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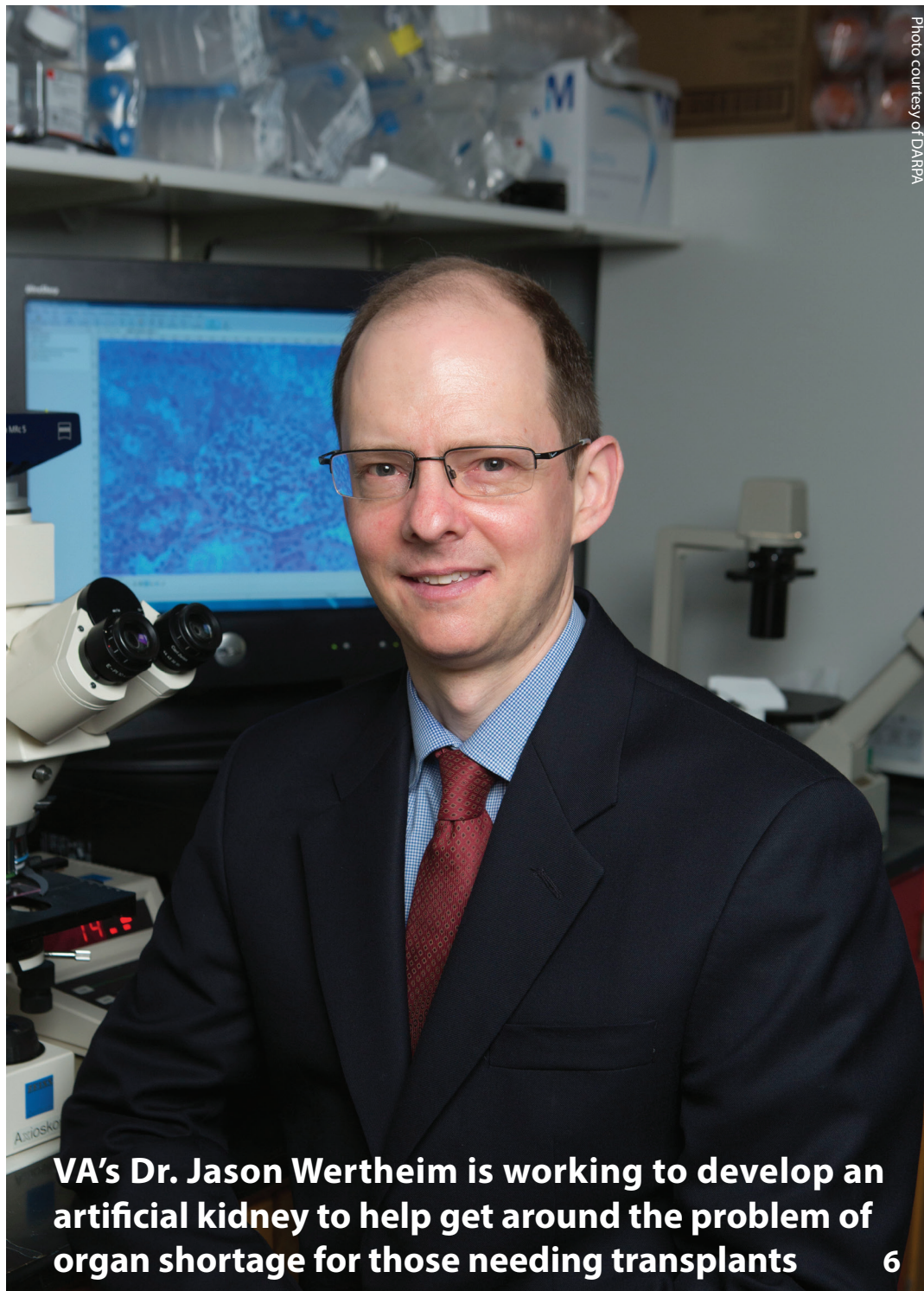


Photo courtesy of DARPA

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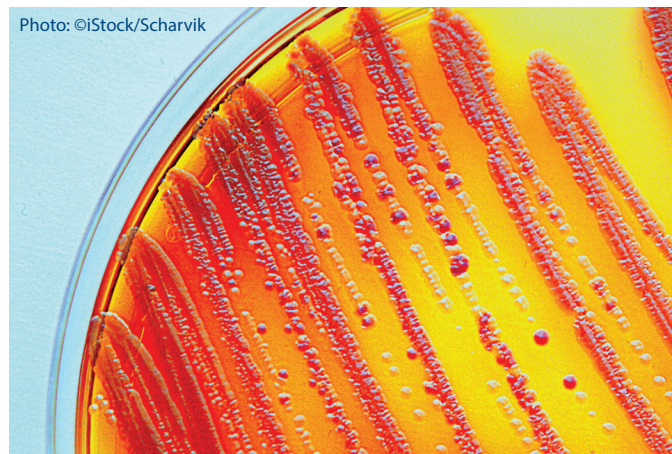
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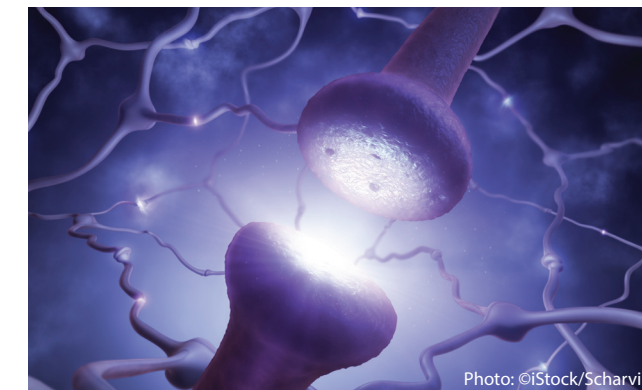
Drug-resistant bacteria on the rise in patients with spinal cord injury

Patients with spinal cord injury and related disorders are at an increased risk of drug-resistant bacterial infection, according to a study of 130 VA medical centers. Researchers found that more than a third of gram-negative bacterial infections found in patients over a nine-year period were drug-resistant. Over that period, drug-resistant strains of bacteria became increasingly common. Infections may be more common in spinal cord injury patients because of altered bodily function as a result of the injury. Infections may also be diagnosed later than usual because of the loss of sensation. Priority should be given to controlling the spread of resistant bacteria and studying epidemiologic trends in spinal cord injury patients, say the researchers. (*Journal of Spinal Cord Medicine*, Feb. 15, 2017)

