FALL 2014

VA RESEARCH CURRENTS

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

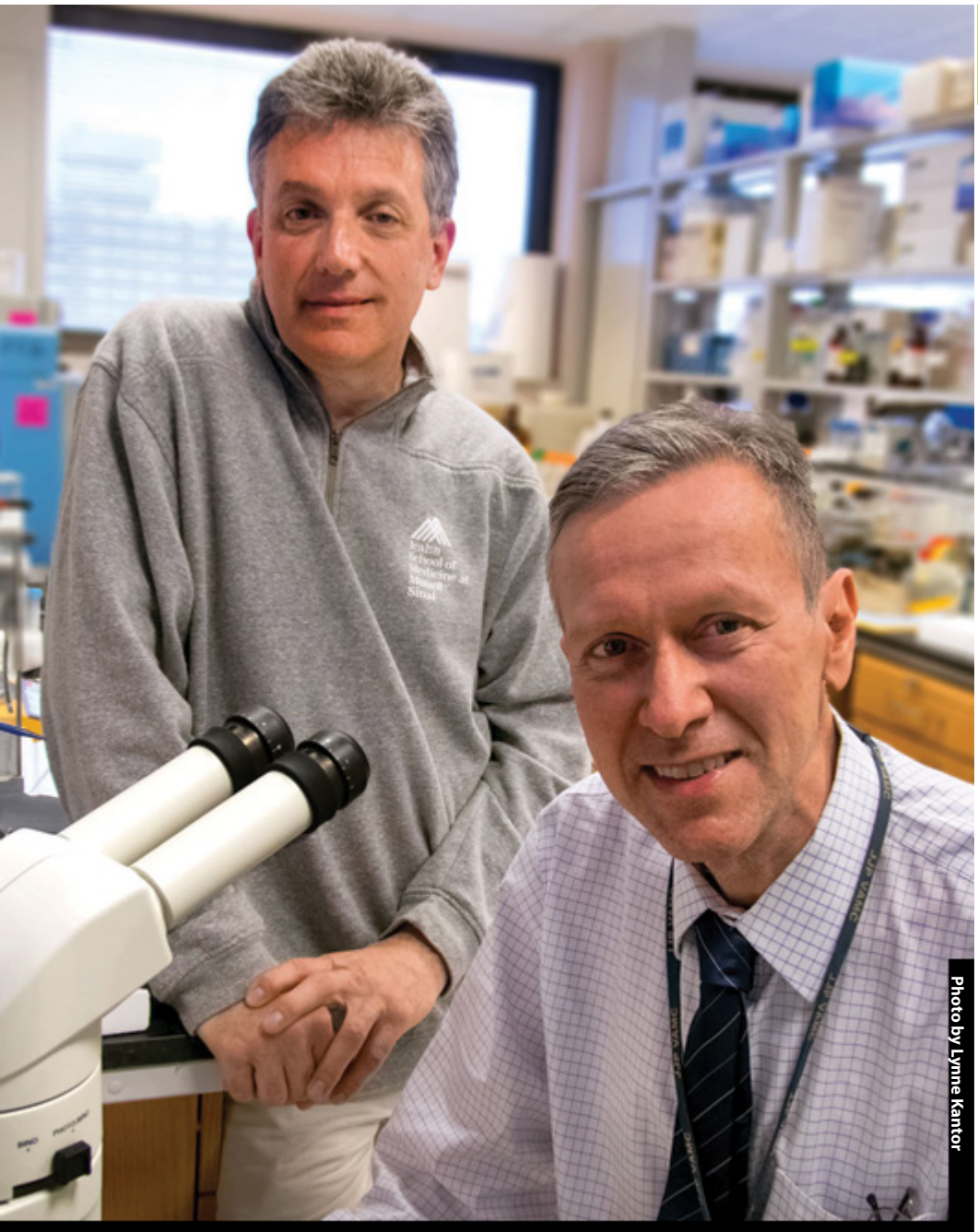

Photo by Lynne Kantor

Drs. Sam Gandy (left) and Greg Elder, with the Bronx VA Medical Center, are studying an experimental Alzheimer's drug that not only blocks plaque-forming amyloid, but also spurs new brain cells.

WHAT'S INSIDE ▸ ▸ ▸

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U.S. Department of Veterans Affairs
103 S. Gay St., Ste. 517
Baltimore, MD 21202
410-962-1800x223
410-962-0084 (fax)

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Editor: Mitch Mirkin
Assistant Editor: John Crawford

Nurse Adrienne Wagenblast teaches about diabetes during a shared medical appointment at the Durham VA.

