

RESEARCH QUARTERLY UPDATE

Office of Research and Development

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An overview of key accomplishments and initiatives in VA research

Spring 2018 • This Issue: Chronic Disease Care

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VA



U.S. Department of Veterans Affairs

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Rachel B. Ramoni, D.M.D., Sc.D.
Chief Research and Development Officer

Transforming innovations in research into care for Veterans

This year, the theme of VA [Research Week](#) is “InnoVAtion to Implementation.” This theme captures our special mission to ensure that our research results in real-world benefits to our Veterans—whether the goal is to help them regain their health, resume an active lifestyle, or reclaim their vital roles in family and community.

Translating VA Research into real-world impact for our Veterans is one of my three strategic priorities for the Office of Research and Development. The other two strategic priorities are to increase our Veterans’ access to high-quality clinical trials and to transform VA data into a national resource.

There are synergies among my three priorities. For example, through our collaboration with the National Cancer Institute, we are launching an initiative to allow more Veterans to participate in cutting-edge clinical trials for cancer. These clinical trials will not only bring Veterans living with cancer new hope for cures, they will also generate gold-standard knowledge that will help us discover the best treatments for cancer in the Veteran population.

We want it to be easier to bring high-quality clinical trials to Veterans in VA. Dr. Grant Huang, director of the VA Cooperative Studies Program, is part of the [Clinical Trials Transformation Initiative](#)—a group of more than 80 organizations that aims to improve the quality of clinical trials. He and his colleagues recently published a [paper](#) on the difficulties that investigators can experience when trying to recruit enough patients into clinical trials. The team proposed several strategies to make it easier for Veterans and other patients to join a clinical trial, and to help research teams communicate with their patients in the most effective way. You’ll read a summary of their recommendations in this issue.

Another important issue that affects Veterans is the effective delivery of health services. It isn’t enough to develop new medications and treatments, if Veterans cannot access them in a timely manner. In this issue of *VARQU*, we speak with Dr. Walid Gellad, a physician and research scientist at VA

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Pittsburgh Healthcare System. Dr. Gellad is considered a national expert on prescription drug pricing and helping patients take their medications as prescribed.

He and his team are examining the issues that might face “dual users”—in this case, Veterans who get their medications both from the VA health system and from Medicare. In a [study](#) published in the *American Journal of Public Health*, Gellad says that Veterans who obtain opioid medications from both VA and Medicare may be at greater risk for receiving higher doses of opioids or additional medications that could interact badly together. He says improving data-sharing between VA and other federal health systems is the first step to addressing this problem that endangers the well-being of Veterans.

Research Week is also a great time to highlight VA’s extraordinary researchers and the innovations they make possible. Dr. Geoffrey Gorse is a prime example of the excellence that characterizes VA investigators. He is infectious disease specialist and physician at VA St. Louis Health Care System. I was privileged to be present at the VA St. Louis Research Week ceremony to see Dr. Gorse receive a Lifetime Achievement Award—recognizing more than 25 years of clinical research activities in VA. Dr. Gorse is a senior investigator whose important work has provided the foundation for the development of the present-day flu vaccine.

These are exciting times for VA research and the Veterans we serve, as we push the envelope to develop new innovations in care and make them available to patients sooner. I hope you enjoy reading about these and other new developments in this issue of *VA Research Quarterly Update*.

Rachel B. Ramoni, D.M.D., Sc.D.
Chief Research and Development Officer



Celebrating VA researchers and innovations

VA health systems throughout the country celebrated National VA [Research Week](#) in a number of different ways. All of them were designed to recognize the importance of VA research and to share new developments and individual achievements. Research Week programs ranged from Veteran luncheons and Q&A sessions to scientific presentations and poster displays by researchers and lab tours for media and congressional representatives. They also included recognition of research volunteers and their efforts to support Veterans' health.

VA Research Week was officially celebrated during the period May 14–18. This year's theme, "InnoVAtion to Implementation," recognized VA's efforts to quickly drive the results of research into clinical practice, so that Veterans will benefit from the latest developments in treatment.

VA researchers are working to develop new therapies to make life better for Veterans. Research Week is an opportunity to recognize their achievements.

VA St. Louis held its Research Day on April 20, 2018. Dr. Ziyad Al-Aly is the associate chief of staff for the Research and Education Service at the VA St. Louis Health Care System. He is also director of the VA St. Louis [Clinical Epidemiology Center](#).

The St. Louis research and development program has a vibrant basic science, translational, clinical, and outcomes research portfolio that is supported through funding by VA Research and Development, the National Institutes of Health, the Department of Defense, and other agencies, according to Al-Aly.

Dr. Rachel Ramoni, VA's chief research and development officer, was the guest speaker. "VA research represents the promise of a brighter tomorrow for Veterans," Ramoni has said in remarks quoted on the VA Research website.

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“The research process in VA starts with a close focus on the everyday needs of Veterans. Solutions are developed through careful, rigorous research in labs and clinics, and then applied to patient care as rapidly as possible.”

A number of awards were presented to VA St. Louis investigators, beginning with a Distinguished Service Award to Dr. Fredric Metzger and Investigator of the Year award to Dr. Daniel Kreisel.

