



# RESEARCH CURRENTS

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



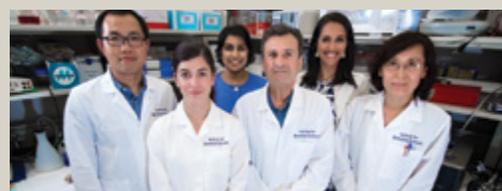
Photo by Christopher Pacheco

**Research highlights successes of new hepatitis C drugs**

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31 Hopkins Plaza, Ste. 102  
Baltimore, MD 21201  
443-759-3456  
410-962-0084 (fax)  
varesearchcurrents@va.gov

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Editor: Mitch Mirkin  
Layout: Michael Escalante

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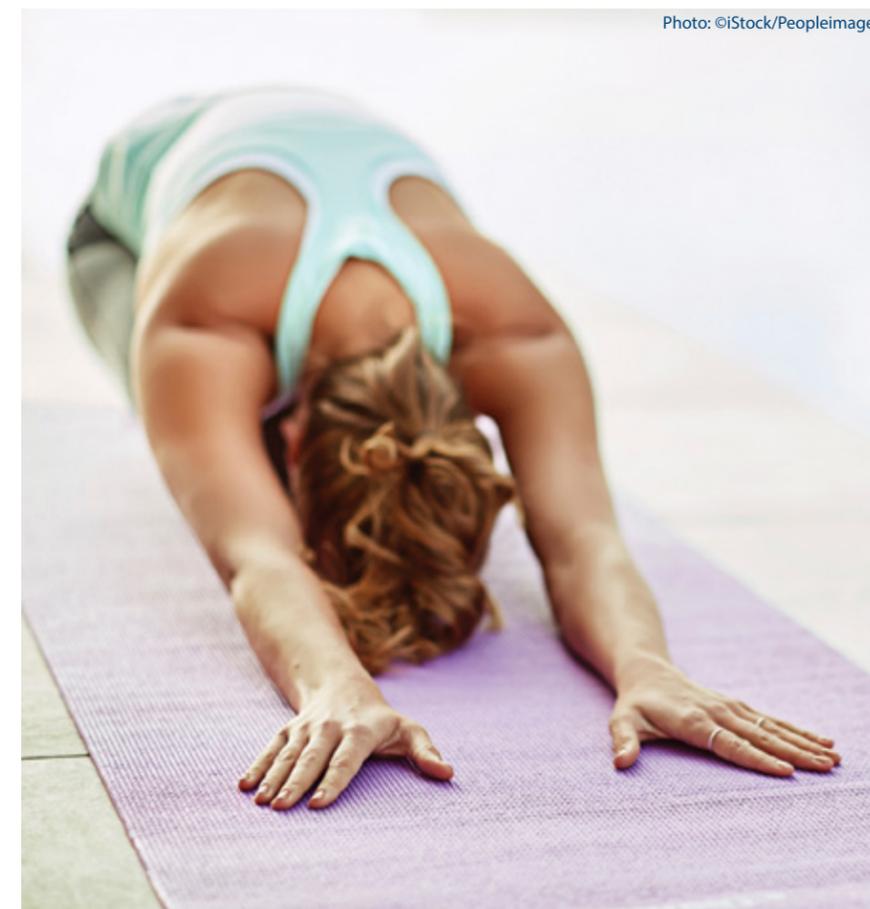


### New technique to test Alzheimer's disease drugs

Researchers at the Edith Nourse Rogers Memorial Veterans Hospital in Bedford, Massachusetts, have demonstrated a new way to test Alzheimer's disease drugs in lab models. They used stem cells from patients' blood to create 3D cell cultures of brain tissue, and were able to measure drug penetration on the sample. Modeling Alzheimer's disease in the lab is hard because of the extremely complex anatomy of the brain, but new drugs need to be tested this way before they are used in humans. This new approach with 3D cell cultures could allow scientists to test drugs more accurately than in traditional 2D cultures by more closely modeling the biology of the brain. (PLOS ONE, Sept. 29, 2016)

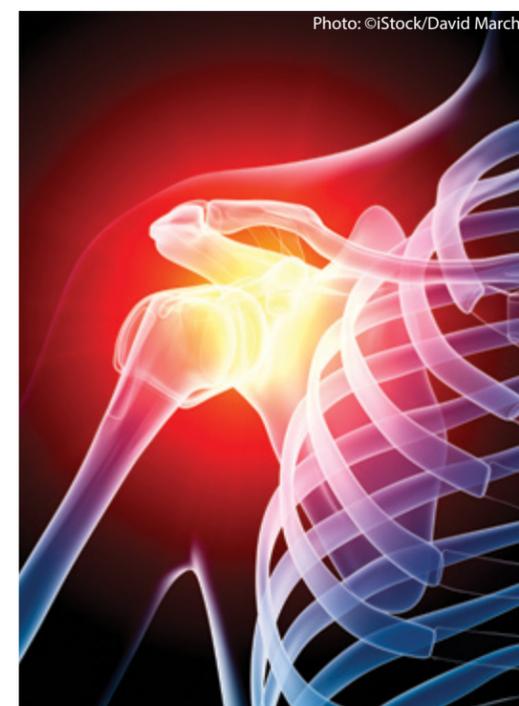
### Depression risk factors among lung cancer patients

The main risk factors for depression among patients with lung cancer are younger age, female sex, low income, not being married, and being a smoker, found a study involving 15 VA medical centers. Researchers suggest that these risk factors should be monitored closely in this population. Patients with depression in this group had worse health-related quality of life, vitality, cancer-specific symptoms, and social support, although the study showed increased mortality only among patients with more lung cancer symptoms or less social support. (Lung Cancer, October, 2016)



### No objective benefits of yoga or aerobic exercise on sleep in midlife women

A study found no objective effects of yoga and aerobic exercise on sleep in menopausal women with hot flashes. Although yoga and exercise have been suggested as useful for midlife women experiencing sleep disturbances, researchers found no significant differences in sleep patterns between those who practiced yoga or exercise and those who did not. The researchers used actigraphy—the continuous measurement of movement to track periods of sleep and wakefulness. While some women reported small sleep improvement after yoga or exercise, these effects could not be objectively measured. (Journal of Clinical Sleep Medicine, Sept. 9, 2016)



### New device for self-administered pain relief after upper-limb injury

Patient-controlled analgesia (PCA) allows patients to manage their own pain while being treated in hospitals. However, Veterans and service members with limb dysfunction or loss are often not able to use these devices. This problem led to the design of a new PCA adapter for patients with severe upper-limb injuries. The new device features a large surface area that fits around traditional PCA equipment, allowing for easier use. Initial case studies show that patients and clinicians were happy with the device, which could improve treatment and functional independence of Veterans and service members with upper-limb injuries. (Military Medicine, August 2016)

## Aortic aneurysm repair

Two procedures to repair aneurysms (widening of an artery that could rupture and cause internal bleeding) in the aorta have similar health and cost outcomes, according to a multicenter VA study. One procedure involves open surgery to repair the aorta. In the other, called endovascular repair, a surgeon uses X-rays to thread a stent through the arteries to the damaged part of the aorta. Researchers found that survival, quality of life, and costs were not significantly different between these two procedures. Selection of either procedure can be guided by patient and physician preference, say the researchers. (JAMA Surgery, Sept. 14, 2016)