Mapping brain activity in PTSD and mild TBI

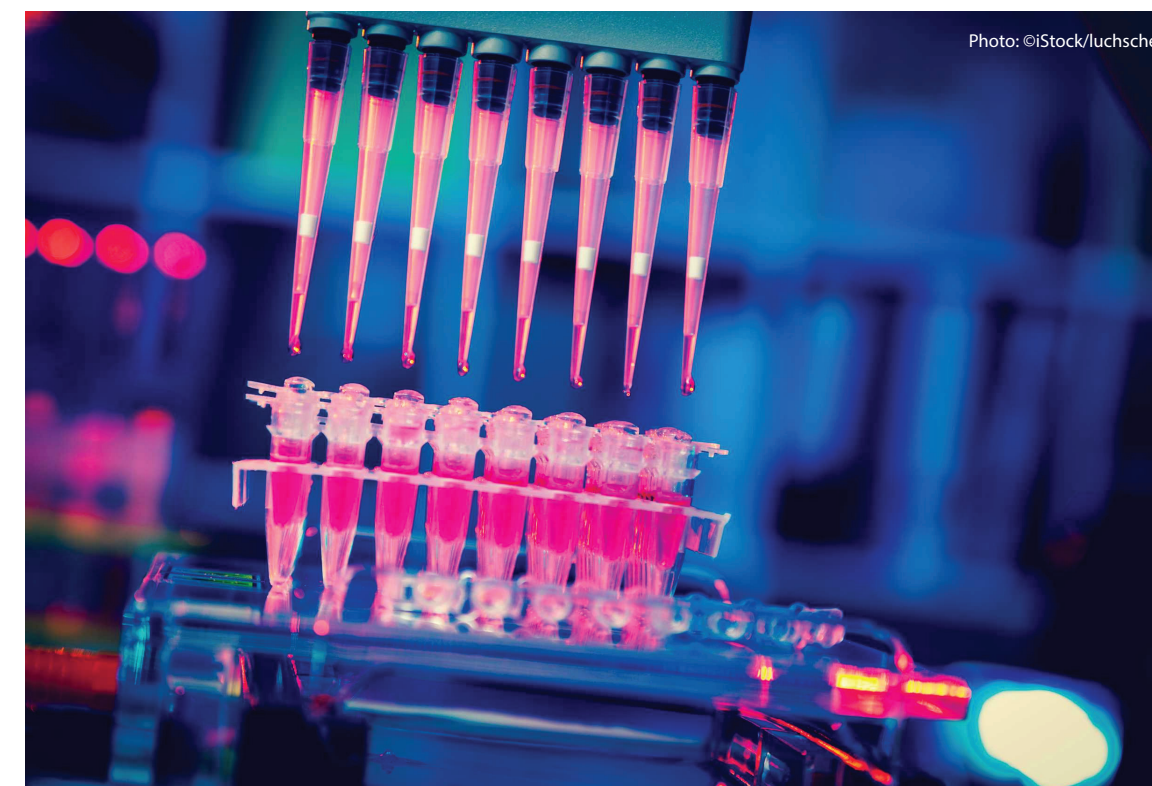
Researchers from two VA health care systems and their colleagues used a technique called magnetoencephalography to map activity in the brains of patients with PTSD and mild traumatic brain injury. Magnetoencephalography records the magnetic fields produced by electrical currents in the brain. The researchers found that alpha brain waves showed reductions in network structure — the

interconnected system of neurons within the brain — in PTSD. The scans also showed a shift in connectivity from alpha bandwidth electrical activity to theta bandwidth in both conditions. There was also increased randomness associated with PTSD and increased structure with traumatic brain injury. The study shows the potential of magnetoencephalography to analyze brain activity in these two conditions, and to distinguish between them when similar symptoms occur, say the researchers. (*Brain Connectivity*, February 2017)



Case study points to better strategy for monitoring liver cancer

A recent case study suggested that screening for liver cancer at the molecular level for high-risk patients could help manage the disease. The hepatitis C virus is a major risk factor for liver cancer. An international team including a researcher from the Iowa City VA Health Care System followed a patient with hepatitis C and liver cancer. The patient had three tumors treated and removed. He then achieved sustained virologic response — when the hepatitis C virus is not detected in the blood. The researchers then compared RNA molecules from the patient with samples from other patients with liver cancer and hepatitis C. The comparison showed that the patient was at high risk for the cancer to return. By screening for cancer more frequently, at three-month intervals, the care team was able to detect a liver lesion early and treat it. They say the molecular biomarker test could help with early cancer detection in the growing population of hepatitis C patients. (*Hepatology*)



New technique for artificial lung manufacturing

Researchers with the VA Ann Arbor Healthcare System have come up with a new way to manufacture microfluidic artificial lungs that may have applications for human patients. Artificial lungs have been used for years to supplement patients' breathing, and recent microfluidic artificial lung technology has shown potential for great improvement in function. But microfluidic artificial lung material is hard to scale large enough for human use. The researchers have found a way to assemble a lung structure through continuous "rolling" and bonding of a single, patterned layer

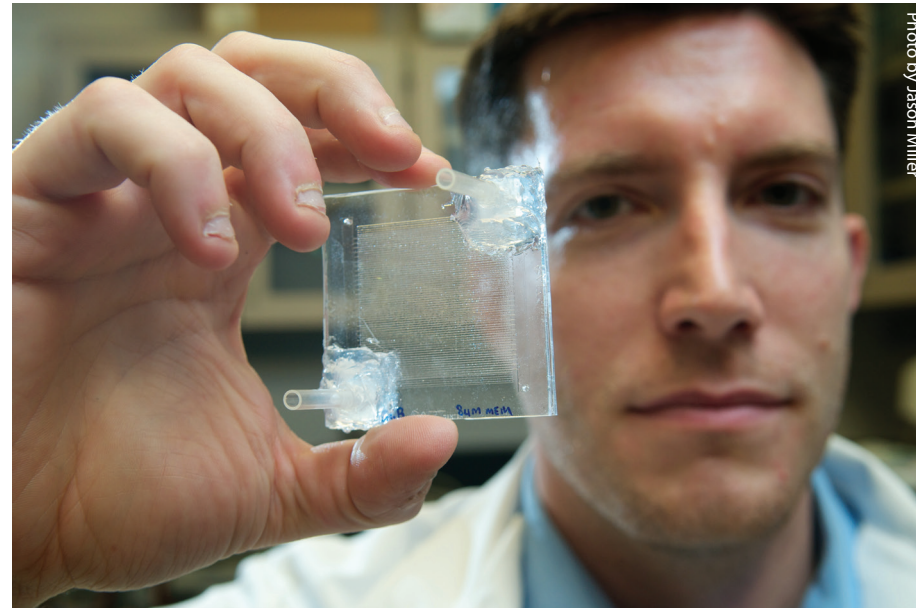


Photo by Jason Miller

A small-scale, rolled-membrane microfluidic artificial lung designed towards future large area manufacturing.

of polydimethyl siloxane. They expect that this technique will work to construct microfluidic artificial lungs large enough for human use. (*Biomicrofluidics*, April 2017)

Evaluation reveals areas for improvement in Veterans Choice Program

Researchers at the Louis Stokes Cleveland VA Medical Center used the Lean Six Sigma quality-improvement strategy to evaluate the Veterans Choice Program (VCP), which allows eligible VA-enrolled Veterans to get certain health services at non-VA sites in their communities. The study found that key issues to target for improvement included inefficient exchange of information between staff and patients, shortages of VCP-participating providers, appointment duplication, declines in care coordination, and lack of program adaptability. Using evaluations such as Lean Six Sigma could help identify further ways to improve the program, suggest the researchers. (*Medical Care*, April 13, 2017)



Photo © iStock/Sturiti

Bulk of VA testosterone use for off-label purposes

Only a small portion of testosterone prescriptions given in VA were for conditions for which testosterone has been approved by the FDA, according to a study of VA system data. The FDA approves testosterone only for diseases of the testis, pituitary, and hypothalamus. Yet only 6.3 percent of prescriptions in the VA were for these conditions over a five year period. The results show a need for more efforts to optimize testosterone-prescribing practices, say the researchers. They do note that there may be valid therapy reasons for off-label testosterone use. (*Journal of General Internal Medicine*, March 2017)

Many wet wipes contain potential allergens

Two studies by Minneapolis VA Medical Center researchers found that many commonly used wet wipes contain a high number of potential allergens. The researchers examined ingredient lists for 178 facial wipe and 54 personal hygiene wipe products. They found that a majority of wet wipes on the market contain ingredients that could cause allergic contact dermatitis. The most common potential allergens in both types of wipes were fragrances, botanicals, preservatives, and propylene glycol. Preservatives such as methylisothiazolinone are the ingredients most likely to cause contact dermatitis, according to an earlier study by the same researchers and their colleagues that involved more than 9,000 patch-tested patients. It is important to consider the ingredients in wet wipes when evaluating contact dermatitis, say the researchers. (*Dermatitis*, March 23, 2017)



Photo by April Ellers

Combination of two therapies may be effective treatment for those with PTSD and borderline personality disorder

A combination of dialectical behavior therapy and prolonged exposure therapy may be a safe and effective means of treating Veterans with both PTSD and borderline personality disorder, found a Minneapolis VA Health Care System study. Twenty-two Veterans underwent a 12-week intensive outpatient program combining the two treatments. After the treatment, 91 percent of participants showed a significant reduction in PTSD symptoms. Dysfunctional coping styles (e.g., self-harm) were also reduced, as was suicidal ideation. Patients with borderline personality disorder are often excluded from PTSD treatments out of concern for an increased suicide risk. Combining the two treatments shows promise for treating this difficult population, say the researchers. (*Journal of Traumatic Stress*, March 22, 2017)



Photo © iStock/Highwaystare-Photography

Dr. Wertheim holds a bioreactor that cultures cells that play a role in creating the artificial organ.