The Lifetime Achievement Award was presented to Dr. Geoffrey Gorse. Gorse is an internal medicine physician at VA St. Louis and a notable infectious disease investigator. He has also been chairman of VA St. Louis’ institutional review board since 1994. Gorse is credited with research leading to the [development](#) of the present-day flu vaccine—as well as the [anthrax](#) and [coronavirus](#) vaccines. Gorse was also a principal or co-investigator on multiple [HIV vaccine](#) trials.

“Chances are,” said Al-Aly, “that many Veterans have directly benefitted from Dr. Gorse’s research if they got their flu shot this year.”



Researchers are looking for better ways to encourage Veterans to enroll in clinical trials. (Photo for illustrative purposes only. @iStock/Steve Debenport)

Proposing a new framework for clinical trials recruitment

Recruiting for clinical trials can present many challenges for researchers. For this reason and others, the [Clinical Trials Transformation Initiative](#) (CTTI) was created to “develop and drive adoption of practices that will increase the quality and efficiency of clinical trials.” CTTI comprises more than 80 member organizations, coming from government, private industry, professional societies,

patient advocacy groups, and others.

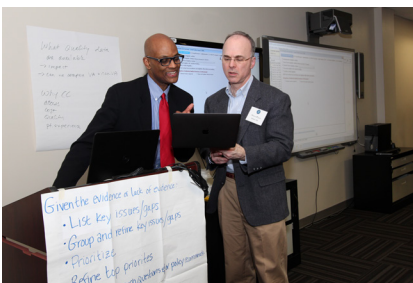
The CTTI convened a [project](#) team to come up with actionable recommendations for improving the clinical trials recruitment process. The team included Dr. Grant Huang, director of the VA Cooperative Studies Program, and stakeholders from Eli Lilly, Janssen, Duke University, and the Association of Clinical Research Professionals. They came together to examine the challenges and barriers to successful clinical trials recruitment and to create a strategic plan to improve the recruitment process going forward.

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In a [paper](#) published February 2018 in *Contemporary Clinical Trials*, the project team noted that despite the importance of patient recruitment to successful clinical trials, many researchers fail to meet patient recruitment goals. In a 2015 [analysis](#), investigators found that 19 percent of clinical trials failed to meet recruitment targets and were closed down or terminated early. In addition, clinical trials commonly have difficulty recruiting patients within an allotted time period—the authors say 86 percent of clinical trials do not reach their recruitment targets in time.

The clinical trial planning and design phases can be a critical time to address factors that can positively affect later recruitment efforts, they said. The project team identified multiple factors that could improve CT recruitment efforts. Important areas to consider, they said, are better trial design; adequate staffing; targeted recruitment strategies; participant convenience; financial support for patient recruiters; and incentives and/or compensation for participation.

After collecting input from a literature review, web survey, and expert interviews, the project team concluded that creating a strategic framework to guide a CT recruitment plan was better than just addressing individual activities and tools. To that end, they developed a list of evidence-based recommendations that fell under three broad areas: trial design and protocol development; trial feasibility and site selection; and communication. Recommendations included limiting protocol complexity, establishing realistic metrics, and developing tailored patient messaging.



Dr. Leo Greenstone (left), a researcher at the VA Ann Arbor Healthcare System, and Dr. Steve Pizer, chief economist at VA Boston Healthcare System: both were participants at the 2018 care coordination conference in Baltimore. (Photo by Mitch Mirkin)

VA state of the art conference on care coordination

The VA Health Services Research and Development (HSR&D) service held an invitation only two-day state of the art (SOTA) [conference](#) on care coordination on March 20-21, 2018, in Baltimore, Maryland. The purpose of the SOTA was to explore the state of care coordination within VA and in collaboration with community partners. Invited experts

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sought to develop a research agenda that focused on improvements and innovations in care coordination, and to identify evidence-based recommendations for VA policymakers.

Co-chairs Denise Hynes, Ph.D., and Kristin Mattocks, Ph.D., worked with a SOTA planning committee to develop materials and key questions that were provided ahead of time to invited participants as background for the discussions and consensus building at the SOTA.

The SOTA opened with a plenary session in which the co-chairs and David Atkins, M.D., director of HSR&D, welcomed the participants and discussed the key issues in care coordination that are challenging the VA health care system, providers, and Veterans.

A Veteran's perspective was provided by Tara Jones Molloy, a psychiatric mental health nurse practitioner with the VA Maine Healthcare System community-based outpatient clinic in Saco, Maine. Molloy is a combat Veteran who served in the U.S. Air Force as a pilot. She shared her own experiences with care coordination when she was referred by VA to a community hospital for care during her pregnancy and delivery.

Following the presentations, the attendees separated into three work groups to discuss 1) care coordination within VA; 2) care coordination between VA and non-VA caregivers in the community; and 3) measures, models and definitions. They were charged to reach consensus on knowledge gaps and research questions that would address them. In addition, they were to reach consensus on evidence-based innovations/strategies to improve care coordination and policy recommendations and next steps to implement them into VA practice.

On day two of the SOTA, the three work groups presented their findings to the full group for discussion. There was also a keynote presentation by Dr. Jody Hoffer Gittel, professor of management at Brandeis University's Heller School for Social Policy and Management, and executive director of the Relational Coordination Research Collaborative.

Once the conference participants review and consolidate their recommendations, they will be disseminated through briefings to VA leadership and through targeted cyber-seminars, and published in a future special supplement of the *Journal of General Internal Medicine*.