Shared appointments help diabetes patients

A VA team's review of past research gives a thumbs up to shared medical appointments for diabetes patients.

Shared medical appointments are growing in popularity in primary care. They are seen as a way to cut waiting times and boost care for those with chronic diseases like diabetes or high blood pressure. They also reduce costs.

In VA, the approach is common. Typically, a multi-disciplinary team meets with anywhere from 8 to 20 patients for up to two hours. Researchers who have studied the model say patients get support from their peers and learn new strategies from them, and that they like the team care. The professionals who work with the groups report a high sense of camaraderie.

But do patient outcomes improve? The new study says yes. A team led by Dr. David Edelman at the Durham VA Medical Center and Duke University reviewed 17 past studies that compared shared medical appointments with usual care for patients with diabetes. The shared appointments worked. On average, patients saw significant drops in blood sugar levels and blood pressure, although there were no improvements in LDL ("bad") cholesterol.

The researchers say there wasn't enough data to

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draw conclusions about other outcomes, such as patients' overall use of health care or costs. (*Journal of General Internal Medicine*, online Aug. 9, 2014)

PTSD tied to autoimmune disorders

In a study of more than 666,000 Veterans of Iraq and Afghanistan, those with PTSD were more likely to have autoimmune disorders such as rheumatoid arthritis, multiple sclerosis, lupus, inflammation of the thyroid, and inflammatory bowel disease.

The study, led by Dr. Aoife O'Donovan at the San Francisco VA Medical Center, found a twofold increased risk among those with PTSD, compared with those who had no psychiatric diagnoses.

When the Veterans with PTSD were compared against those with other psychiatric disorders, the risk of autoimmune disease among the PTSD group was still greater—by 51 percent.

The new findings jibe with those from smaller studies.

The reasons for the linkage are unclear. O'Donovan's group says it could have to do with immune or hormonal changes brought about by PTSD. Or, it could be due to health habits that are more common in those with PTSD, such as smoking, drinking, poor diet, or impaired sleep. A third theory is that pre-existing genetic or environmental risk factors might lay the groundwork for both conditions.

In any event, the study doesn't show that PTSD *causes* autoimmune disease—only that there's a relationship.

The study adds to others showing a link between PTSD and various physical conditions, including heart disease.

"Our findings… contribute to the growing literature highlighting the increased risk for other chronic physical diseases in veterans with PTSD and other psychiatric disorders," wrote the authors. (*Biological Psychiatry*, online June 28, 2014)

Possible weapon against triple-negative breast cancer

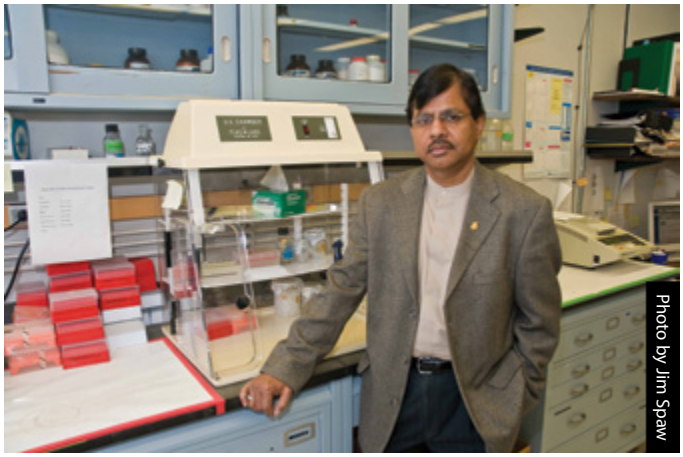
VA researchers in Kansas City, Mo., gained more insight on a protein that they say may thwart an aggressive form of breast cancer, and pancreatic cancer as well.

The team figured out the mechanisms behind CCN5, a protein they say keeps certain cancers from progressing.

CCN5 is part of a family of proteins that help with organ and blood-vessel growth and other functions. In past studies, the Kansas City group found the protein is relatively absent in invasive breast cancer, and more abundant in less aggressive tumors. That led to the discovery that it helps stop cancer from spreading, at least in animal models.

Now the team, led by Dr. Sushanta Banerjee, has identified key pathways in the process. CCN5, they learned, boosts output of a tumor suppressor protein known as p27Kip1 and moves it to the nucleus of the cell. When CCN5 is absent, the tumor-squashing protein is found mostly in the cytoplasm, the liquidy gel that surrounds the cell nucleus. That appears to allow the cancer cells to grow and spread.

Banerjee's group did the experiments with human breast cancer tissue samples and cell lines.



Dr. Sushanta Banerjee and his Cancer Research Unit at the Kansas City (Mo.) VA Medical Center are seeking a new approach to treat triple-negative breast cancer.