## PTSD therapies are still effective in presence of TBI

Both prolonged exposure (PE) and cognitive processing therapy (CPT) are effective treatments for Veterans with PTSD regardless of traumatic brain injury (TBI) status, according to a Salem (Virginia) VA Medical Center study. PE therapy involves emotionally reliving trauma in a safe and controlled manner. CPT focuses on evaluating and changing upsetting thoughts. Some clinicians have been reluctant to use PE for patients with both PTSD and TBI out of fear that they would be less able to tolerate the therapy or that cognitive limitations would make the therapy less effective. A previous study showed that Veterans with PTSD and TBI could benefit from PE. The current study showed that the presence or absence of traumatic brain injury did not change the effectiveness of either therapy and that PE provided greater PTSD symptom reduction than CPT. The researchers note important limitations to this study, including that it was not a randomized trial and the sample size was small. (Journal of Traumatic Stress, October 2016)

## Injectable antipsychotic leads to cost-savings for Vets with schizophrenia

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

## Liver transplant outcomes after circulatory death

Liver transplants from younger donors after circulatory death had better outcomes than those from older donors after brain death, found researchers with the University of Wisconsin and William S. Middleton Memorial Vet-

erans Hospital. Liver donation after circulatory death is generally considered to have worse outcomes than donation after brain death. However, this study showed that livers from circulatory death donors younger than 50

fares better than those from brain death donors older than 60. The researchers suggest that more liver donations after circulatory death should be accepted, which could lead to shorter transplant wait times. (Liver Transplantation, September 2016)

## Disclosing adverse surgical events

Fully disclosing adverse effects to patients after surgery benefits both patients and surgeons. To study how often surgeons fully shared details with patients and their family, investigators surveyed surgeons at three VA medical centers. They found that after a negative event, most surgeons were likely to explain why the event happened, express regret and concern for the patient's welfare, disclose the event within 24 hours, and discuss steps taken to treat any subsequent problems. Fewer surgeons were likely to apologize to patients or discuss whether the event was preventable and how recurrences could be prevented. Surgeons who were less likely to disclose details were more likely to experience



negative effects such as anxiety. The researchers believe better understanding surgeons' attitudes and experiences can help ensure full and open disclosure to patients and their families. (JAMA Surgery, July 20, 2016)



## Personal stories more engaging for managing high blood pressure

African-American Veterans felt more engaged when viewing interventions about hypertension management that included personal stories from other Veterans, compared with information-only interventions. The study included 618 African-American Veterans with uncontrolled hypertension from three VA medical centers. One group was shown a DVD of information about hypertension, while another was shown a DVD featuring other African-American Veterans telling stories about successfully managing their hypertension. The Veterans who watched real patients tell their stories were more emotionally engaged and reported intentions to change their behavior than the other group, showing that personal stories may be an effective tool to teach patients how to manage their condition. (Patient Education and Counseling, September 2016)



Veteran Ian Phillips was successfully treated with the new-generation hepatitis C drugs. Read his story on page 8.

Photo by Christopher Pacheco

## Study confirms **high cure rates with new hepatitis C drugs**

A large database study found that new drug regimens for hepatitis C have resulted in “remarkably high” cure rates among patients in VA, the nation’s largest provider of care for the condition.

A database study has found that new drug regimens for hepatitis C have resulted in “remarkably high” cure rates among patients in VA’s national health care system.

The study appeared in the September 2016 issue of the journal *Gastroenterology*.

Of the more than 17,000 Veterans in the study, all chronically infected with the hepatitis C virus at baseline, 75 percent to 93 percent had no detectable levels of the disease in their blood for 12 or more weeks after the end of treatment. The therapy regimens lasted 8 to 24 weeks, depending on patient characteristics.

The VA researchers analyzed data from four subgroups of patients infected with hepatitis C—genotypes 1, 2, 3, and 4—and found that genotype 1 patients showed the highest cure rates and genotype 3 the lowest. Genotype 1 was by far the most common type of infection among the four subgroups

### ‘Surprisingly high’ response rates among those with cirrhosis

The study group of more than 17,000 Veterans included more than 11,000 patients with confirmed or likely cirrhosis, a liver disease that can result from hepatitis C, among other causes. The study team found “surprisingly

high” response rates of around 87 percent in this group.

The overall results were consistent with those from earlier clinical trials that led to FDA approval of the three new drug regimens in the study: sofosbuvir (SOF), ledipasvir/sofosbuvir (LDV/SOF) and paritaprevir/ritonavir/ombitasvir and dasabuvir (PrOD).

The drugs, introduced in 2013 and 2014, have been credited with

revolutionizing hepatitis C treatment, which means a cure is now in reach for the vast majority of patients infected with the virus. Previously, using earlier drug regimens, most patients could expect, at best, only a 50 percent chance of a cure.

“Our results demonstrate that LDV/SOF, PrOD and SOF regimens can achieve remarkably high SVR [sustained virologic response] rates in real-world clinical practice,” the VA researchers wrote.

### New regimens free of interferon

The new drug regimens examined in the study do not contain interferon, which has troublesome side effects such as fever,

fatigue, and low blood counts. The newer drugs are considered far more tolerable than the older interferon-based antiviral regimens, although they are far more expensive.

The researchers extracted anonymous data on all patients in VA care who received HCV antiviral treatments between January 2014 and June 2015 using the VA Corporate Data Warehouse, a national, continually updated re-

**“Modern direct-acting antiviral drugs for hepatitis C far outperform our older options in terms of efficacy and tolerability.”**

pository of data from VA’s computerized patient records.

The study’s optimistic finding bodes well for Veterans and others infected with the hepatitis C virus, according to coauthors Dr. Lauren Beste and Dr. George Ioannou, specialists in internal medicine and hepatology, respectively, with the VA Puget Sound Health Care System in Seattle.

“Modern direct-acting antiviral drugs for hepatitis C far outperform our older options in terms of efficacy and tolerability,” said the two researchers in an email interview. “With older drugs, most patients could not undergo antiviral treatment be-

cause they had contraindications or medication side effects. With newer options, almost anyone can safely undergo treatment for hepatitis C.”

### VA spending \$1 billion for FY 2016 on new hepatitis C drugs

This comes as VA is dedicating significant funds to help greater numbers of patients with hepatitis C. For fiscal year 2016, VA anticipates spending about \$1 billion on new hepatitis C drugs, compared with nearly \$700 million in FY 2015. The increased funding has led to far more Veterans being treated than ever before for the condition.

Ioannou notes that “since February 2016, all VA facilities in the country have had unrestricted access to all antiviral meds for all patients. VA has allocated money for these drugs in the quantity needed and to my knowledge is the only health care system in the world to have done so.”

VA has long led the country in screening for and treating hepatitis C. As of mid-September 2016, the agency had treated more than 100,000 Veterans infected with the virus. More than 68,000 of these patients had been treated with the new highly effective antivirals.

VA research continues to expand knowledge of the disease through scientific studies focused on effective care, screening, and health care delivery. Some studies look at particular groups of hepatitis C patients—for example, female Veterans, or those with complicated medical conditions in addition to hepatitis C.

Veterans can find more information on VA care for hepatitis C at [www.hepatitis.va.gov](http://www.hepatitis.va.gov). ★

## Coast Guard Vet cured of hepatitis C following lengthy battle with virus

For more than two decades, Ian Phillips lived with an active case of hepatitis C. He was mostly asymptomatic, although like many other Veterans the virus caused him to acquire cirrhosis, a deterioration of the liver.