Dr. Walid Gellad, a researcher at the VA Pittsburgh Health Care System, has identified potential safety risks when Veterans use both VA and Medicare Part D to fill their opioid prescriptions. *(Photo by William A. George)*

‘Dual use’ Veterans may be at risk for unsafe opioid use

Dr. Walid Gellad is a primary care physician and health services researcher with the Center for Health Equity Research and Promotion at the VA Pittsburgh Healthcare System. He is also director of the Center for Pharmaceutical Policy and Prescribing at the University of Pittsburgh. He is considered a national expert on prescription drug pricing and patient medication adherence.

Gellad’s research is focused on developing more effective prescribing practices for physicians and Veterans, and improving the way the VA health care system functions—in terms of better access to medications and safer prescribing practices. His research has been funded in large part through VA’s Health Services Research and Development service.

VARQU spoke with Gellad about a recent [study](#) in which he and his coauthors examined Veterans who used both the VA health care system and Medicare Part D to receive prescription opioid medications, and the potential for harm that practice poses.

Welcome, Dr. Gellad. Does VA follow the Centers for Disease Control and Prevention guidelines for the safe prescribing of opioid medications, or does it have its own guidelines?

The VA is actually required by law to adopt some of the CDC guidelines. So, I would say yes, it does follow CDC guidelines. The VA has been moving in that direction well before the official CDC guidelines came in. The CDC guidelines are really about trying non-pharmacologic therapy first, and then if you have to use medications, trying non-opioid drugs first.

The guidelines advocate using strategies like not using opioids first-line, starting opioids at a low dose, not starting with long-acting opioids, and being aware of the dosage of opioids that you are putting a patient on. Those strategies are all focused on establishing functional goals. Physicians are really asking, “What do I want the opioid to do for the Veteran, to help them function?”

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VA researcher Dr. Walid Gellad is a national expert on prescription drug pricing and medication adherence. (Photo by William A. George)

There are many people who think physicians should limit the amount of opioids patients receive. Can you explain what morphine milligram equivalent means, and why that is important?

The morphine milligram equivalent (MME) is a way to standardize the dose of opioids across different opioid medications. So if you have one patient who is taking Vicodin and another patient who is taking Percocet and yet another one who is taking morphine, those drugs have different potencies. Some are a lot stronger than others when it comes to opioids: If you are on 10 mg of morphine that's not the same as 10 mg of oxycodone. So this is a way to standardize the opioid prescription across all types of opioids; you just use the term morphine milligram equivalent.

Is there a standard opioid dosage recommendation for patients?

That's where there is a lot of controversy now. I think there is no fixed answer—it's very complicated. There are more adverse events as the opioid dose gets higher. There's no doubt about that. So I think everyone is in agreement that the lowest dose one gets improvement on is the best dose. There are specific thresholds in the CDC guidelines, like 50 MME and 100 MME or 90 MME. Where policy experts really start worrying about safety is at 50 MME, and they say people generally shouldn't be on 90 MME or you should try and get them below 90 MME. That's just a reflection of wanting to get Veterans and all patients on the lowest dose possible.

The concern is that some physicians are using that dosage level as a fixed cut-off—and if a patient is over that then they automatically need to be cut down below that level of morphine equivalent. That's where the controversy lies. But most would agree that the higher the MME dose, the greater the side effects and the greater the risk of adverse events.

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Your study looks at Veterans who received their drugs both through the VA health system and Medicare Part D. Is that a common occurrence?

It's very common that Veterans use both VA and Medicare Part D, if you put opioids aside for a minute. The statistic that people most often use is that about half of Veterans enrolled in the VA health system are also in Medicare. But not all of them sign up for Part D. Of those Veterans who are in Medicare (half of Veterans), about a third are also in Part D. So that's a lot of Veterans who are enrolled in both VA and Part D. A subset of those will actually get prescriptions from both VA and Part D, and a subset of those will get opioids from both VA and Part D.

One of the premises of the study was that if you get medications from two different places—the VA and outside the VA, paid for by Medicare—there's a risk that you are going to get a higher dose or drugs that interact, because generally, the VA physicians are not talking to the non-VA physicians. And until very recently, there has not been a lot of use of prescription drug monitoring programs to see what was being dispensed outside of the VA and vice versa. Providers outside the VA couldn't see what was happening within the VA.

So there is a big risk—because of the fragmentation of care, because of the lack of communication, because these are different providers who are prescribing—that you will have overlapping meds, inappropriate meds, and more risky prescribing.

Can you talk about your study methods and conclusions?

For this particular study that is out now, we used data that were linked between VA and Medicare Part D. The VA does have this data available for research purposes, but it is older, so it is a few years outdated. And we used this linked data to look at anyone in the year 2012 who had filled an opioid prescription either in VA or Medicare Part D. Then we looked at those who had received opioids in VA only, Medicare Part D only, or both. In that year, 13 percent of Veterans had received opioids from both VA and Medicare. And in many of those cases, it was actually overlapping—the opioids were prescribed at the same time in both VA and Medicare.

So the point of the paper was to describe the prevalence of that problem, because it hadn't really been known before. And also we looked at the dosage that people received and identified that those who get their opioids from both VA and Medicare are more likely to get doses that many would consider

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too high. There's a quality measure that is used in Medicare for dosage. We looked at the proportion of Veterans who were identified as potentially on unsafe doses of opioids. That's 90 consecutive days: So for 90 days in a row you have a morphine equivalent level of over 120. We found that there was a much higher risk among those Veterans who received opioids from both systems for having that high dosage.