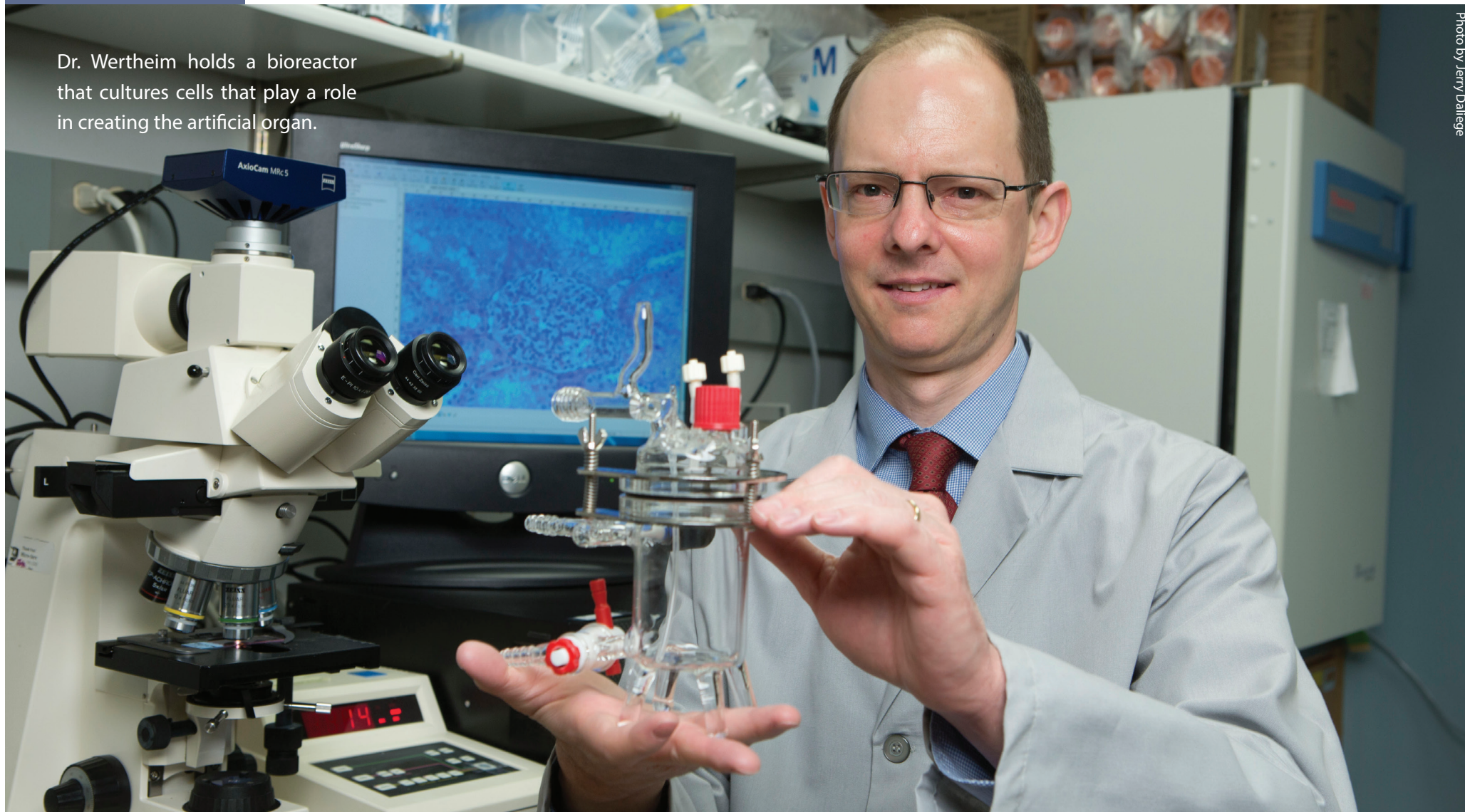


Photo by Jerry Dallage

VA surgeon researching cell-based tools to create artificial kidney

Dr. Jason Wertheim, a surgeon and biomedical engineer at the Jesse Brown VA Medical Center in Chicago, is leading a bioengineering effort to develop tissue for a replacement kidney and thus circumvent the problem of organ shortage.

Chronic or end-stage kidney failure is a serious health problem in the United States. Some 25 million adults, including many Veterans, have the disease. That means for the rest of their lives they may be on dialysis, the purification of blood as a substitute for a kidney's normal function, or they may receive a kidney transplant — in hopes of avoiding long-term health complications or even death.

Kidney transplantation has a much higher survival rate than dialysis over a five-year period. Despite such success, there aren't enough transplantable kidneys for every person with permanent loss of kidney function who gets cleared for a transplant. An estimated 100,000 patients with the condition, also known as end-stage

renal failure, are awaiting a kidney transplant in the U.S. Only about 18,000 such procedures take place each year.

Dr. Jason Wertheim, a surgeon and biomedical engineer at the Jesse Brown VA Medical Center in Chicago, sees many patients with permanent loss of kidney function. With an eye on the dearth of kidneys that are available for transplantation, he's researching ways to compensate for the loss of that organ. Among

other projects, he's leading a bioengineering effort to develop tissue for a replacement kidney and thus circumvent the problem of organ shortage.

The kidney, a critical organ, cleans blood by removing excess fluid, minerals, and wastes to make urine. Its inability to properly filter blood can cause a buildup of wastes, the hallmark of chronic kidney disease. Diabetes and high blood pressure are the top causes of kidney disease.

"Transplantation has been very successful in being able to give patients a new lease on life," Wertheim says. "And because organ transplantation is both life-saving and life-improving, patients that have end-stage disease need and want a transplant in many cases. But the quality of cadaveric organs that we get can change over time just based on demographics. Obesity is prevalent in our society, and that leads to livers that might have too much fat content in them. Hypertension can cause progressive kidney dysfunction. So not every organ offered for transplantation is usable. That's why we have more patients that need replacement organs and tissues than the number of donor tissues that are available. There's hope that one day in the future we can develop those tissues for patients who need it."

Kidney project part of NIH consortium

Wertheim is immersed in that effort. His bioengineering project calls for developing three-dimensional scaffolds that originate from animals to support nephron segments, the basic structural and functional units of the kidney, as templates for new cells. After their natural cells are removed, the scaffolds are repopulated with immature kidney cells. The hope is that they will multiply and grow into many adult kidney cell types.

The scaffolds, which contain proteins that give organs their structure, are "replicative of the natural environment of the kidney," Wertheim says. The scaffolds are intended to support the growth of tissue that will eventually become a new kidney.

The project is part of (Re) Building a Kidney (RBK), a consortium led by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) at the National Institutes of Health. The consortium, which includes about 25 biologists and engineers from around the country, is trying to develop tools that will facilitate development of an artificial kidney in the future. Its goals are to create and implement feasible strategies for engineering replacement kidney tissue, and to devise ways to stimulate regeneration of nephrons in their natural position to restore failing kidney function.

Continued on next page

Dr. Deborah Hoshizaki, program director of NIDDK's Division of Kidney, Urologic, and Hematologic Diseases, is director of the consortium, a five-year program that began in 2015.

"We're delighted to have Jason," she says. "He's meticulous, he's doing the right experiments, and he's a wonderful team player. There's added value not only for the consortium to have Jason on board — I think the consortium provides him with added value in terms of direct access to a lot of the expertise that will help move his project forward."

"There just aren't enough kidneys for transplant," she adds. "If we could get everyone to donate kidneys upon their death, that would help out a lot. But in the meantime, can we get a substitute for a donor kidney, and can we bioengineer the kidney? That's where Jason's work is coming together."

Wertheim, who also works on cell-based projects on liver and muscle regeneration and blood vessel development, has been involved in his kidney endeavor for five years. He's the consortium's only researcher with VA affiliation. He does his lab work at the Jesse Brown VA and at nearby Northwestern University, where he's a transplant surgeon and an assistant professor of surgery.