Phillips, who spent 10 years in the Coast Guard, rarely volunteered to others that he was carrying hepatitis C. But all along he was fighting a personal battle, worrying that the virus was eating away at his liver, and that he was inching closer to needing a transplant.

It was like a “ticking time bomb,” he says.

### Finally, a cure

That bomb has been defused for now. The hepatitis C virus (HCV) has been undetectable in Phillips’ blood for the past year, and his cirrhosis has stabilized, allowing him to regain some liver function. His doctors tell him his hepatitis is totally cured and will not come back unless he gets re-infected.

All of that is thanks to his three-month stint on the drug regimen ledipasvir/sofosbuvir - a relatively new but very expensive combination that is becoming more available to Veterans with hepatitis C (see main story). The regimen also included ribavirin, which has been in use for some time. Phillips, who was treated in regular clinical care, says he experienced minimal side effects from the drugs.

He hopes never to relive what was a wrenching period in his life.

“It was difficult for many years while the virus was still active,” he says. “Hep C is not something you want to go around and tell everybody about. It’s a tough thing.”

Phillips was treated at the VA Puget Sound Health

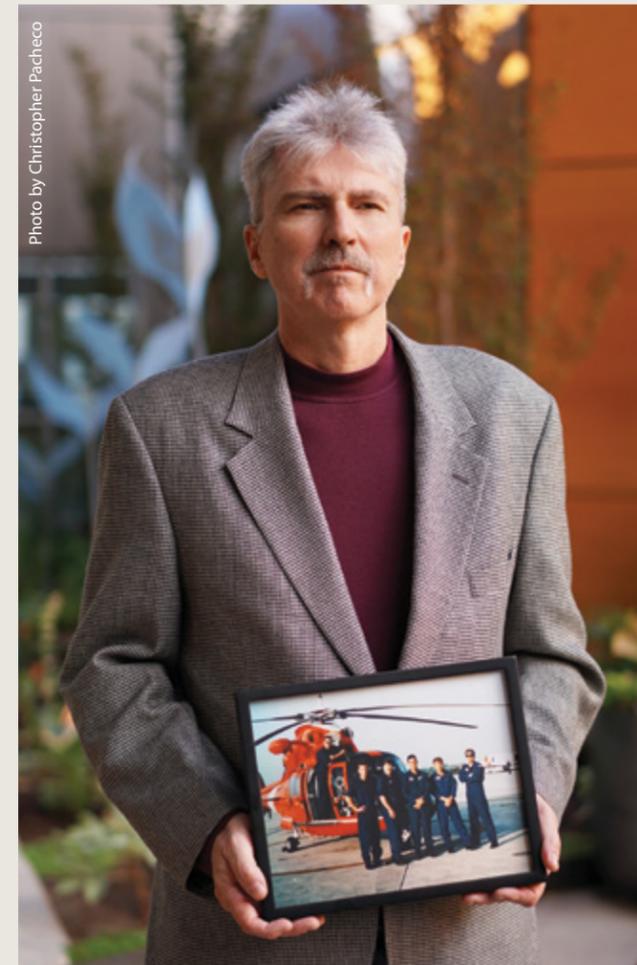


Photo by Christopher Pacheco

Coast Guard Veteran Ian Phillips was cured of hepatitis C after a two-decade ordeal with the virus.

Care System in Seattle by Dr. Lauren Beste, a specialist in internal medicine.

“Dr. Beste is one of the most fantastic doctors I’ve ever encountered,” he says. “And to consider that she saved my life and has been just wonderful all the way through, almost like a family member. Pretty incredible. She really cares.”

### A participant in past clinical trials

Phillips, now 52, began serving in the Coast Guard in 1984 and was eventually stationed in Miami as an HH-65-A helicopter flight mechanic from 1993 to 1997, with responsibilities for fueling and maintenance. He earned his aircrew wings at the time.

In 1993, Phillips became part of operations Able Manner and Able Vigil, in which Coast Guard vessels rescued thousands of Haitian and Cuban migrants in the Caribbean and prevented them from illegally entering the United States. Phillips, with cuts on his hands from working in the engine room as a mechanic, helped a lot of the migrants off of their boats and onto his cutter. Wearing gloves that were much thinner and less durable than those required today, he came in contact with bodily fluids and human wastes.

Shortly after, while donating at a Red Cross blood drive in Miami, he was told he had hepatitis C.

“That’s where it all started,” he says. “It was really frightening.”

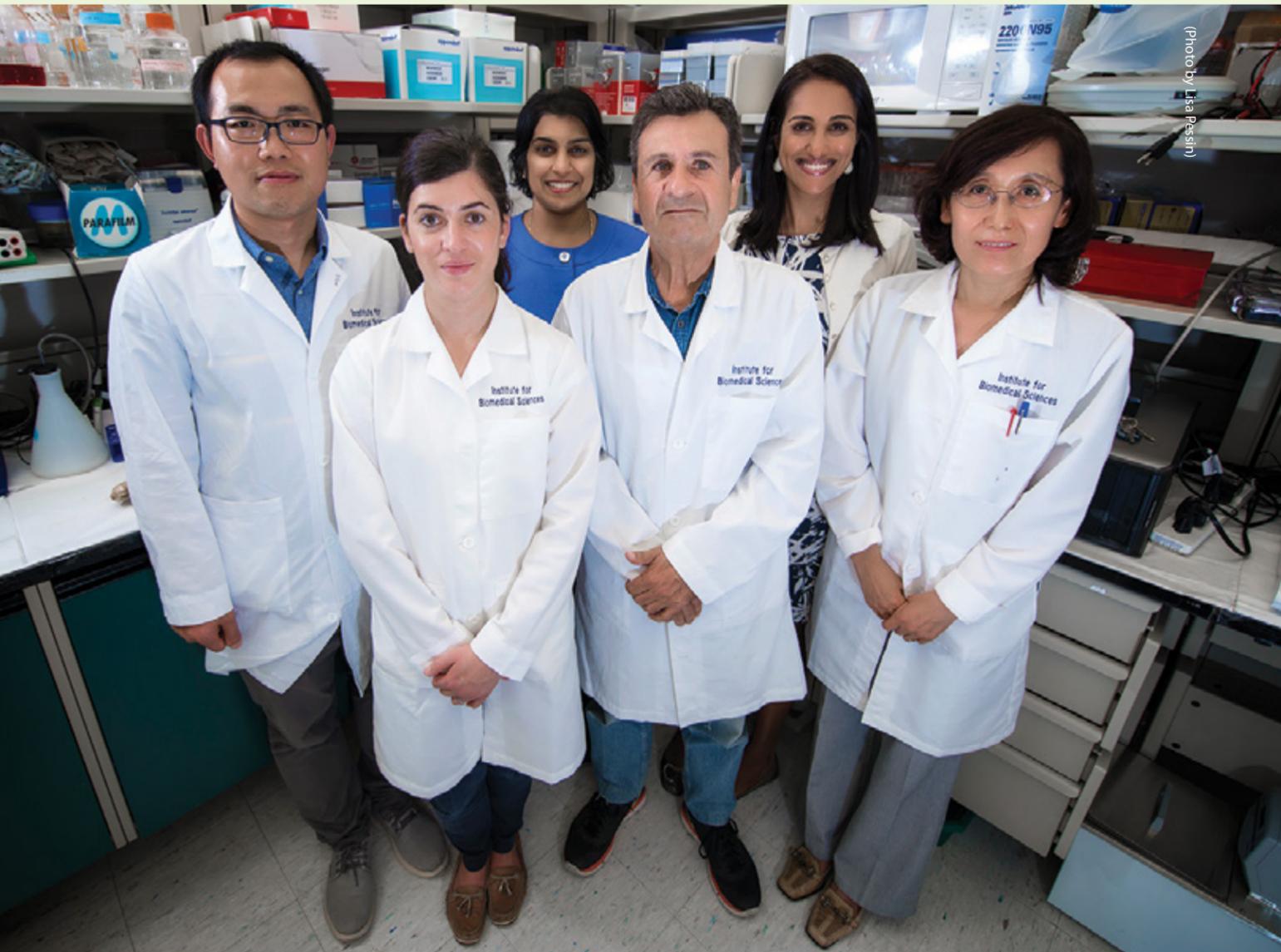
Later in the 1990s, Phillips took part in two HCV trials at the University of Miami and one at the University of Washington. All of the studies involved the drug interferon, which can cause nasty side effects, combined with ribavirin. None of the treatments worked, compounded by the fact that Phillips experienced body aches and other flu-like side effects from the interferon.

