

The business principle is the same as in even the simplest operations: "If you know how to make hot dogs and get down the process," says Przygodzki, "you can pump out hot dogs day and night. You don't want to have every facility making one hot dog."

Informatics challenges

Working out such economies of scale is only one of Przygodzki's challenges. Another key area related to his mission is informatics. He works closely with the team at the Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC) who run the Genomic Information System for Integrated Science. The system ties together the huge and disparate pools of data in MVP, from different sources, that have to be linked.

"We're trying to use genomic research to find new solutions and move those into Veterans' care."

For starters, there's the biospecimen—the actual bar-coded blood sample, which gets deep-frozen at minus 30 Celsius in the VA biorepository in Boston. Robots help process and retrieve the samples for investigators.

There are molecular data that emerge from the analyses done on these samples. What gene variants are present? Are there proteins expressed in abnormal amounts?

There are self-reported data that Veterans fill out in their surveys—including about their military experiences. Were they in combat? Exposed to blasts or chemicals?

There are also clinical data from VA electronic health records, and from other clinical databases in VA. Demographics, lab values, diagnoses—it all goes in the mix. (Names and other personal identifiers are omitted.)

An important related resource is the VA Informatics and Computing Infrastructure, which gives VA researchers access to VA data in a secure virtual workspace, with sophisticated tools for analysis and reporting.

Then there are data from non-VA sources such as the Centers for Medicare and Medicaid Services. Many VA patients also receive health care outside VA, and researchers want to look at this also.

Przygodzki says that to get "MVP rocking and rolling, we need to look at how these systems work together. We need to synch up the genomic data with the medical record data."

Earlier this year, VA funded a set of four studies—beta tests—designed to help work out some of these informatics issues. They'll focus on chronic illnesses

Twitter: A vital tool for aspiring doctors?

More than 75,000 health professionals worldwide share information and discuss treatments on Twitter. In a recent study, VA and university researchers looked at how medical students are using the popular social media platform to fast-track their careers.

Read more at www.research.va.gov/currents/1215-5.cfm

Photo: ©iStock/pixdeluxe

like heart or kidney disease, but they'll also help iron out processes, especially when it comes to integrating various data sources, that will set the stage for future large-scale studies based on MVP.

Taking Veterans' preferences into account

Another frontier entails ethics more than technology. As of now, Veterans who enroll in MVP are not given back any results from their personal genomic analysis. The current system is not set up for that. Among other factors, MVP blood samples are generally not processed in CLIA-certified labs, which is a federal requirement whenever samples are used for diagnosis or treatment.

So MVP participants are not told, for example, if they have a genetic mutation that may increase the risk of a certain cancer, or Alzheimer's disease. By and large, Veterans who enroll do so for altruistic purposes—to help their fellow Veterans, future generations, others in general.

The process may change, though. Przygodzki is looking at what steps would be needed to start informing individual Veterans of their results. Based on past focus group findings, he believes most Veterans would in fact welcome such information.

"The Veterans believe we ought to be doing something with these samples to help others, as well as themselves," he says.

As researchers develop more genomic insights, Veterans' blood tests could yield concrete data to guide treatment. Those with diabetes, for instance, may learn they are good candidates for a certain new drug.

"If this is something that helps them be healthy, from an ethical standpoint we have to provide the information," says Przygodzki.

At the same time, some patients might not want to learn of certain types of results. Think about the Alzheimer's example: Some people might not care to learn that they are at especially high risk for the disease. Without a good treatment on the horizon, that information might cause anxiety and do more harm than good.

The key, says Przygodzki, will be giving patients a choice. That's the direction he wants VA's genomics program to go in: not just setting policy based on general findings from focus groups, but letting each patient decide what VA does with his or her information.