His project uses an extracellular matrix, a collection of fibrous material that holds cells together within tissues and organs. The matrix contains signals that drive cell differentiation, the process by which a cell becomes specialized in order to perform a specific function. The system serves as a model for nephron development within a full-scale kidney scaffold and sets the stage for further cell differentiation in a perfusion bioreactor, which cultures cells much longer than traditional laboratory-based cell culture. The ability to develop extracellular

scaffolds and to add back donor cells to the matrix allows researchers to analyze growth and maturation of the cells in three dimensions.

Figuring out where the cells should be

Here's the challenge: At least 20 different cell types make up a kidney. They would all need to be part of an engineered kidney that replicates the organ's natural functions. Knowing exactly where the cells must be within the engineered organ is tricky. Solving that equation is critical to someday taking a discarded human kidney and growing a replacement kidney with new cells.

"At this stage in the technology," Wertheim says, "we're first looking at how cells respond to the extracellular matrix, what the cells become, and how changes to the matrix can influence how they function."

Wertheim and his team have been experimenting with small animal models, mainly rodents. They remove the kidney from the animals and extract its native cells, leaving only the three-dimensional matrix that gives the kidney its structure, before repopulating the matrix with new cells. "Then through the vasculature [blood vessels in the organ], we can permeate the scaffold to spread the nutrients that support cell growth," Wertheim says. "The cells will grow within the three-dimensional scaffold."

Wertheim says focusing on small animal models has been beneficial "because we can observe how cells grow and interact with the matrix on a smaller scale." He and his colleagues have used some pig kidneys and are in the process of "scaling up" to experiment with larger animals more consistently. They've built many extracellular scaffolds, he says.

Hoshizaki: "The value of the approach that Jason's using is basically being able to take kidneys, in a sense discarded kidneys, being able to strip out

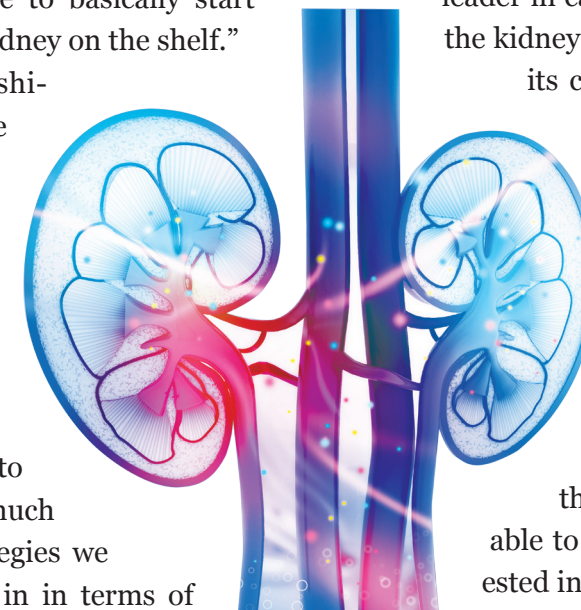
the cells, but still using the matrix that's left behind. He's then trying to rebuild a kidney with all of the right cell types to be able to basically start developing, in a sense, a kidney on the shelf."

Wertheim and Hoshizaki say it's premature to predict how long it will take to create an implantable and functional human kidney once the consortium wraps up. At the end of the five-year life of the consortium, according to Hoshizaki, "we'll have a much better idea of which strategies we should invest our money in in terms of creating a new kidney, but right now no one in the consortium knows what will work."

The consortium is trying to be critical in that regard and is "casting a broad net unlike a lot of other efforts," she says. "We don't know what's going to be the best strategy from a research standpoint that would provide us with more information to develop something that can be commercialized."

At the forefront of kidney replacement research

Wertheim isn't the first researcher in the scientific community who has used a naturally made scaffold for the purposes of building a tool to grow a replacement kidney. Still, his work is "innovative and unique," Hoshizaki says.



The kidneys clean blood by removing excess fluid, minerals, and wastes to make urine. (©iStock/HYWARDS)

"He's at the forefront of folks who are doing this," she says. "And I think it's fair to say that he's a leader in carrying out this approach, in taking the kidney from a small animal, stripping it of its cells, and using that as the scaffold for creating a new kidney."

She admires Wertheim's pragmatic approach.

"His project is one of the few [that are] taking a very systematic, perhaps not flashy, view of how we can start to populate these matrices," she says. "And I would say that that's one approach the consortium is interested in being able to advance the science. We are interested in the much more bioengineered type approach, which is one of several approaches we think could be valuable."

Wertheim is one of several researchers in the consortium who is working on developing scaffolds. The others are silk-based scaffolds, he says.

"We need to look at all different types of scaffolding materials," he says, "because the goal of the consortium, which is quite wide, is to try to tackle the problem from different angles. But really the out-of-the-box thinking is that maybe we could combine some of our natural materials with the synthetic structures that our collaborators are developing to make a hybrid approach. That shows synergy and collaboration within the group, and that's something that's going to be important as the field moves forward." ★



Photo by Michael Moody (test label seen in photo, with doctor name but no patient name)

Testosterone therapy: Is the verdict now in?

A landmark seven-part study funded by the U.S. National Institute on Aging called the Testosterone Trials (TTrials) has produced mixed results.

Testosterone treatment is a billion-dollar industry. But here's the million-dollar question: Is it worth the risk?

Studies have reached myriad conclusions on the pros and cons of testosterone therapy. It's used mostly by aging men with low testosterone levels — a condition called hypogonadism — but is exploited by others looking to stop the normal testosterone decline that's part of male aging and, in a sense, to relive their youth. Testosterone is a key male hormone that affects sex drive, bone mass, the production of red blood cells, and muscle size and strength.

Now, a landmark seven-part series funded by the U.S. National Institute on Aging called the Testosterone Trials (TTrials) has produced mixed results. It found that testosterone treatment increased bone density and corrected anemia, a condition that develops when one's blood lacks enough healthy red blood cells, or hemoglobin.

But the treatment also failed to improve memory in men with age-associated memory problems, and it increased the volume of noncalcified plaque in blood vessels supplying the heart, or coronary arteries.

Plaque buildup can cause arteries to narrow, leading to heart disease, heart attack, or stroke.

The TTrials were published in five separate papers. One of the papers, which included results from three of the studies, appeared in the *New England Journal of Medicine* in February 2016. The other four papers appeared in either the *Journal of the American Medical Association (JAMA)* or *JAMA Internal Medicine* in February 2017.

The TTrials amounted to the largest study ever of testosterone treatment in older men, based on the number who participated (788). The placebo-controlled study was designed to provide definitive answers about the short-term benefits and risks of testosterone treatment, while addressing the limitations of prior studies. Those limitations included small numbers of men studied, the inclusion of men with normal testosterone levels, the use of too little or too much testosterone, a short treatment period, and nonvalidated outcome measurements.

New answers on short-term benefits

TTrials co-author Dr. Alvin Matsumoto, an endocrinologist and geriatrician in the Geriatric Research, Education, and Clinical Center at the VA Puget Sound Healthcare System in Seattle, acknowledges the mixed results. But he says the research still provides new and more definitive answers on the short-term or lack of benefits of testosterone treatment in older men. The studies included 788 symptomatic men age 65 and older with clearly and consistently low testosterone levels for no apparent reason other than age.

“The TTrials was a landmark study,” he says. “But it was too small a study, and the duration of the testosterone treatment was too short to provide answers regarding longer-term clinical benefits and risks related to, for instance, bone fractures, prostate cancer, or cardiovascular events such as heart attack and stroke. A larger and longer study is needed to

know the impact of testosterone treatment on those health issues.”

Dr. Rajat Barua, director of cardiovascular research at the Kansas City VA Medical Center, says he finds nothing surprising in the results of the TTrials. He agrees that larger, long-term studies are needed to reach definitive answers on the risks of testosterone therapy. Barua did not participate in the TTrials. But he's the author of past studies on testosterone treatment in relation to Veterans and is also involved in ongoing research on the topic.

“Plaque growth alone is not an indication of heart attacks and stroke,” he says. “Plaque growth may cause symptoms of angina [severe chest pain caused by an inadequate blood supply to the heart], but not necessarily events such as heart attacks that lead to death.”