The harsh daily reality continued for Phillips, a genotype 3 patient, one of the least common but most difficult-to-cure hepatitis C infections. But he ultimately became a candidate for HCV therapy with the newer drugs. He started on the ledipasvir/sofosbuvir and ribavirin regimen in February 2015 at the VA Puget Sound.

Today, Phillips resides in Port Orchard, Washington, near Seattle, and spends time helping his brother-in-law, a Vietnam Vet, get treatment for leukemia.

Phillips says he is living with what he calls a “new lease on life.”

“I don’t have the virus hanging over my head,” he says. “I have the chance that I could have complications like liver cancer, because you have a high percentage of people getting that with cirrhosis. But knowing that the hep C is no longer attacking my liver... I feel healthy, I hike, I’m active. I’m no longer carrying around that stigma, the ticking time bomb of the virus. It’s a wonderful thing.” ★



(Photo by Lisa Pessin)

## Lab team spins ginger into nanoparticles to heal inflammatory bowel disease

Researchers with VA and the Institute for Biomedical Sciences at Georgia State University have developed “edible ginger-derived nanoparticles” that they believe may be good medicine for Crohn’s disease and ulcerative colitis, the two main forms of inflammatory bowel disease. The particles may also help fight cancer linked to colitis, according to experiments in mice.

A recent study by researchers at the Atlanta VA took them to a not-so-likely destination: local farmers markets. They went in search of fresh ginger root.

Back at the lab, the scientists turned the ginger into what they are calling GDNPs, or ginger-derived nanoparticles. The process started simply enough, with your basic kitchen blender. But then it involved super-high-speed

Dr. Didier Merlin (front row, center) and colleagues with VA and the Institute for Biomedical Sciences at Georgia State University are exploring the use of edible ginger-derived nanoparticles to treat inflammatory bowel disease.

centrifuging and ultrasonic dispersion of the ginger juice, to break it up into single pellets. (Don’t try this at home!) The research team, led by Dr. Didier Merlin with VA and the Institute for Biomedical Sciences at Georgia State University, believes the particles may be good medicine for Crohn’s disease and ulcerative colitis, the two main forms of inflammatory bowel disease (IBD). The particles may also help fight cancer linked to colitis, the scientists believe.

They reported their findings, based on experiments with cells and mice, in the September 2016 issue of *Biomaterials*.

### Efficiently targeting the colon

Each ginger-based nanoparticle was about 230 nanometers in diameter. More than 300 of them could fit across the width of a human hair.

Fed to lab mice, the particles appeared to be nontoxic and had significant therapeutic effects:

- Importantly, they efficiently targeted the colon. They were absorbed mainly by cells in the lining of the intestines, where IBD inflammation occurs.
- The particles reduced acute colitis and prevented

Photo: ©iStock/hudiemm

chronic colitis and colitis-associated cancer.

- They enhanced intestinal repair. Specifically, they boosted the survival and proliferation of the cells that make up the lining of the colon. They also lowered the production of proteins that promote inflammation, and raised the levels of proteins that fight inflammation.

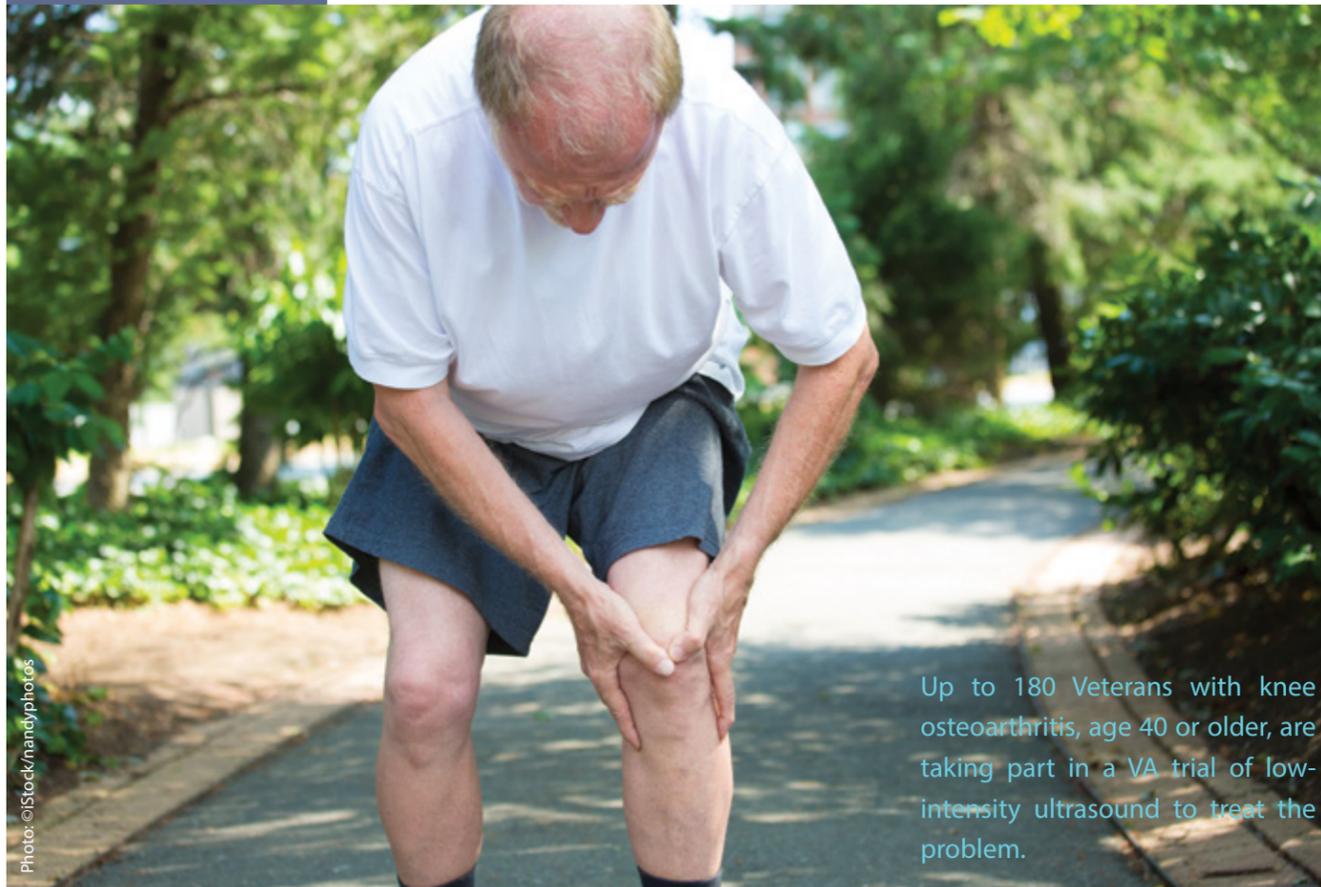
Part of the therapeutic effect, say the researchers, comes from the high levels of lipids—fatty molecules—in the particles, a result of the natural lipids in the ginger plant. One of the lipids is phosphatidic acid, an important building block of cell membranes.