What are the next steps? Where would you like to take your research beyond this?

In this particular paper we focused on an outcome looking at opioid dosage. We have other work where we are looking at different outcomes that are evidence of potentially risky prescribing or unsafe prescribing, whether it's opioids interacting with another medication, or other aspects of prescribing. So we are looking at several different outcomes now—and looking at the association between receiving care in both VA and Medicare.

And then also we have data not just on opioid prescribing—we have been able to link in data on overdose death. We are now looking at the relationship between some of these measures that we've looked at for dual use and opioid prescribing, and actually seeing who dies from an opioid overdose. This work is ongoing.

How would you propose to address the problem of dual users—Veterans who are getting medications from both systems?

There are things that VA can do, and then there are things that individuals can do. For the Veterans it reemphasizes the importance of keeping track of all their medicines that they are taking, whether it is from VA or outside VA. And letting the clinicians know what those medicines are, even if they don't ask. The providers they see in the VA and outside the VA are going to want to know the medicines they take, regardless of where they get those medicines from.

In my experience, often the patients don't realize that when they split getting their medicines from VA and outside the VA, there are some risks involved, even though in some cases it can be a little easier and sometimes a little cheaper to get medications outside of VA. I think many of the Veterans don't think about those risks. When something is dispensed in the VA, there are automated systems to look at drug interactions. That can't be done when a medication is dispensed outside the VA—the VA can't look at that information.

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I'm currently working to improve data-sharing between these large federal systems, VA and Medicare, so the VA can know a little bit more about what is happening in Medicare. That's an ongoing process. These are two large federal systems, and they are both trying to care for these large, and in some cases, overlapping populations. That's where the implementation part of this research is going.

To clarify, VA can see only what is inside Veterans' electronic health records, and that system does not communicate with outside systems in the community. Correct?

Yes. VA has done a tremendous amount to address prescription opioid use among Veterans to improve safety. All of that effort has focused within VA, because that is what they are measuring. There is still not an easy way to nationally measure opioids that Veterans might be getting outside the VA. And not just opioids, it could be interacting medicines like benzodiazepines or muscle relaxers or sleep drugs. So that is the problem: There is no mechanism for VA to systematically include those non-VA prescriptions into its utilization management and all the reviews it does for safety.



Research by Dr. Erin Krebs, a physician at the Minneapolis VA Health Care System, has questioned whether opioid medications are better than non-opioid drugs to treat long-term back and knee pain. (Photo by April Eilers)

Dr. Erin Krebs is a physician and researcher at the Minneapolis VA Health Care System. In March 2018, she and her colleagues published a [study](#) in *JAMA* that compared the use of opioid medications with non-opioid medications for the treatment of chronic knee, hip, or back pain. The results of the Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) trial were surprising: treatment for 12 months or more with opioid medications was not superior to non-opioids when it came to improving pain-related function. And, in fact, non-opioid medications were more effective than opioids for reducing pain intensity.

VARQU asked Dr. Krebs for her thoughts on the media attention her

study has received, and where she thinks future research efforts will be focused.

Q What influence has your study had so far?

Although it's a bit too early for our study findings to be incorporated into guidelines, I have heard from many individual clinicians that this study has influenced their clinical practice and teaching of trainees. I expect our results to be interpreted as providing support for recent guideline recommendations. The 2016 Centers for Disease Control and Prevention opioid guideline advised that non-drug therapies and non-opioid medications are preferred for chronic pain, and the 2017 VA opioid guideline advised against starting

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long-term opioids for chronic pain. These recommendations were based on expert opinion and data about opioid-related harms. Our study contributes long-term evidence on the benefit side of the equation—we found no advantages to opioids that would outweigh their greater risk of serious harm. The results should reassure clinicians that following current guidelines is not likely to result in undertreatment of pain.

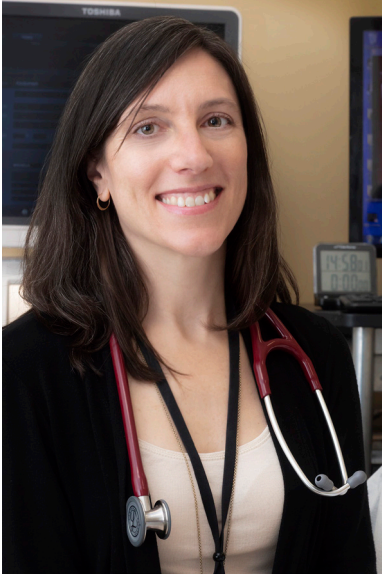
Q Has the study been misrepresented in some cases?

Misleading media reports about the study's findings (e.g., *The New York Times* "Well" story "For Arthritis Pain, Tylenol Works as Well as Opioids") generated a lot of confusion and questions from patients and caregivers. My experience with advocates criticizing SPACE is similar to what I experienced when I participated in the 2016 CDC opioid prescribing guideline development process. In both cases, social media and internet-based criticism focused on claims that the work was biased and therefore illegitimate. I suspect this type of criticism is fueled less by misleading media reports than by misleading industry-supported advocacy. We would all benefit from a more nuanced discussion of

long-term opioid prescribing that acknowledges the many remaining uncertainties. We certainly know much less about benefits and harms of long-term opioids for chronic pain than we know about most other commonly used medications.

Q Do you plan any research comparing opioids with non-drug therapies?