According to Matsumoto, the TTrials were the culmination of about 20 years of work that began with a proposal put forth by him and Dr. Glenn Cunningham, a former VA researcher and co-author of the TTrials, for a six-year randomized, controlled trial involving 6,000 men at least 65 years old. The proposal was part of a collaboration between the VA Cooperative Studies Program, which is responsible for planning and conducting large clinical trials and epidemiological studies in VA, and the National Institute on Aging.

But the Efficacy and Safety of Testosterone in Elderly Men (ESTEEM) trial, which was to examine the potential effects of testosterone treatment mainly on bone fractures, but also sexual function, memory, vitality, prostate cancer, and cardiovascular events, never took off because of a lack of funding. Subsequently, the Institute of Medicine (now called the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine), a non-governmental group that provides research and recommendations on public health and science policy, called for a coordinated set of studies with the belief that the short-term benefits

Continued on next page

of testosterone needed to be set before researchers pursued long-term studies, hence the TTrials.

Participants in the TTrials received a testosterone gel or placebo gel on the skin daily for one year. Levels of testosterone were measured at one, two, three, six, nine, and 12 months, with an extra year of follow-up. In addition to signs of androgen deficiency, or lower levels of male sex hormones, particularly testosterone, the presence of complaints such as reduced sexual desire, difficulty in walking, or low energy were a prerequisite for participation.

“This was not an overly healthy group of individuals,” Matsumoto says. “But I can’t say they were high-risk, either. They were chosen with low prostate cancer risk, but I can’t say they had high cardiovascular risk.”

Plaque increase in participants ‘concerning’

The researchers studied blood counts, bone density, plaque levels in the coronary arteries, and memory. The participants were also monitored for risk of prostate cancer, with the testosterone group showing more men with a PSA, the measurement used to assess the risk of prostate cancer, greater than 1.0. “That reading triggered a urology referral,” Matsumoto says. “But a one-year study can’t answer the question of prostate cancer risk.”

Those in the testosterone group saw improvements in sexual function, mood and depression symptoms, bone mineral density and strength, and anemia. The bone improvements were in the trabecular bone, tissue found at the ends of long bones and in the pelvic bones, ribs, skull, and vertebrae in the spinal column. The treatment helped correct anemia, whether caused by low iron or an unidentifiable factor. The anemia “increases may be of clinical value ... but the overall health benefits remain to be established,” the researchers write.

“As in all therapeutic decisions, the decision to treat should be based on the balance of benefits versus risks of therapy”

But the drug didn’t improve energy, walking distance, or cognitive function in men with age-related memory loss, and it increased the amount of noncalcified plaque in blood vessels supplying the heart. None of the men in the testosterone group or the placebo group were reported to have a major cardiovascular event. “The plaque increase is concerning,” Matsomoto says, “but the clinical importance of this finding is unknown and may depend on different types of plaque in the coronary arteries.”

Matsumoto has treated younger men with low testosterone levels due to disorders of the testicles, pituitary gland, or brain, a form of hypogonadism. They have improved in many of the outcomes measured in the TTrials when treated with testosterone, he says.

For that reason, he wasn’t too surprised to see the improvements in sexual function, mood, depression, bone density, and anemia in the TTrials, but he says it’s a bit surprising the treatment didn’t improve energy. However, he notes, the signs of low testosterone among the participants were “non-specific” and can be caused by other chronic conditions



Veteran Ron Deluca receives a prescription from pharmacy technician Patrick Malloy at the VA Pittsburgh Healthcare System.

related to aging, such as obesity and diabetes, that don’t improve with testosterone treatment.

Mixed results in VA studies on cardiovascular impact

In relation to the Veteran community, which likely has higher levels of chronic illness and obesity and uses more medications that can lower male testosterone levels, compared with the general population, Matsumoto says, two prior VA studies produced mixed results.

A 2013 study found that men with heart problems may be at greater risk of heart attack, stroke, or even death if they receive testosterone therapy. More than 1,200 Veterans took the therapy through gels, patches, or injections. At three years and after the researchers adjusted for many naturally associated medical conditions, 26 percent of the men had died or suffered a heart attack or stroke, compared with 20 percent who didn’t receive the therapy. Before adjustment, there were fewer cardiovascular events in testosterone-treated men.

A 2015 database study led by Barua of more than 83,000 patients found that men whose low testosterone was restored to normal through gels, patches, or injections had a lower risk of heart attack, stroke, or death from any cause, versus similar men who were not treated. The study excluded men with a history of heart attacks or strokes, but it included those with existing heart disease.

Matsumoto cautions that those were “observational studies that only provide clues to the presence or absence of safety signals,” instead of more definitive studies like the TTrials. “In contrast to a randomized, controlled trial, observational types of studies are susceptible to confounding influences, so you can’t be sure that men treated with testosterone are similar to those not treated with testosterone, for instance, with regard to cardiovascular risk. There have been plenty of suggestions that observational

studies are very, very useful in hypothesis generation and figuring out what you want to study and how you want to study it. But by and large, they can’t be [relied upon alone] to practice medicine.”

Based in part on available evidence from published studies, the U.S. Food and Drug Administration (FDA) concluded there is a possible increased cardiovascular risk linked to testosterone use. As a result, the watchdog agency mandated pharmaceutical companies to pursue a randomized, controlled clinical study to more clearly address the question of whether testosterone users are at increased risk of heart attack or stroke. The trial is expected to start sometime in the coming months. The FDA also required drug makers to include warnings on labels about a possible increased risk of heart attack and stroke in men taking testosterone.

Testosterone is FDA-approved as a replacement therapy only for men who have low testosterone levels due to disorders of the testicles, pituitary gland, or brain.

Meanwhile, with the full verdict not in yet, what’s a man to do? How should men who could potentially benefit from testosterone treatment weigh its pluses and minuses?

“As in all therapeutic decisions, the decision to treat should be based on the balance of benefits versus risks of therapy,” Matsumoto says. “Because long-term benefits and risks of testosterone therapy in older men are not known, the decision to treat with testosterone should be preceded by an informed-consent-like discussion of short-term benefits and risks, all of which were addressed in the TTrials, and the absence of information about the long-term benefits and risks. The discussion should consider patient-centered goals, the presence and treatment of associated chronic medical conditions, and medications that could contribute to symptoms and low testosterone levels.” ★



Dr. Huisheng Xie, director of the Chi Institute of Traditional Chinese Veterinary Medicine in Florida, trains students in administering electroacupuncture to a horse. He collaborated with VA's Dr. Fletcher White and others on a study of the therapy's mechanisms. (Photo: ©Chi Institute/2016-2017)

Study: Electroacupuncture eases pain through stem-cell release

Research involving an international team has generated new scientific insight into how acupuncture works in the body.

A series of tests involving humans, horses, and rodents has provided the most thorough picture yet of how electroacupuncture—a modern version of the ancient Chinese healing art—eases pain and promotes tissue repair. The study included a VA researcher and more than 40 other clinicians and scientists

The findings, by researchers at several institutions in the U.S. and South Korea, appeared online March 16 in the journal *Stem Cells*.

“We have discovered a mechanism which explains the benefits of electroacupuncture for treatment of injury-induced pain, and for tissue regeneration,” said Dr. Fletcher A. White, one of more than 40 authors who contributed to the work.

The key finding was that electroacupuncture triggers the release of mesenchymal stem cells (MSCs) into the bloodstream. These are adult stem cells found mainly in the bone marrow. The hardy cells, which multiply easily and turn into various tissue types in the body, are being widely studied for their healing potential.

Mechanism involves brain's hypothalamus

The research was the culmination of efforts by four senior authors: Dr. Maria B. Grant, a professor of ophthalmology at Indiana University, began the work with Dr. Huisheng Xie, director of the Florida-based Chi Institute of Traditional Chinese Veterinary Medicine, in 2011 at the University of Florida. The work continued at Indiana University with the support of Dr. Mervin Yoder, director of the Herman B. Wells Center for Pediatric Research, and White, a neuroscientist at the Richard L. Roudebush VA Medical Center in Indianapolis, and a professor of anesthesia and pharmacology at Indiana University School of Medicine.