The particles also retained key active constituents found naturally in ginger, such as 6-gingerol and 6-shogaol. Past lab studies have shown the compounds to be active against oxidation, inflammation, and cancer. They are what make standard ginger an effective remedy for nausea and other digestion problems. Traditional cultures have used ginger medicinally for centuries, and health food stores carry ginger-based supplements—such as chews, or the herb mixed with honey in a syrup—as digestive aids.

Delivering these compounds in a nanoparticle, says Merlin’s team, may be a more effective way to target colon tissue than simply providing the herb as a food or supplement.

Continued on page 23





Up to 180 Veterans with knee osteoarthritis, age 40 or older, are taking part in a VA trial of low-intensity ultrasound to treat the problem.

## Can ultrasound help rebuild knee cartilage?

A VA team is testing a potential new therapy that promises to regenerate cartilage. The researchers hope it can eventually be a viable alternative to drugs or surgery to treat arthritis.

For the 30 million or so Americans who have osteoarthritis, joint pain and stiffness can be a daily battle. Various treatments can offer some relief, but, says VA's Martha Finco, "there are currently no FDA-approved treatments that build new, or repair damaged, cartilage."

Along with inflammation, the breakdown of cartilage—the smooth, whitish, elastic tissue found in joints—is the hallmark of osteoarthritis, the most common form of arthritis.

Finco's team is testing a potential new therapy that promises to regenerate cartilage. They hope it can eventually be a viable alternative to drugs or surgery.

The therapy is called pulsed low-intensity ultrasound (PLIUS). The pilot trial, now underway in Salt Lake City, San Diego, and Dallas, will

involve 180 Veterans in all, all age 40 or older. It runs through 2019. The study is a phase 2 trial, meaning it's intended to assess safety as well as efficacy.

### Preclinical results encouraging

Finco, the study's national coordinator, says preclinical findings on PLIUS have been positive.

"The results regarding evidence of cartilage regeneration were encouraging in both in vitro models [tests on cells, in Petri dishes] and animal models in the laboratory," she says. Results from a few small clinical trials have been inconclusive. The new VA effort is the largest study of PLIUS to date for knee osteoarthritis.

Ultrasound technology is widely used in medical imaging. One well-known application is showing expectant parents images of the developing baby.

Underlying the technology are sound waves. According to animal experiments, these same waves can mechanically stimulate the growth of new cartilage.

A VA lab study published in 2014 suggested that PLIUS works by coaxing chondrogenic progenitor cells—basically, cartilage precursor cells—to migrate to injured tissue.

### Device already approved to help bone healing

The handheld device being used in the new VA-sponsored

clinical trial, called the Exogen, is already approved by the FDA to promote bone healing after fractures. It's considered an investigational device for the VA study, though, since its utility in cartilage regeneration is unknown.

One group of Veterans in the study will self-apply the treatment to the inner side of the knee for 20 minutes a day for 48 weeks.

"This is the area of the knee that generally bears the patient's weight and is most commonly involved in osteoarthritis," explains Finco.

**"Should PLIUS slow or prevent cartilage degeneration, this would be an important advance in understanding and ultimately treating osteoarthritis."**

A second group of study volunteers will do the same thing—except they will use a sham device that looks and feels like the real thing.

The Exogen kit comes with a neoprene strap that is worn around the body part to be treated—the knee, in this case. Fitted in the strap is a circular transducer, which emits the ultrasound waves.

"It looks like a big wrist-

watch," says VA and University of Utah rheumatologist Dr. Daniel Clegg, lead investigator on the study.

The researchers will take before and after pain measures for both groups, and use MRI scans to check for new cartilage growth.

The Veterans in the study, as well as their caregivers and the researchers, will be "blinded" as to whether the real or sham treatment was received.

### Results will be especially relevant for Vets

Finco notes that even if the results from the clinical trial are positive, further research would be needed before the treatment can be approved by the FDA and become widely available.

That said, she notes that "should PLIUS slow or prevent cartilage degeneration, this would be an important advance in understanding and ultimately treating osteoarthritis."

The findings will be especially relevant for Veterans, a population in which Clegg says osteoarthritis is "rampant." That's partly because of their military experience, he notes. He cites a 2011 study by Army researchers that found higher rates of the condition in military populations than in comparable age groups in the general population, presumably because of the physical strain entailed in military service. ★

## Closing in on biomarkers for suicidal behavior

An enzyme called ACMSD, involved in brain inflammation, could become an important target for new drugs aimed at preventing suicide.



Photo: ©iStock/the-lightwriter

An enzyme called ACMSD—part of a chain of biochemical reactions called the kynurenine pathway, activated by inflammation—could become an important target for new drugs aimed at preventing suicide.

The enzyme shows reduced activity in people who have tried to kill themselves, according to a study published online Aug. 2, 2016, in *Translational Psychiatry*. And downstream effects of the sluggish enzyme—namely, abnormal levels of two acids in the body—could potentially be measured in blood tests to help identify patients at high risk, say the researchers.

The study was conducted with Swedish patients but involved collaborators in three other countries, including in the U.S. at VA's Rocky Mountain Mental Illness Research, Education, and Clinical Center (MIRECC) for Suicide Prevention in Denver, and at the Van Andel Research Institute in Michigan.

“We now want to find out if these changes are only seen in individuals with suicidal thoughts or if patients with severe depression also exhibit this. We also want to develop drugs that might activate the enzyme ACMSD and thus restore balance between quinolinic and picolinic acid,” said Dr. Sophie Erhardt of the Karolinska Institutet in Stockholm, one of the leaders of the study.

Senior author on the study was Dr. Lena Brundin at Van Andel. Representing VA was Dr. Teodor Postolache, a clinical and research psychiatrist with VA's Rocky Mountain MIRECC for Suicide Prevention. Postolache is also an investigator with VA's MIRECC in Baltimore, and a professor at the University of Maryland School of Medicine.

### The immune system and mental health

An increasing body of evidence in recent years has implicated the immune system—particularly inflammation—as a possible contributing factor in both depression and suicidal behavior. Inflammation is one way the body responds to stress. But the link is

complex, and researchers are still far from grasping exactly how the pieces fit together, and whether the findings can be used clinically to advance suicide prevention.

The new study, conducted in several phases, involved more than 300 Swedish patients and other volunteers. The researchers took samples of blood and cerebrospinal fluid from those who had attempted suicide, immediately after the suicidal episode and at intervals thereafter, and compared them with samples from healthy controls.