We chose to compare opioids to non-opioid medications because this seemed to be the most direct and relevant comparison. I'm not sure a head-to-head comparison of opioids versus non-drug therapies would be as useful, since medications and non-drug therapies are typically combined in clinical practice. I'm currently leading a multi-site VA trial—funded by the Patient-Centered Outcomes Research Institute—that is testing approaches to improving non-opioid pain management while reducing opioid doses in patients with persistent pain despite long-term high-dose opioid therapy. This study, the Veterans Pain Care Organizational Improvement Comparative Effectiveness (VOICE) Trial, is comparing two primary care-based collaborative care interventions: lower-intensity pharmacist telecare versus higher-intensity integrated pain team care.



Dr. Anna Jovanovich is a nephrologist at the VA Eastern Colorado Health Care System in Denver. Her research focuses on cardiovascular health in Veterans who have chronic kidney disease. (Photo by Shawn Fury)

Staying heart-healthy: The importance of phosphorus for Vets with chronic kidney disease

Dr. Anna Jovanovich is a kidney specialist and a clinical researcher at the VA Eastern Colorado Health Care System in Denver. She splits her time between seeing patients and conducting research. She is also an assistant professor at the University of Colorado, Denver.

The thrust of her clinical research is investigating the effects of kidney disease on the body—specifically cardiovascular or heart disease. Veterans and others with chronic kidney disease are at a much higher risk of developing heart disease, compared with the general population. In fact, they are more likely to suffer a cardiovascular event, such as a heart attack, than progress to needing dialysis or transplant.

They also may need help managing the level of certain chemicals within their bodies. In a healthy person, the kidney monitors and controls the level of many hormones, minerals, and other chemicals within the body. One of those is phosphorus—a mineral found in certain types of food, like milk. In the body, phosphorus is a necessary component for many cellular functions. One form of phosphorus—phosphate—is essential for building healthy bones and driving cellular metabolism.

People with advanced kidney disease may not be able to adequately control the level of phosphorus within their body. If diet modification does not work, they may need to take phosphate binders—drugs that bind to excess phosphate in the gut and help the body excrete it.

VARQU spoke with Jovanovich about her Career Development Award to study the potential effectiveness of phosphate binders in preventing cardiovascular disease.

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Can you explain what chronic kidney disease is?

Chronic kidney disease is the gradual loss of kidney function over time. The main job of the kidneys is to balance what we take in and what we put out, basically. Substances like water, salt, and other electrolytes are regulated by the kidneys. And the kidneys also excrete toxins in the urine. So when the kidneys fail, they can't do that job anymore.

The kidneys are also important for regulating blood pressure, and they produce hormones that control red blood cell production and vitamin D, as well as regulate phosphorus and calcium homeostasis. Again, if the kidneys fail, some of these processes are disrupted. Usually, people with chronic kidney disease don't feel sick or ill until their disease is very advanced. So it is largely a very silent disease, in terms of how a person actually feels.

How prevalent is chronic kidney disease in the general population?

Chronic kidney disease in the general population in the U.S. has a prevalence of about 13 to 15 percent, depending on what year you look at. But in the Veteran population that is treated at VA, the prevalence is much, much higher. Some studies have reported it to be 20 percent, and one recent [study](#)—in a single region—has reported the prevalence of chronic kidney disease to be 47 percent in Veterans. This is significantly higher than in the general adult U.S. population.

How is chronic kidney disease usually diagnosed?

Because it is such a silent disease, the only way we can tell if people have chronic kidney disease is through blood and urine tests. If a Veteran receives usual care through a primary care doctor at the VA, it's pretty standard to do at least annual blood tests. And part of these blood tests measure kidney function. There is a substance called creatinine, which is made by the muscles and excreted through the kidneys. When kidney function declines, the level of creatinine rises in the blood—so that is what we test for. We look for higher levels of creatinine in the blood to indicate chronic kidney disease. Protein and/or red blood cells in the urine can also indicate kidney disease.

Why is it important to regulate the level of phosphorus in a person's blood?

Phosphorus is needed by the body—it is one of the main minerals for structure and strength. Eighty-five percent of our body's total phosphorus

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Spotlight on Career Development Awardees

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is found in the bone and teeth. And it's also important for energy—the main energy compound within the cells uses phosphorus. We get phosphorus from the foods we eat and excrete the excess into our urine via the kidneys.

As the kidneys fail, they are not as able to excrete extra phosphorus, so blood levels of phosphorus rise. Even phosphorus that is on the high-end of the normal laboratory range has been associated with a higher risk of cardiovascular disease, in large epidemiologic studies.

Most people with moderate and even severe kidney disease can control their phosphorus levels with diet alone. That means avoiding foods that are high in phosphorus. But some people with very severe advanced chronic kidney disease, certainly people on dialysis, have to take phosphate binders—which are medications that you take with food. When the food and phosphate binders mix in your intestines, the phosphate binders attach to the phosphorus in your food so that the phosphorus is not absorbed into your intestine. With these medications, along with a low phosphate diet, we can control the blood levels of phosphorus.



Dr. Anna Jovanovich and her research assistant are next to a scanner in the vascular lab, which is used to measure the elasticity of blood vessels. (Photo by Shawn Fury)

Let's talk about your Career Development Award. Can you tell us what your research is about?