The study involved functional brain scans, blood tests, artery imaging, gene sequencing, and other lab methods. The researchers were able to trace electroacupuncture's actions on the brain and nervous system, resulting in the release of MSCs. The researchers believe the cells may be responsible for a range of therapeutic effects, such as the release of proteins that quell inflammation, and of the body's own natural opioids.

“We have discovered a mechanism which explains the benefits of electroacupuncture for treatment of injury-induced pain, and for tissue regeneration.”

The main brain region affected was the hypothalamus, which controls the body's autonomic nervous system. This system works on an involuntary and reflexive basis, without our conscious thought, to regulate heart rate, blood pressure, digestion, and many other body functions.

In the study, functional MRI scans, which track blood flow in the brain, showed increased connectivity between the hypothalamus and the amygdala, the brain's emotion center.

“We have discovered a mechanism which explains the benefits of electroacupuncture for treatment of injury-induced pain, and for tissue regeneration.”

The study showed how stimulating the peripheral nervous system with needles leads to “rapid activation of the hypothalamus,” according to White. This happened within 9 to 22 minutes, depending on the species. And then, within two hours, MSCs surged within the bloodstream.

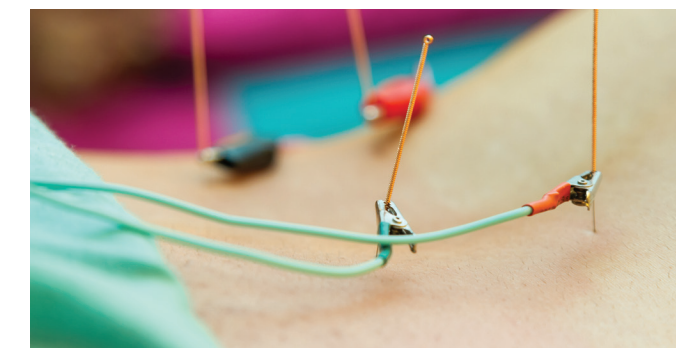
Findings complement existing theories on acupuncture

Previous studies have suggested various theories for how acupuncture works, at least for pain. These have focused on the release of neurotransmitters, neuropeptides, and immune signaling proteins, or cytokines, in the central nervous system, and endogenous opioids into inflamed tissue.

The new findings don't necessarily contradict any of these theories, but add new insight, relating to the role of MSCs in the pain-relief process.

The downstream effects of MSCs are being studied further in the lab, says White. He believes they can be harnessed as a therapeutic tool in their own right.

To that end, a study is set to begin this spring at the University of Florida on using electroacupuncture-mobilized cells for treating acute tendon



Electroacupuncture uses the same points on the body as traditional acupuncture but relies on small electrical currents, in addition to the needles themselves, for stimulation.

Continued on next page

injuries in horses. The study will harvest the MSCs mobilized into the blood and expand them “ex vivo,” or in culture in the lab. The aim is to get the cells to multiply without changing their properties. The researchers will then inject them back into the injured horses. The team hopes their findings will lead to FDA approval of the treatment for horses. Meanwhile, Grant and Yoder are pursuing the same approach in human studies.

The benefits of acupuncture — including the electric form — are well accepted, even in mainstream medicine, for pain and some other conditions. Like traditional acupuncture, electroacupuncture involves inserting needles into the body to stimulate certain points, as described in traditional Chinese medicine. But with the electric version, the stimulation comes from a small current, not just from the needle. A similar technique, called transcutaneous electrical nerve stimulation, or TENS, supplies a current from electrodes taped to the skin.

Conventionally, TENS has been applied specifically to the injury site. More recently, clinicians are using it on traditional acupuncture points, as a needle-free form of electroacupuncture. Either way, White and his colleagues believe it, too, has the potential to trigger the release of MSCs, and that this may help explain its therapeutic action.

Different points trigger release of different reparative cells

In some of the experiments, when the researchers stimulated a different set of points, the result was a release not of MSCs but of immune cells resembling macrophages. The name is Greek for “big eaters,”

and these immune cells gobble up pathogens.

“Based on traditional medicine, different immune points in humans will activate the immune system in different ways,” explained White. “We are conducting additional experiments to better understand the release of specific cell types.”

Importantly, the results from stimulation — whether the release of MSCs, or macrophage-life cells — were consistent across humans, horses, rats, and mice.

“While the effect of EA on analgesia [pain relief] is well-accepted, until now the effect of EA on the release of reparative cell populations was largely unknown,” wrote the study team in their paper. “Of equal importance is that the effect of EA is uniform across four species.”

The horses used in the study had been injured during training for national dressage competitions. Veterinarians often use electroacupuncture as a treatment option, says White.

The six people who took part in the study were healthy volunteers. Even though they weren’t in pain, images of their brain still showed the effects of the electroacupuncture treatment — namely, the activation of the hypothalamus and increased blood flow between it and the amygdala.

According to the study authors, it’s unclear whether the exact same effects would be seen with standard acupuncture. That would require more research.

The study was funded mainly by the National Institutes of Health. ★

VA-Defense study aims to track mild TBI over decades

An ambitious federally funded study is enrolling at least 1,100 service members and Veterans who fought in Iraq or Afghanistan to learn more about mild traumatic brain injury (TBI) and how it can be best evaluated, and perhaps prevented and treated. Though ongoing funding is not guaranteed, the researchers hope to follow the cohort 20 years or more to better understand the long-term neurologic effects of mild TBI and other deployment-related conditions.

The research group reported recently on the first stages of the study in the journal *Brain Injury*. As of today, more than 700 volunteers are participating.

About 80 percent of those being enrolled have a history of at least one mild TBI, while the others have no TBIs. That will allow the researchers to compare the two groups. The focus is strictly on mild TBI; those with more severe brain injuries are excluded.

The study is under the auspices of the Chronic Effects of Neurotrauma Consortium (CENC), one of two consortia funded through the National Research Action Plan in 2013. The other consortium focuses on PTSD — like mild TBI, a “signature” injury of the wars in Iraq and Afghanistan. Both efforts combined received \$107 million in funding. They involve broad collaborations of researchers from VA, the Department of Defense, other federal agencies, and academia.

Among the most rigorous TBI studies to date

Leading the new study is Dr. William Walker, a TBI expert at the Richmond VA Medical Center and Virginia Commonwealth University, where CENC is based. He says the long-term observational study is one of the most comprehensive TBI projects to date in terms of size, scope, and rigor.

“The cornerstone of this study is that we’re doing a very intensive standardized interview to get at all of the lifetime potential concussive events,” he says. “Many of these individuals have had multiple

concussions throughout their lifetimes. We’re looking at it from an epidemiologic standpoint of lifetime exposures.”

At the core is an in-depth interview that study volunteers undergo at the outset. It’s like a thorough medical history, but with a focus on head injuries.

In other words, the research team wants to know not only about any mild TBIs that may have occurred in combat zones, but also those that may have occurred earlier in life, or perhaps after military service. Walker’s group is using a specialized interview they developed in earlier research.

“We’ve built on that and fine-tuned it,” says Walker. “And we’re deploying it in this study in a larger way. We’re mapping their entire lifetime, to look at whatever head impacts [they can recall], whether as a child falling off a swing set and hitting their head, or an automobile accident with a whiplash injury, or a military deployment with a blast that went off nearby. We’re cataloging each of these potential concussive events, and then we take each one and do a diagnostic interview to determine whether it was in fact a TBI.”

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



A U.S. Army soldier heads back to base after a patrol in Afghanistan’s Logar province in 2010. (Department of Defense photo)



Photo: ©iStock/Solange Z

Probing the value of peer mentors for homeless Veterans

A recently published VA study explored the role of peer mentors — in this case, Veterans who were once homeless themselves — in improving the health outcomes of currently homeless Veterans.

Nearly a decade ago, the White House and VA announced an ambitious plan to end Veteran homelessness. VA, in collaboration with state and local officials, has since led a series of initiatives that have helped fuel a precipitous decline in the number of former U.S. service members who are homeless.

Still, about 40,000 Veterans experience homelessness on a given night. They need as much support and guidance as possible to understand what's available through the VA health care system and to learn about job, educational, and housing opportunities.