In the suicidal patients,

**“We also want to develop drugs that might activate the enzyme ACSMD and thus restore balance between quinolinic and picolinic acid.”**

the ratio between picolinic and quinolinic acid was out of whack—too little of the former, too much of the latter. Picolinic acid is protective, whereas quinolinic acid is toxic to the brain and nervous system.

The changes were most pronounced in the cerebrospinal fluid, the clear liquid that cushions the brain and spinal cord. The abnormal levels persisted at least two years in repeated tests of the fluid. The changes also showed up in blood tests, albeit less markedly. But

blood tests are much easier to perform than spinal taps, so they could represent a more practical clinical option.

#### Gene tests confirm results

The researchers knew from past studies that ACSMD modulates the levels of the two acids. They confirmed the link in the current study through a genetic analysis. They found that a particular variant of the ACSMD gene was more prevalent in suicide attempters, and was associated with increased quinolinic acid.

Targeting ACSMD with a drug to boost its activity could, in theory, normalize the ratio between the two acids it affects, say the researchers.

But the study wasn't designed to show a direct causal relationship between ACSMD activity and suicide risk. So it's not clear that raising ACSMD activity and restoring the picolinic-quinolinic ratio would actually curb suicidal behavior.

The next step in exploring that, say the researchers, would be lab tests with an animal model of depression. Lab animals that exhibit traits typical of depression, such as lack of interest in normal activities, as well as traits such as impulsivity, are commonly

studied by scientists looking at suicidal behavior.

#### Combating inflammation over long term may be best

Further research may also shed light on issues of timing. To the extent that inflammation does drive suicidal behavior, it could be a problem that is years in the making, and that demands long-range strategies.

Dr. John Krystal, a psychiatry researcher with VA and Yale School of Medicine, is the editor of the journal *Biological Psychiatry*. He was quoted in response to a study in the journal last year that showed increased levels of inflammation-causing immune chemicals called cytokines in suicidal patients:

“Inflammation affects every organ in the body,” noted Krystal. “It is increasingly evident that we need to take a long-term perspective on the effects of inflammation on the brain. The path to preventing suicide may be to intervene early in long-term processes that increase the risk for suicide, rather than to focus solely on the elusive short-term predictors of suicide.” ★

## Exploring other angles in suicide prevention

In related work, Postolache is now funded by VA to study the links between the brain-infecting pathogen *Toxoplasma gondii* and suicidal behavior. Past research has implicated the pathogen in this and other serious behavioral problems. Veterans may be at particularly high risk for *T. gondii* infection because it is common in some areas of the world where U.S. troops have been deployed, including the Middle East.

The study will recruit 600 Veterans in mental health care at the Denver, Baltimore, and Atlanta VA medical centers—half with a history of at least one suicide attempt, and half without. They will undergo extensive evaluations, including a blood test to determine whether they have been infected with *T. gondii*.

Postolache's team will probe the interaction among the *T. gondii*, inflammation, and the kynurenine pathway. They will pay special attention to how the traits of impulsivity and aggression—strongly associated with suicide—are affected.

“One working hypothesis is that a high picolinic-quinolinic acid ratio will result in a reduced vulnerability to infection with *T. gondii* and to inflammation,” explains Postolache.

Dr. Lena Brundin of the Van Andel Research Institute will collaborate with the VA group to help measure several molecules of interest, including picolinic and quinolinic acid.

In other work, Postolache is co-investigator with Brundin, the principal investigator, on a National Institute of Mental Health grant focused on the potential role of ACSMD in depression and suicide attempts in mothers after delivery.

All in all, Postolache says a good deal of research is still needed to firm up the understanding of ACSMD in suicide, and to explore potential clinical applications.

“We are far from affirming a causal relationship,” he says. “We need interventional and longitudinal studies to advance our understanding of this potentially key molecular relay, and to determine if [the associated] inflammation or infection is resulting in impairment of brain function.”

Assuming the ACSMD-suicide theory continues to hold up in further research, Postolache says it will likely be another 5 to 10 years at least, given current funding levels, before it can find clinical application. ★



Researchers are exploring whether exposure to the pathogen *Toxoplasma gondii*—often spread through contact with cat feces—may be a factor in suicide risk among U.S. troops.

## Document search tool may boost treatment of Vets with congestive heart failure

Clinicians and informatics experts at the VA Salt Lake City Health Care System have designed a system that uses natural language processing to help improve care for Veterans with heart failure.



Photo by Tod Peterson  
Dr. Jennifer Garvin and doctoral student Youngjun Kim review the architecture of the CHIEF system, which uses natural language processing to extract information from the electronic records of heart failure patients.

A specialist in biomedical informatics, Dr. Jennifer Garvin has long been interested in improving the care of heart failure patients through evidence-based medical therapy. Cardiovascular disease, the number-one killer of Americans, is the leading cause of hospitalization in VA.

Garvin, with the VA Salt Lake City (Utah) Health Care System,

thus obtained VA funding and collaborated with colleagues to advance care in this area.

She focused on the use of natural language processing, technology similar to that used by IBM Watson in VA. It allows computers to make sense of free text, such as that found in doctors' notes. She planned to put the technology to work reviewing electronic health record documents, hoping it would eliminate the need for doctors to invest hours and hours into manually doing the same.

"The overall goal was to reduce the burden on primary care providers and the health care system, to undertake quality measurements, and to use the data in applications such as clinical decision support," Garvin says.

A VA study led by Garvin shed light on the capabilities of a new automated tool, the Congestive Heart Failure Information Extraction Framework, otherwise known as CHIEF. It is part of the Automated Data Acquisition for Heart Failure project, her VHA

endeavor aimed at improving the care of heart failure patients.

### Streamlining patient treatment

Garvin's study shows that an extraction system has the potential to virtually eliminate the need for primary care providers to conduct tedious searches in free text for critical details. After accessing data on his or her patient through the VA electronic health record in the standard way, a clinician can have a summary from CHIEF to see if that patient, for example, is receiving proper medication for cardiovascular disease. The result is a streamlined document review system for patients with congestive heart failure.

**"The more text documents we have, the better we can train the system so it can learn from various presentations of the data."**

Through the CHIEF software prototype, VA can also accurately process Veterans' records with minimal to no manual chart review to learn if they received recommended care, suggests Garvin's research. Use of the technology aligns with the VA Blueprint for Excellence, which offers strategies for VA to evolve as a model health care provider, and other strategic initiatives.

The study, published recent-

ly in the Journal of the American Medical Informatics Association, included 1,083 heart failure patients who were discharged from VHA medical centers in 2008 and 2009. Clinical notes were extracted from the patients' electronic health records stored in the VHA Corporate Data Warehouse. CHIEF scanned the records and processed the data into a table that allowed for analysis.

Researchers gauged the effectiveness of CHIEF based on these factors:

- Did Veterans undergo a proper assessment of the thickest of the heart's chambers, the left ventricle, which is responsible for pumping blood to tissues all over the body?

- Were Veterans prescribed medications recommended by clinical guidelines, and if not, why not?

The software hunted for references to two drug therapies recommended by the American College of Cardiology Foundation and the American Heart Association. The medications are widely prescribed for primary hypertension with the aim of reducing mortality rates: angiotensin converting enzyme inhibitors and angiotensin receptor blockers. The latter is an alternative for patients who can't take inhibitors.