They also injected cancer cells into mice to see the effect of CCN5 on tumor growth.

The samples and cells were from patients with triple-negative breast cancer (TNBC), a form of the disease that doesn't respond to hormonal therapy as does other breast cancers, and that can be especially aggressive and prone to reoccur.

"TNBC is a devastating disease" for which effective treatment is lacking, says Banerjee. "Our studies found that CCN5 can prevent the progression of TNBC, at least in an animal model. Thus, activation of CCN5 may have the therapeutic potential to kill TNBC." He says the same is true of pancreatic cancer, based on past studies in his lab. (*Oncogene*, online Aug. 18, 2014)

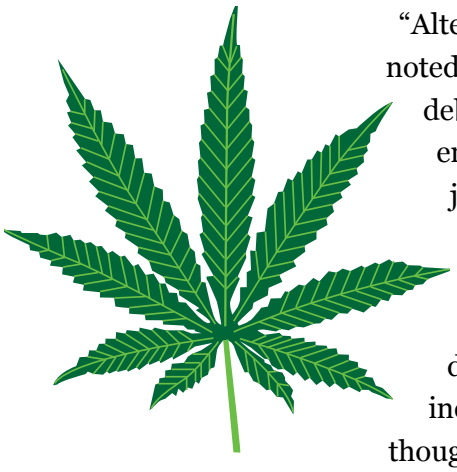
Study reveals link between medical marijuana, opioid overdoses

States that allow medical marijuana tend to have lower rates of overdose from opioid painkillers. That's the conclusion of researchers with VA and the University of Pennsylvania.

Their study tracked data from all 50 states, including the 13 that had passed medical marijuana laws by 2010. Today, 23 states in all, plus the District of Columbia, have such laws on the books.

Based on data from 1999 through 2010, the states with medical cannabis laws had about a 25 percent lower rate of deaths from opioid overdoses, on average, compared with states without the laws. The overdose rates tended to drop lower with each year following the enactment of the laws.

Lead author Dr. Marcus Bachhuber, a Robert Wood Johnson Foundation Clinical Scholar at the Philadelphia VA Medical Center, told *news@JAMA* that the study was prompted by his discussions with many patients who had found marijuana effective for their chronic pain. He and his coauthors thought they might see a trend wherein patients were increasingly replacing or supplementing opioid drugs with marijuana, thereby lessening overall opioid use—and, in turn, overdose rates.



"Alternatively," he noted, "there is still debate about whether medical marijuana might lead patients to use other drugs, so opioid overdose might have increased. We thought there could be a change in either direction, and that's why we decided to study it."

Bachhuber, also with VA's Center for Health Equity Research and Promotion, said further study is needed to better understand how medical marijuana laws interact with policies aimed at cutting opioid overdose. (*JAMA Internal Medicine*, online Aug. 25, 2014)

Delays in filling prescriptions for heart drug linked to worse outcomes

The anti-clot medication clopidogrel (sold as Plavix) is prescribed as part of follow-up care for patients who have had balloon angioplasty and stenting to clear a blocked or narrowed artery. The drug helps prevent blood clots that could cause a heart attack or stroke.

But some patients delay filling their prescription. According to a new VA study, those patients might be at more than twice the risk for heart attack or death within 90 days of hospital discharge.

Senior study author Dr. Michael Ho and colleagues at the Denver and Boston VA medical centers analyzed the outcomes of more than 8,000 VA patients who had the heart procedure at any of 60 VA sites.

The researchers pulled data from the VA Clinical Assessment, Reporting and Tracking (CART) Program, which tracks heart procedures at all VA cath labs. They also used VA pharmacy data.

Patients who didn't fill their prescription at

The CART Program tracks heart procedures at all VA cath labs, like this one at the Pittsburgh VA. Researchers used CART to study patient outcomes related to the anti-clot drug clopidogrel.

the VA pharmacy on the day of discharge were considered as having a delay. At the same time, the study excluded those who didn't fill the prescription *at all* within the first month, in the assumption they might have already had a supply of the drug, or that they went to a non-VA pharmacy.

In all, about 7 percent of the patients had a delay. This compared very favorably with the results seen in a similar study that looked at Medicare (non-VA) patients.

However, those VA patients who delayed were 2.34 times more likely—compared with those who received the drug upon discharge—to suffer a heart attack or die within 90 days.

The study also identified wide variation among the VA sites in the study, in terms of how many patients delayed filling their prescription. One best practice noted by the authors: In some VA hospitals, pharmacists deliver medications to patients' bedsides before they are discharged.