We want to find out if a phosphate binder can improve vascular function in people with moderate to severe chronic kidney disease who have normal phosphorus levels and are not yet on dialysis. This is a single-center randomized controlled trial: We are giving half the participants a phosphate binder, and half of the participants a placebo. We will measure vascular function at baseline and then after three months of treatment to see if there is any difference between the two groups, in terms of how vascular function has changed over a three-month period.

We will use two measures. One of the measures is called flow-mediated dilation (FMD), which is a measure of endothelial function. Endothelial cells are the cells that line the inside of blood vessels. FMD has been associated with cardiovascular disease events.

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We will also measure vascular stiffness as another measure of vascular function. We measure this through something called aortic pulse wave velocity. So we are actually able to measure the time it takes the blood to travel from the carotid artery to the femoral artery—from the neck to the groin. The faster the blood travels, the stiffer the vessel. That's another measure of vascular function that has been associated with cardiovascular disease.

By measuring vascular function we can get an idea of the health of the blood vessels, and therefore the health of the heart.

Where would you like to see your research go from here?

This small trial that I am conducting will lay the groundwork for a larger trial looking at endpoints that are more important to patients—like lowering the risks of heart attacks or stroke, sudden cardiac death, or death.

I'm also interested in looking at other factors that are associated with the systemic effects of chronic kidney disease, in particular cardiovascular disease. I'm working on submitting a [VA Merit Review application] looking at how bile acids affect vascular function, and whether dietary changes may affect those levels and possibly improve vascular function—specifically vascular stiffness.

I just received a small grant to look at vascular function after acute kidney injury. Acute kidney injury is an abrupt decline of kidney function, which is usually reversible. However, even if kidney function gets better, people who experience acute kidney injury may go on to develop chronic kidney disease and have a higher risk of cardiovascular events.

So this small grant will look at vascular function after acute kidney injury to see if we can understand how the body changes after acute kidney injury. And we can then look for ways to lay the groundwork to treat the blood vessels after acute kidney injury to eventually lower the risk of cardiovascular disease and other bad outcomes that are associated with acute kidney injury.



Severe combat injuries could elevate high blood pressure risk in Veterans with PTSD

Veterans who served during the Afghanistan or Iraq wars and were severely injured are at greater risk of developing high blood pressure later in life, according to a [study](#) published in *Hypertension*. Researchers say injury severity is an independent risk factor for high blood pressure, and does not depend on later development of posttraumatic stress disorder.

VA researchers have found evidence that Veterans who were severely injured in combat are at greater risk for developing high blood pressure later in life. (Photo @iStock/Bluberries)

Researchers at the Department of Defense Joint Trauma System, the VA Salt Lake City Health Care System in Utah, and other medical institutions reviewed the records of 3,846 service members who were injured in combat during the Afghanistan or Iraq conflicts. Their goal was to examine the relationship between severe physical combat injuries, PTSD, and the development of high blood pressure.

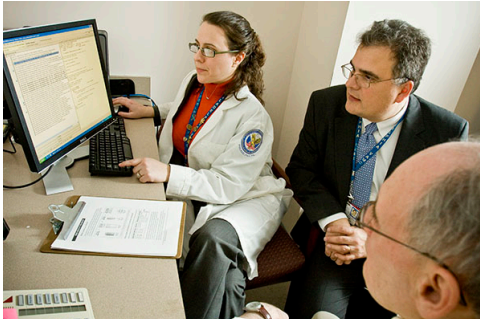
Data was retrospectively collected for military service members who were injured during service in Afghanistan or Iraq, during the period Feb. 1, 2002, to Feb. 1, 2011. The researchers used ICD-9 codes within the medical records to determine each instance of a PTSD and high blood pressure diagnosis after combat injury for a 10-year period.

The overall prevalence of PTSD in that group of Veterans was 42.4 percent, and the overall prevalence for hypertension was 14.3 percent. The median time from first PTSD diagnosis to first high blood pressure diagnosis was 2.3 years. The median injury severity score was 17 (where the range is 1–75).

The researchers found that both PTSD and injury severity on their own were independent risk factors for developing high blood pressure. They estimated that for every 5-point increase in the injury severity score, the risk for high blood pressure increased by 5 percent. Individuals who had an injury severity score greater than 25 and a PTSD diagnosis had the greatest risk for high blood pressure.

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PTSD is associated with a host of poor health conditions, such as obesity, substance misuse, heart disease, and high blood pressure. Studies have shown that psychological stress can cause inflammation within the body, which is a contributing factor in many diseases.



Dr. David Oslin (center), a researcher at the Corporal Michael J. Crescenz VA Medical Center in Philadelphia, is testing the use of genetic information to tailor drug therapies for Veterans with major depression. (Photo by Tommy Leonardi)

Investigating the use of precision medicine to treat depression

VA Health Services Research and Development and VA's [Genomic Medicine Implementation](#) programs are funding a study of precision medicine's role in improving treatment for Veterans with major depressive disorder.

The initiative, PRIME Care (Precision medicine In Mental health Care), is led by [Dr. David Oslin](#) of the Corporal Michael J. Crescenz

VA Medical Center in Philadelphia. It is scheduled to run through June 2022 at more than 20 VA sites across the nation.

Veterans taking part in the effort will submit a cheek swab so researchers can test their DNA. The results could help their providers decide which antidepressant to prescribe—and at what dose, since the test results will tell how well the patient metabolizes the drugs.