The researchers defined accuracy by two methods. "Recall" measures what percent of positive events were correctly predicted, such as prescribing the recommended drugs. "Precision" measures what percent of positive predictions were correct.

With an accuracy rate of at least 95 percent, CHIEF found mentions in the clinical notes of the two drug therapies and of "left ventricular ejection fraction"—the percentage of blood leaving the heart each time it extracts. It also found quantitative values of this important clinical indicator.

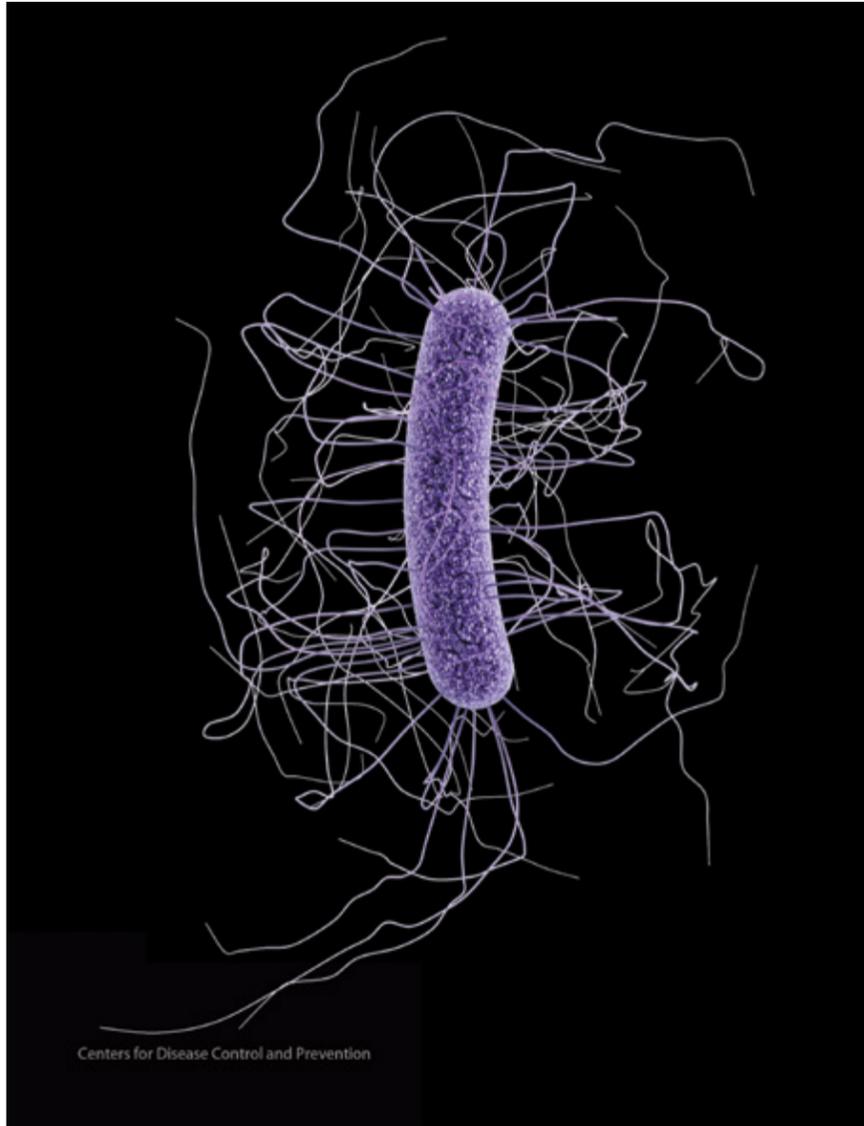
The reasons patients did not take prescribed medications were more difficult to extract. On this front, CHIEF achieved only a 40 percent success rate at best. Garvin's team has been working to improve that aspect.

"The lower accuracy is most likely because the number of patients with reasons not to have these medications prescribed is low," she says, "and there is a lot of variation in how the reasons are written and where they are located in the documents. The rarity of the reasons why patients should not be prescribed these medications makes it harder for CHIEF to learn to process this information."

Large numbers of records are needed to find the many reasons why patients are not prescribed evidence-based medications, she notes.

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## Fecal transplants—what do patients think?



Centers for Disease Control and Prevention

Yuck.

That might be the first thought some people have when they hear about fecal transplants. The procedures are increasingly being used in the U.S. to combat *Clostridium difficile* infections.

But for those actually struggling to rid themselves of *C. difficile*—which often involves severe diarrhea and overwhelming fatigue—the yuck factor involved with fecal transplants might be the least of their concerns. That's according to new research by a team with the William S. Middleton

Most cases of *C. difficile* occur in patients on antibiotics. A study using 2011 data—the largest to date on the topic—found that the bug caused nearly half a million infections in the U.S. that year and directly caused some 15,000 deaths.

Veterans Hospital and the University of Wisconsin-Madison.

The researchers, led by Caroline Zellmer, interviewed 17 patients who had been infected with *C. difficile* and received a fecal transplant. They shared their views on the illness itself, and the treatment.

The findings appeared in the June 2016 issue of the journal *Infectious Diseases and Therapy*.

"Overall," wrote Zellmer and her coauthors, "patient responses reflected an overall acceptance of [fecal microbiota transplantation] as a treatment to rid themselves of *C. difficile* infection."

In other research, the treatment has shown a success rate of 85 percent or better.

### Patients didn't mind finding their own stool donor

One possible barrier for patients in need of fecal transplants is the requirement that they find a stool donor on their own. This could potentially involve some uncomfortable conversations. But even on this count, most of the people surveyed said finding a donor was not difficult and they preferred to select someone on their own—usually a spouse, relative,

or friend—rather than have their health care provider choose one.

Just the same, the researchers believe that the establishment of nonprofit stool banks that would do away with the need for patients to find their own donors would be a welcome development. They say it would lessen the social and emotional burden on patients.

### Handling capsules, enemas was tolerable

How about handling fecal material? While some patients are treated in a clinic, with the fecal matter being delivered into the intestine via a colonoscopy or other means, others self-administer it at home. This means they must handle enemas containing the brown stuff, or in some cases freeze-dried capsules that they swallow.

Even this aspect was tolerable to most of the patients surveyed, despite the odor and appearance of the remedy. They made comments like "[you] got to get it done" and "if you need something it is OK."

According to the study authors, "These comments reflect the extent to which patients were desperate for a solution to their struggles" with *C. difficile* infection. ★

## More about *C. difficile* and fecal transplants

Fecal transplantation, or fecal microbiota transplant, involves removing stool, which contains healthy bacteria, from a donor and inserting it into a sick patient. The procedure actually dates back thousands of years, to ancient China. It has been revived in the past few years as a weapon against the *C. difficile* superbug, which is notoriously tough to banish.

In a healthy person, the bowels are full of healthy bacteria. Antibiotic treatment can upset the balance and allow *C. difficile* bacteria to take hold and spread. The germs cause diarrhea—often severe—along with abdominal pain, weakness, fatigue, and other symptoms. The illness often brings with it distress, anxiety, and depression. Repeated hospitalizations, malnourishment, and dehydration are common. In some cases the infection can be fatal. In 2013, the Centers for Disease Control and Prevention placed *C. difficile* into its top threat category: urgent.

The most common treatments are the antibiotics metronidazole and vancomycin, but a quarter of patients treated with these drugs experience one or more recurrences.