Now, a new VA study explores whether a peer mentor — in this case a Vet who was once homeless — can play an important role in a homeless Veteran's life. The study, published online in February 2017 in *Psychiatric Services*, suggests that many homeless Vets will “engage with peer mentors, who may provide psychosocial support that can complement traditional health care encounters. Peer mentors may serve a key role in building trust between patients and providers to foster engagement with the health care system.”

“The idea was that formerly homeless Veterans had to deal with similar problems and have successfully

navigated the VA system, so they would be good resources for new Veteran patients,” says lead author Dr. Jean Yoon, a health economist at the VA Palo Alto Health Care System in California. “If homeless Veterans can engage with their providers and receive the care they need, they ultimately can have improved health outcomes.”

According to Yoon, the study's main goal was to help homeless Veterans better engage with their VA providers, since mutual trust can be lacking, and to increase primary care and other kinds of outpatient visits. But in that respect she and her team failed to detect a notable difference between the two cohorts, homeless Vets who met with a peer mentor and those who didn't, partly because of a relatively small sample size, she says.

Larger study needed to further assess peer mentors

Patients in the peer mentor group averaged 5.1 primary care visits in the six-month study period, compared with 4.4 for the non-peer cohort. Also, health care costs that included doctor visits and prescriptions were similar: \$18,919 for the peer mentor group and \$17,483 for the other cohort. “If the peer mentor was able to reduce acute care [emergency department visits and hospital

stays] in that group, we would expect those patients to have lower costs overall,” Yoon says. “We didn't find that in our study, but that's one thing we wanted to look at.”

She adds: “We were trying to examine what the effect of the peer

“I saw [the peer] as a facilitator and a person that had information that I needed to help me get back to being a positive member of society again.”

mentors would be. We weren't able to find a significant effect on increasing outpatient visits or decreasing acute care, although the slight difference suggests there could be a potential benefit in terms of engaging with providers. It could be worthwhile to test the effect of peer mentors with a larger sample of patients and longer follow-up periods, to determine whether the mentors can increase use of outpatient care and reduce use of acute care to improve care overall.”

The study was part of a larger ongoing project that is looking at homeless Vets as a population in relation to medical home development, a model designed around improving access to care. The four-part umbrella study is led by Dr. Thomas O'Toole, director of VA's National Center on Homelessness among Veterans (the Center) and

a co-author of Yoon's substudy. His research team is interested in finding feasible, innovative solutions to the poor health outcomes of homeless Vets by bridging gaps that sometimes exist between them and their VA providers.

“VA offers many programs and services that can benefit homeless Veterans, who may not be aware of these services or may not be sure how they can access them,” Yoon says. “A peer intervention with-

in primary care appeared to be a novel approach to helping these Vets.”

The value of peers has been tested in other VA clinical settings, specifically mental health and addiction care. But this is the first time, Yoon says, a peer mentor program was tested with VA homeless patients in primary care.

Her study included homeless patients at four VA clinics. Homeless meant someone was unsheltered, stayed in an emergency shelter or in time-limited transitional housing, or lived in an unstable setting with family or friends. Nearly all of the patients were men, and more than 80 percent had at least one mental health condition, such as depression or anxiety. “Since having a mental health condition can make managing chronic physical health conditions more challenging, these Veterans often have poor

Continued on next page

health status,” Yoon says. Plus, 95 percent were not married, highlighting the lack of social support many homeless people experience, she says.

Of the patients, 195 were randomly assigned to two different VA medical home models that included a peer mentor, and 180 to the same models without a peer mentor. Two of the VA sites used a model called the Patient Aligned Care Team (PACT), and the other two used the Homeless Patient Aligned Care Team (H-PACT) model. PACTs are intended, in part, to provide superb access to primary care for Veterans and regularly integrate general medical and behavioral staff members. In addition to such integration, H-PACT sites provide services for homeless Veterans such as aid with housing, food, and chronic disease management needs, and connections to social services and community resources.

“Homeless patients may do better in H-PACT sites since we found that they have lower overall health care costs, including some types of emergency care, compared with homeless patients in PACTs,” Yoon says. “However, the peer mentor intervention did not seem to be more effective in one setting versus the other.”

Peer mentors brighten outlook for homeless Vets

Patients in the peer mentor group were assigned a mentor over a six-month period, in addition to usual primary care from their PACT and H-PACT clinical teams. The mentors, former homeless Vets with extensive experience in VA health care services, served as role models, assisted Veterans in articulating goals and needs, taught problem-solving techniques, and helped in understanding VA’s health care system and VA benefits. They also reminded patients about medical appointments. “These discussions may have helped improve patients’ relationships with their VA providers,” Yoon says.

The plan called for the Vets to meet with their mentors twice a week for the first month, once a week during months two to four, and once every two weeks in the last two months. Many of the Veterans

held true to the plan, but some had minimal contact with their peers, Yoon says.

The study failed to detect any major impacts of peer mentors on health care patterns or costs. But in another subset of the umbrella study, 83 percent of homeless Veterans said they benefited from visits with a peer mentor. African-American Veterans were more likely to benefit, and Veterans with PTSD were less likely to benefit. Some patients in that subset were quoted as saying:

- “I come in with [the peer], and we talk, and he’s telling me how to do things: ‘This is what you need to do, leave the other stuff alone, don’t worry about it.’ We would talk like brothers and stuff.”
- “I saw [the peer] as a facilitator and a person that had information that I needed to help me get back to being a positive member of society again.”
- “I think [the peer] gave me a better outlook because I was negative when I came here. [The peer] was resourceful. He helped me out with clothing, bus tokens. When I was trying to get a job, he would take me. He would drive me to the places I needed to go. He would help me out with the paperwork. He helped me a lot.”

As Yoon and her colleagues see it, all of this research appears critical to the fate of homeless Veterans, who were once overrepresented in the homeless population. The number of homeless Veterans stood at 400,000 nearly two decades ago, but has plummeted since former VA Secretary Eric Shinseki unveiled in 2009 a comprehensive plan to end Veteran homelessness by 2015. That plan led to innovations such as H-PACTs.

“While the root causes of homelessness remain, and some Veterans will continue to be at risk for and possibly become homeless, we hope that with the continued support of these initiatives and rigorous evaluation of what works and why, we will see more communities and states able to end Veteran homelessness,” O’Toole says. ★

What happens when patients access their mental health providers’ notes?



Dr. Steven Dobscha directs the Center to Improve Veteran Involvement in Care, based at the VA Portland Health Care System. His team has been exploring the use of OpenNotes in mental health care. (Photo by Michael Moody)

Thanks to electronic health records and online portals, more and more patients are being given access to the notes their clinicians write about their health care visits. Research suggests this national movement, known as “OpenNotes,” can empower patients and boost communication and shared decision-making. But what about mental health visits? Experts have been unsure whether this area is equally likely to benefit.

Now, a small study from one Veterans Affairs medical center offers insight into the potential for OpenNotes to help — or hurt — patients’ trust in their mental health clinicians.

“We found that reading mental health notes may strengthen as well as strain patient-clinician relationships by enhancing or undermining trust,” wrote the authors in a report posted online Feb. 1, 2017, in *Psychiatric Services*.

The study was led by a group from the Center to Improve Veteran Involvement in Care (CIVIC), at

the VA Portland Health Care System in Oregon. VA has been studying the benefits and risks of OpenNotes and other pilot features in VA’s MyHealtheVet patient portal. VA became one of the first health systems in the nation to offer OpenNotes access, in 2013. Patients access their notes through the Blue Button feature in MyHealtheVet.

The new study involved interviews with 28 patients. The group included male and female Veterans of various ages, with diagnoses ranging from depression and PTSD to bipolar disorder and schizophrenia. Patients in the study were being treated by psychiatrists, psychologists, and other mental health therapists.