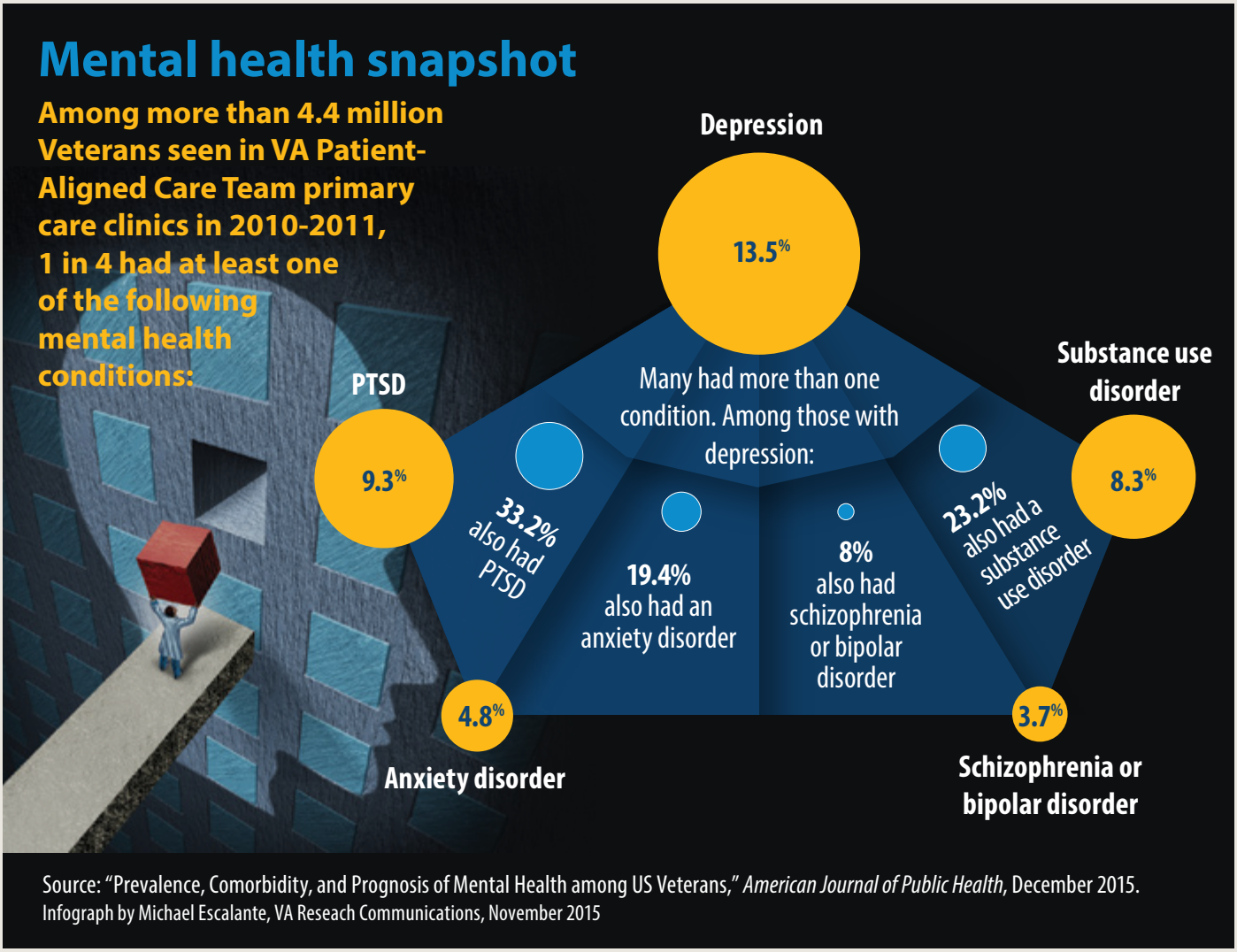
"You have to go the users, the customer base, and find out what they want. If a given person wants to find out, great. If not, that's also great. The free will aspect is important. We need to give Veterans options. By giving everyone a choice, we protect everybody." ★

Photo by Michael Moody

Dr. James Henry receives VA's **Magnuson Award** for advancing tinnitus treatment

James Henry, Ph.D., an audiology researcher widely known for his innovative work on treating and managing tinnitus, is the recipient of the 2016 Paul B. Magnuson Award, the highest honor given to investigators by VA's Rehabilitation Research and Development Service (RR&D).

Henry's work is credited with helping large



Source: "Prevalence, Comorbidity, and Prognosis of Mental Health among US Veterans," *American Journal of Public Health*, December 2015.
Infograph by Michael Escalante, VA Reseach Communications, November 2015

numbers of Veterans and service members. The approach he developed, called Progressive Tinnitus Management, continues to be adopted nationwide in both VA and Defense audiology clinics.

"Patients have often been told to go home and learn to live with [their tinnitus], nothing can be done—and it's not really true," says Henry.

Henry is a research career scientist at the RR&D National Center for Rehabilitative Auditory Research, based at the VA Portland Health Care System. He is also on the faculty at Oregon Health and Science University and Portland State University.

Tinnitus and hearing loss are the top disabilities among Veterans. As of 2013, more than 1.1 million Veterans had a service-connected disability rating for tinnitus. Veterans are at higher risk than the general population because of their exposure to loud noise.

Those with the disorder perceive ringing, buzzing, whistling, or other sounds in their ears. Each person can hear something a bit different. The condition can disrupt sleep, affect a person's work and social life, and sharply increase the risk of depression or anxiety. In short, in more severe cases, it can potentially be debilitating.

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

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Did you know?

February is National Heart Month. Depending on their individual medical circumstances, many Americans are advised by their doctor to take a daily baby aspirin. Aspirin therapy reduces the activity of the blood's clotting cells, or platelets. For certain patients, this can help ward off a heart attack. One of the early clinical trials that helped establish aspirin's role in heart health—namely, for men with unstable angina—was conducted by VA's Cooperative Studies Program and published in the *New England Journal of Medicine* in 1983. Led by a team at the Kansas City (Mo.) VA Medical Center, the study included more than 1,200 Veterans.

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