A 2015 review study by VA investigators in Minneapolis found that fecal transplantation, by and large, is an effective method for battling stubborn *C. difficile* infections.

The review looked at two randomized control trials and an additional 33 uncontrolled case series studies or case reports. Overall, the studies involved data from more than 500 patients with *C. difficile*. Fecal transplants proved successful in treating 85 percent of patients with recurring infections. They helped 55 percent of patients who weren't responding to standard drug treatments. For initial infections, or those cases deemed "refractory" (non-responsive to treatment), success rates were more variable.

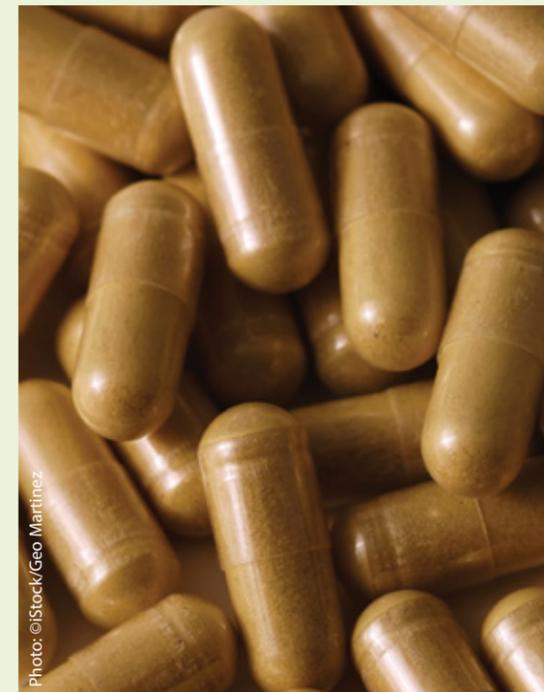


Photo: ©iStock/Geo Martinez

Fecal transplants can be administered via capsules, among other methods.

## Study finds added burden on caregivers of Vets with PTSD and dementia

VA investigators recently published the first known study on the impact of co-existing PTSD and dementia on family caregivers, who provide the bulk of care to Veterans with those conditions.

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



A recent VA study focused on family caregivers whose loved ones have both dementia and PTSD.

## Treatment of congestive heart failure

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Garvin says her team focused on congestive heart failure because of its prevalence in Veterans and the U.S. population in general.

“Congestive heart failure is associated with difficult and recurring symptoms, suffering by both the patient and the family, and a decreased lifespan following diagnosis of this condition,” she says. “The use of evidence-based treatments can decrease symptoms, improve patient functioning, and prolong life.”

### CHIEF may be used to study other aspects of heart failure

Garvin says her group may now try to use the software to better understand other aspects of heart failure, such as how patients go from one stage of the condition to the next. She is also interested in testing CHIEF’s ability to extract information on other illnesses.

The CHIEF system has great potential, Garvin says, with both recall and precision now at least 95 percent accuracy for most information. Further improvements, she says, could focus on teaching CHIEF to accurately extract reasons for not prescribing recommended medications, and to read data addressing other aspects of heart failure.

If the research pans out, says Garvin, CHIEF could be imple-

mented throughout the VA health care system to process larger volumes of data on a variety of Veteran ailments.

“This would improve recall and precision,” she says. “The more text documents we have, the better we can train the system so it can learn from various presentations of the data.”

Garvin’s team included University of Utah researchers Dr. Stephan Meystre, who designed the CHIEF software prototype, as well as Youngjun Kim and Drs. Glenn Gobbel and Michael Matheny, all of whom helped Meystre develop the technology. ★

## Ginger nanoparticles

Continued from page 11

The idea of fighting IBD with nanoparticles is not new. In recent years, Merlin’s lab and others have explored how to deliver conventional drugs via nanotechnology. Some of this research is promising. The approach may allow low doses of drugs to be delivered only where they are needed—inflamed tissue in the colon—and thus avoid unwanted systemic effects.

### Ginger could be cost-effective medicine source

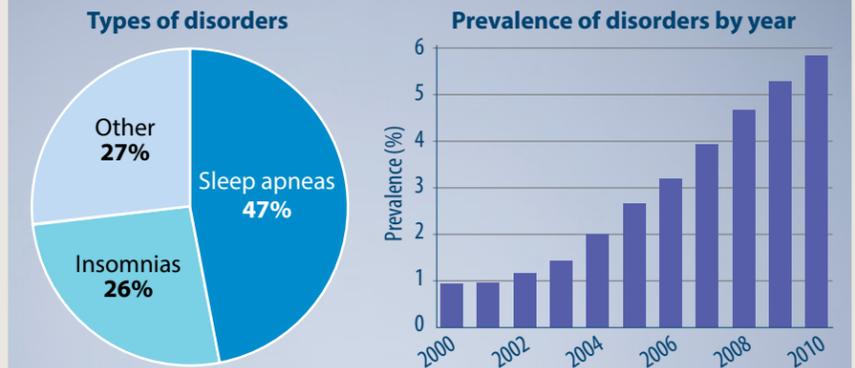
The advantage of ginger, say the researchers, is that it’s non-toxic, and could represent a very cost-effective source of medicine.

The group is looking at ginger, and other plants, as potential “nanofactories for the fabrication of medical nanoparticles.”

Merlin and his VA and Georgia State University coauthors elaborated on the idea in a report earlier this year titled “Plant-derived edible nanoparticles as a new therapeutic approach against diseases.” They wrote that plants are a “bio-renewable, sustainable, diversified platform for the production of therapeutic nanoparticles.”

The ginger nanoparticle work was supported by VA, the National Institutes of Health, and the Crohn’s and Colitis Foundation of America. ★

## Prevalence of sleep disorders in VA patients



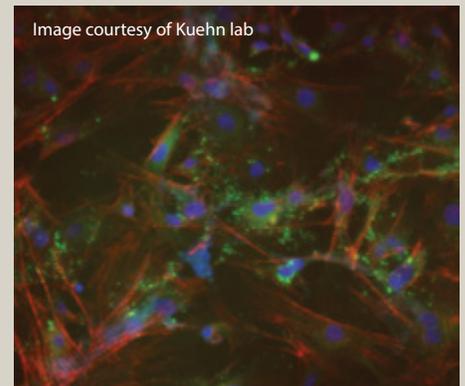


# RESEARCH CURRENTS

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

## Did you know?

January is National Glaucoma Awareness Month. Some 285,000 Veterans are affected by the condition. Researchers at the VA Center for the Prevention and Treatment of Visual Loss in Iowa City focus on the early detection of potential blinding disorders of the Veteran and general population, including glaucoma, retinal disease, and traumatic brain injury. They are also seeking new treatments. Recently, investigators with the center and the University of Iowa showed in lab experiments that an infusion of stem cells could help restore proper drainage for fluid-clogged eyes at risk for glaucoma. Learn more at [www.research.va.gov/currents/0716-5.cfm](http://www.research.va.gov/currents/0716-5.cfm).



This microscope image shows trabecular meshwork cells created from induced pluripotent stem cells in the lab of Dr. Markus Kuehn.



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Veterans Health Administration  
Office of Research and Development

VA Research Communications | 31 Hopkins Plaza, Ste. 102 | Baltimore, MD 21201  
[varesearchcurrents@va.gov](mailto:varesearchcurrents@va.gov) | 443-759-3456



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