Transparency fosters trust

Among the positive themes that emerged in the interviews:

- Patients appreciated seeing consistency between what had occurred during their appointments and what they later viewed in the clinical notes. Such transparency was important in fostering trust. They liked it, for example, when their clinicians had openly and directly discussed a diagnosis with them before documenting it in the record.
- They felt respected, and reported greater trust, when the notes showed evidence that their clinicians had truly listened to and understood their personal stories, and had taken note of their individual strengths. One patient said he felt he was “not just a repeat from the last PTSD person [the clinician] talked to, but an individual with PTSD.”

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

KEY FINDINGS



Dr. Sanjay Asthana studies Alzheimer's disease at the Geriatric, Research, Education, and Clinical Center at the William S. Middleton Memorial Veterans Hospital in Madison, Wisconsin. (Photo by Donald Lewis)

Study points to myelin changes as early marker of Alzheimer's

A VA study suggests that changes in myelin, a fatty white substance in the central nervous system that surrounds nerve fibers, may be a very early sign of Alzheimer's disease.

Dr. Sanjay Asthana, a VA clinician and researcher who specializes in gerontology and geriatrics, recently co-authored a study that points to a possible preclinical biomarker in the progression of Alzheimer's. The study, published in January 2017 in *JAMA Neurology*, suggests that early risk factors for developing the disease are linked to changes in myelin, a fatty white substance in the central nervous system that surrounds nerve fibers and ensures that electrical signals between neurons move quickly.

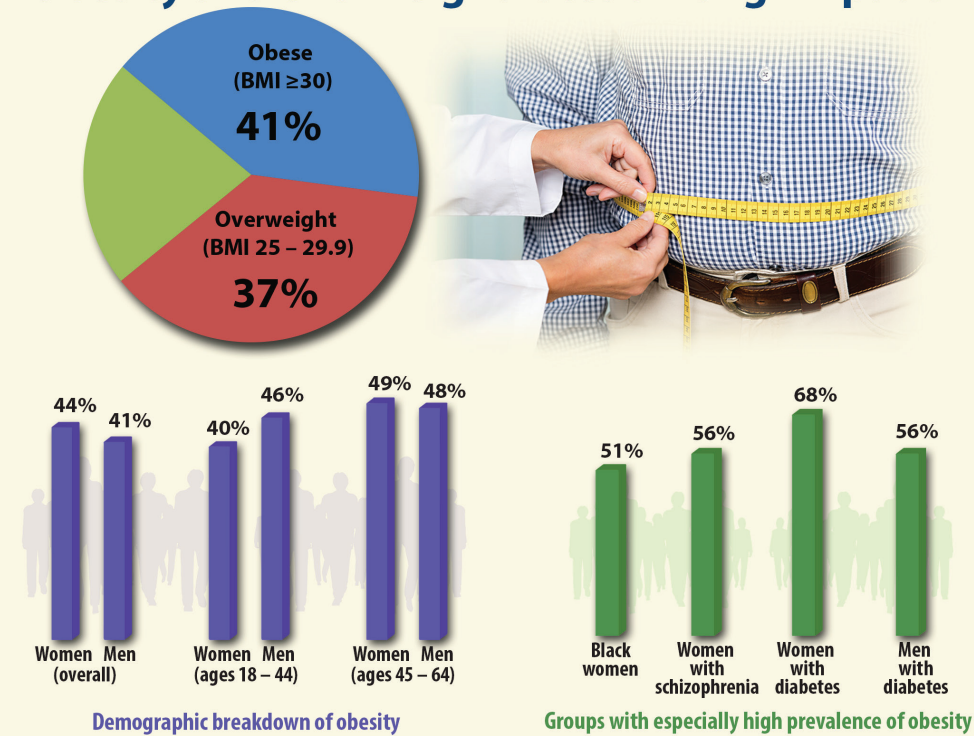
Myelin changes in Alzheimer's are suspected by many researchers but have been understudied in humans. Tissue consisting of myelinated fibers is called white matter.

"The results from this paper suggest that those changes may play a key role in the onset of the disease," says Asthana, head of the Geriatric, Research, Education, and Clinical Center at the William S. Middleton Memorial Veterans Hospital in Madison, Wisconsin.

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

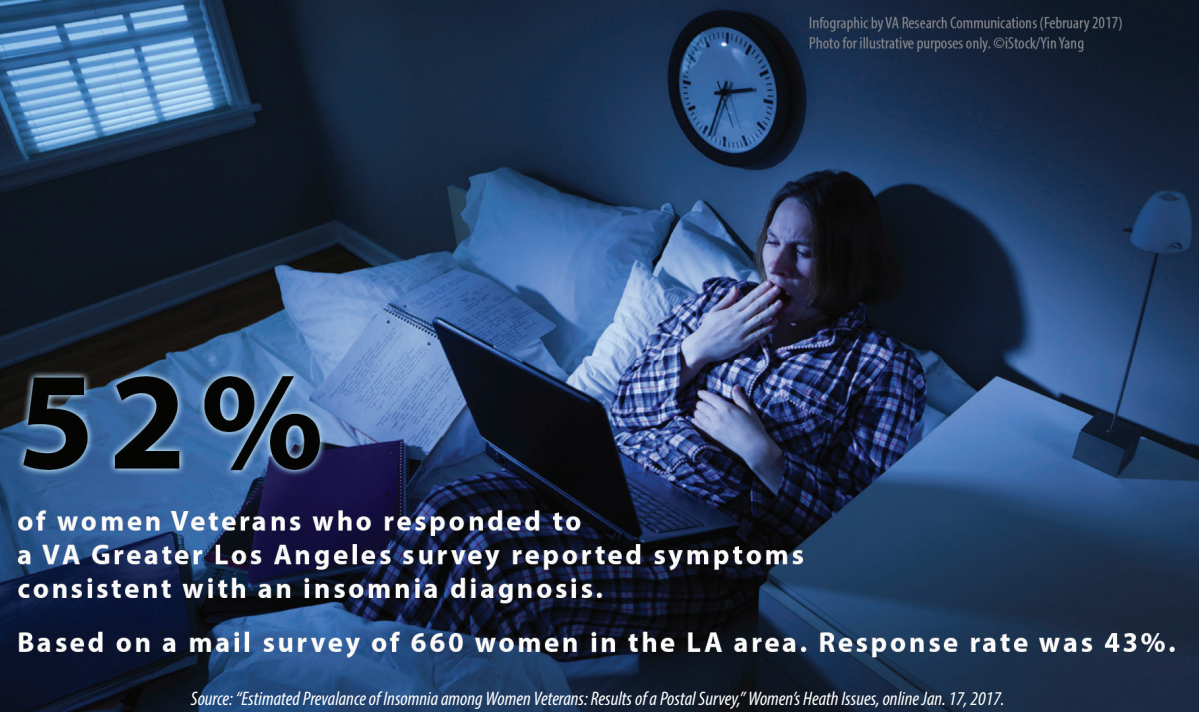
INFOGRAPHS

Obesity and overweight rates among VA patients



Source: "The Obesity Epidemic in the Veterans Health Administration: Prevalence Among Key Populations of Women and Men Veterans." Based on data on nearly 5 million Veterans Health Administration patients in 2014. JGIM, online March 7, 2017. Infograph by VA Research Communications, March 2017 (Photo ©iStock/FredFroese)

Insomnia among women Veterans



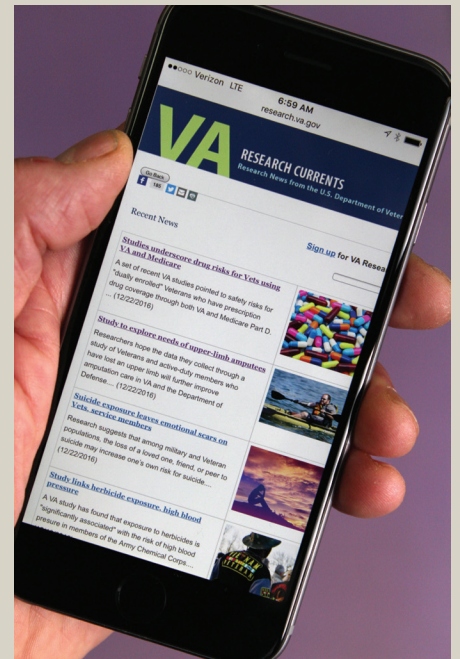


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