In May 2016, a VA QUERI Evidence-based Synthesis Program (ESP) [brief](#) confirmed that pharmacogenomics (the study of how genes affect response to drugs) might help identify optimal treatments for those with depression by helping predict how they might respond to particular antidepressants.

Oslin's group will provide genomic test results for Veterans with major depressive disorder to both the patients and their providers, in hopes of establishing the clinical validity of pharmacogenomic testing.

They plan to recruit 2,000 Veterans and their providers for the study. Half the patient-provider pairs will receive genomic test results at the start of

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the study. The other half, serving as a control group, will get the results six months later. The researchers have hypothesized that the first group will have higher rates of remission of depression than the other group. They also believe that the genomic testing could lead to fewer contraindicated medications being prescribed to patients.

In a [summary](#) of the study, Oslin explains that “to achieve remission from depression, patients and providers must be persistent and try multiple treatments until they find one that is both tolerable and effective.” But each round of unsuccessful treatment takes its toll on the patient. Oslin’s group hopes that genomic testing could lead to earlier successful treatment, leading to more rapid depression remission.

Besides looking at the Veterans’ outcomes, the study will examine the most effective ways to provide these results to Veterans and health care professionals. Proponents hope the study will help guide similar studies of other illnesses and medications.

Dr. Kewchang Lee, a psychiatrist at the San Francisco VA Medical Center, recently signed up for the study. He told the [San Francisco Chronicle](#) how the testing could change his care. “Different people for genetic reasons metabolize things differently,” he explained. “With fast metabolizers, I might not necessarily change the antidepressant, but might target a higher dose. If a patient is a slow metabolizer, I might consider changing the antidepressant itself depending on the side-effect profile of that drug.”

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Dr. Keith Humphreys

‘Our other prescription drug problem’

High rates of opioid misuse and addiction have precipitated a public health crisis in the U.S.—driving opioid-related overdoses and deaths. However, opioids are not the only problematic class of drugs with the potential for abuse. In a *New England Journal of Medicine* [editorial](#), Dr. Keith Humphreys, a researcher with the VA Palo Alto Health Care System, and his colleagues write about the dangers of inappropriate prescribing for benzodiazepines. Benzodiazepines are a group of anti-anxiety drugs that, when taken long-term, have the potential for dependence and misuse.

The authors fear that concerns over excessive opioid prescribing may have masked concern for the very real potential for abuse of benzodiazepines. They note that three-quarters of the deaths related to benzodiazepines also involve an opioid medication. “We believe that the growing infrastructure to address the opioid epidemic should be harnessed to respond to dangerous trends in benzodiazepine overuse, misuse, and addiction as well,” write the authors.

Humphreys and his coauthors also recommend the use of state prescription-drug monitoring programs and expanded education targeted to physicians who prescribe benzodiazepines.

Benzodiazepines cause a range of negative side effects including over-sedation, rebound anxiety, cognitive decline, falls, and even death. They can also precipitate dangerous drug interactions when taken along with opioid medications. During the period 1999-2015, overdose deaths related to benzodiazepines increased from 1,135 to 8,791, a nearly 700 percent increase, according to the National Institute on Drug Abuse.

‘General internists in pursuit of diagnostic excellence in primary care: A #ProudtoBeGIM thread that unites us all’

In an [editorial](#) written to accompany a [study](#) published in *Journal of General Internal Medicine*, Dr. Hardeep Singh, a researcher at the VA medical center in Houston, and his colleague Dr. Janice Kwan write about the importance of making a correct and timely



Dr. Hardeep Singh

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diagnosis in patient care. Given a lack of time and competing priorities in the typical primary care office, the history and physical can be given short shrift, said the authors. An abbreviated history and physical can delay a prompt diagnosis for an urgent condition such as cancer.

Researchers at Harvard University and other institutions conducted a cross-sectional record review that identified 300 adults with rectal bleeding. Of those patients, 90 percent met the criteria for a colonoscopy, yet only 74 percent were actually referred for the procedure. Of those patients referred for colonoscopy, less than 60 percent actually underwent the test within a year's time.

Singh and his colleague attribute failures like this to widespread system-level breakdowns. They recommend a physician-led push to ramp up diagnostic safety efforts in outpatient care.

“We have learned from many studies,” they said, “that faulty data synthesis and an inadequate history and physical are leading contributors to diagnostic error.” The authors suggest that the creation of systems that build in oversight; diagnostic reliance on clinical reasoning and bedside skills; and improvements in measuring the success of patient diagnoses can do much to reduce diagnostic error.



Dr. Timothy Wilt

‘Hypertension limbo: Balancing benefits, harms, and patient preferences before we lower the bar on blood pressure’

In the March 2018 [issue](#) of the *Annals of Internal Medicine*, VA researcher Dr. Timothy Wilt and colleagues laid out their concerns about adopting a more stringent guideline for managing blood pressure control. The American College of Cardiology recently came out with new guidelines for defining and treating high blood pressure. Those guidelines were a significant departure from the current standards of care, and are much more aggressive than those of other organizations like the American College of Physicians.

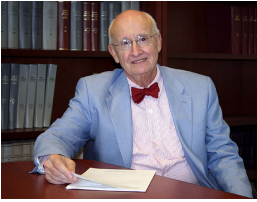
While the newer ACC guidelines do espouse the importance of lifestyle modification and blood pressure measurement techniques, the authors

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worry that there is not enough consideration given to potential patient harms. “The guideline falls short in weighing the potential benefits against potential harms, costs, and the anticipated variation in individual patient preferences,” they write.

Aggressively lowering systolic blood pressure in older adults could put them at greater risk for symptomatic hypotension and fainting. The authors also note that there are no randomized controlled trials that show a benefit in treating adults to diastolic pressures of less than 80.

Older guidelines define high blood pressure as a measurement of 140 over 90 or greater. For adults who are older than 60, the guidelines recommend pharmacologic treatment for a systolic blood pressure greater than 150. The ACC has lowered the threshold for high blood pressure to 130 over 80, and advocates pharmacologic treatment for low-risk individuals whose blood pressure is 140 over 90 or greater.



Dr. Kenneth Heilman is a researcher at the Geriatric Research, Education, and Clinical Center at the Malcom Randall VA Medical Center in Gainesville, Florida.

VA RESEARCHERS WHO SERVED

Dr. Kenneth Heilman, Malcom Randall VA Medical Center

Dr. Kenneth Heilman, who joined VA in 1977, has devoted more than four decades of his life to the agency. The Air Force Veteran served as chief of the neurology service at the Malcom Randall VA Medical Center in Gainesville, Florida, from 1996 to 2009. There, he helped train more than 70 post-doctoral fellows in behavioral neurology and neuropsychology. He's now in the Geriatric Research, Education, and Clinical Center at the Gainesville VA and is a distinguished professor emeritus of neurology at the University of Florida. He received distinguished career awards from the International Neuropsychology Society and the Society for Behavioral and Cognitive Neurology, and he's an honorary member of the American Neurological Association and a fellow of the American Academy of Neurology.

What drove you to military service?

My grandmother lived in Belorussia (present-day Belarus and Poland) when she was pregnant with my mother. But she wanted to raise her children in a country where they could be free and not harassed. Therefore, she immigrated to the United States. She loved America and wanted her grandsons to serve this country. I was also on the Berry Program. Although I had several years of deferment, I could not decide if I should go into neurology or stay in internal medicine. In addition, the war in Vietnam was growing, and the military did not have enough doctors. After doing two years of medical training at Cornell University-Bellevue Hospital, I volunteered for active duty and entered the Air Force in 1965.

What inspired your research career?

From the time I was a boy growing up in Brooklyn, New York, I saw people suffering from medical diseases. I learned that when I was six months old in 1938, I had meningitis. A new form of medication, sulfonamides, saved my life. My family consisted of reformed Jews who strongly believed in "Tikkun olam," a concept in Judaism to bring on the Messianic Age by

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“upholding the falling, healing the sick, freeing the captives, and comforting all who suffer.” What more could I do to make my life meaningful than take care of the sick and do research to heal the sick and reduce suffering?

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

In addition to my family, three mentors had a great influence on my career. My first mentor was Abraham Goodman, my high school geometry teacher. He taught me the joyful reward of solving a problem. The chair of Harvard University’s neurological unit, Dr. Norman Geschwind, was another key mentor. He introduced me to the methods by which we can learn how cognitive activities are performed by the brain and what happens to these activities when the brain is injured. My third major mentor was Dr. Melvin Greer, chair of the neurology department at the University of Florida. He hired me as a member of the faculty. He taught me that great leaders do not ask, “What can you do for me?” Instead, they ask, “What can I do for you?”

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

When I entered the military in 1965, the Air Force didn’t have a hospital in Vietnam. So I was named chief of medicine at the NATO hospital in the western Turkish city of Izmir. While there, I held clinics for the sick members of our military and their family members. I also cared for sick military members from other NATO countries, except for Turkey. I was responsible for hospitalized American patients with serious medical diseases, and I consulted with and supervised other physicians at the hospital. After completing my service in 1967, I took a residency and a fellowship in the neurological unit at Boston City Hospital. I joined the faculty at the University of Florida in 1970.

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

I’m the author-editor of 16 books, more than 100 chapters, and more than 600 journal publications on neurological issues. Together with my co-workers, I’ve described new neurological diseases, such as orthostatic tremor, a rare movement disorder marked by a rapid tremor in the legs that occurs when standing, as well as possible treatments. I’ve also helped to better understand the science behind neurobehavioral deficits, such

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as spatial neglect, apraxia, poor emotional communication, aphasia, and amnesic disorders. The brain disorders that trigger those forms of neurological deficits are most often caused by stroke, degenerative brain diseases, and head trauma. Those three diseases are major causes of Veteran disability and suffering.

Does being a Veteran give you a greater emotional tie to the work you're doing or more insight into Veterans' needs?

I've always had great admiration for our Veterans because they have risked their lives and health for the benefit of humanity. I've always felt honored to be able to care for our Veterans.

Based on your life experiences to date, what do you believe are the keys to success? What motivational tips would you share?

I've authored several books on those topics, including *Matter of Mind, Creativity and the Brain*, and *PGY1: Lessons in Caring*. Some of the most important motivational factors are finding joy in learning, being curious and showing an eagerness to investigate, working hard and persisting until you are successful, having empathy, and trying to make the world a better place.

What's the next step for you in your VA career?

One of my most important activities today is teaching and mentoring students, residents, and cognitive-behavioral neurology fellows. My colleagues and I have trained many fellows who are now world leaders in cognitive and behavioral neurology. We are continuing this training. I also plan to continue caring for Veterans with neurological disorders and to continue my research efforts in an attempt to reduce disabilities and suffering.

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