The authors say future studies should focus on this and other ways to ensure timely filling of clopidogrel prescriptions. (*American Heart Journal,* September 2014)

Compound in Asian fruit may fight retinal disease

The mangosteen—no relation to the mango—is a tropical fruit, grown mainly in Asia, that has a long history of use in folk medicine. Scientists have recently begun tapping into this knowledge, and now an international team including a VA researcher has found that a compound in the fruit may help combat a dangerous eye condition.

In lab studies, the team, from Georgia Regents University, Mahidol University in Thailand, and the Augusta (Ga.) VA Medical Center, found that a compound in the fruit limits the abnormal growth of tiny blood vessels in the retina. The vessels can leak blood into the retina and disturb function, sometimes causing vision loss. The condition occurs as a complication of diabetes or as the result of a blockage to the main vein in the retina.

The compound, alpha-mangostin, is one of several beneficial phytochemicals called xanthones that are found in the mangosteen. In other lab research, the natural antioxidants have been shown to have anti-tumor, anti-viral, and other health effects.

Study coauthor Dr. Ruth Caldwell, in addition to her VA role, is with the Vision Discovery Institute at Georgia Regents. (*Microvascular Research*, May 2014)

The mangosteen, an exotic tropical fruit, may contain a compound helpful for treating abnormal blood vessel growth in the retina, say VA researchers.

Helping those with vision loss **find their way**

Thanks to technology, blind people and those with low vision are now able to find their way around independently with greater ease. VA has been a leader in the field historically, and today, several wayfinding projects are in the works at the Center for Visual and Neurocognitive Rehabilitation, based at the Atlanta VA Medical Center. Here's an overview:

- **Researchers are developing a smartphone app** that takes advantage of "sensor fusion" to track user movement. An outdoor version of the product fuses data from GPS with data from the magnetic compass, gyrocompass, and accelerometers found in most smartphones. This provides highly accurate location information that could help users easily find destinations such as a crosswalk or building entrance.
- **The center is also investigating the use of radio-frequency identification (RFID),** which uses electromagnetic fields to transfer data. It's the same technology that allows people to scan items at the store or drive through a tollbooth with an E-ZPass tag. One project is exploring RFID tags on Braille signs as a way to send information automatically to smartphones that can read the tags. This would be an alternative to Low Energy Bluetooth transmitters. VA engineer David Ross says, "The advantage of RFID tags is that they require no power, while the Bluetooth transmitters run on batteries that must be changed every couple of years."
- **In another project, researchers are working with commercial partners on fast-darkening sunglasses** for people with age-related macular degeneration or similar conditions. A special "electrochromic" film applied to the lenses helps them darken and lighten in just a few seconds, much quicker than traditional transition lenses. The glasses are equipped with light sensors that automatically trigger the changes.

  One advantage, says Ross, is that the film "adjusts dynamically as the light changes while moving around outdoors. If a cloud comes over the sun, it adjusts automatically to the best level for the person for the level of light in that moment. Also, for those who still drive, it automatically adjusts as you drive, so as the sunlight changes, or you go into the shadow of buildings and back out into sunlight, it adjusts for you automatically." He notes that transition lenses rely on UV light from the sun to adjust. Since car windshields block this UV light, transition lenses do not dynamically adjust while users are driving.
- **The center is collaborating with University of Maryland computer scientist Dr. Jon Froelich** on a Department of Defense-funded project called HandSight. A tiny camera small enough to embed in a false fingernail is worn by the

VA engineer David Ross models his RFID indoor wayfinding system.

user and connected to a smart watch. The watch vibrates to signal that the user has placed his finger on a line of text, and then scanning the finger along the text activates software that translates the text into spoken output heard on a Bluetooth earpiece. When the user touches an article of clothing, software in the watch recognizes the colors and patterns and helps with coordinating an ensemble.

The researchers also plan to have HandSight serve as an interface to a smartphone. It will treat the surface of the user's hand as the touch screen.

Says Ross: "Users will be able to open and run apps simply by touching the palm of their hand. They will be able to set up specific parts of the hand as 'favorites' for commonly used functions, such as finding out the time or calling a friend. A user might touch his ring finger, for instance, to call his wife." ★

To learn more about VA vision research, visit www.research.va.gov/research_topics

Photo by Christian Fischer via Wikimedia Commons

Chemo without the side effects

Tiny gold nanocages and a chemical originally found in the European fire-bellied toad are helping researchers advance toward targeted chemotherapy—treatment that kills cancer cells but not healthy tissue.

Read more at www.research.va.gov/currents/fall2014/fall2014-4.cfm

VA spinal cord researchers receive Service to America award

Photo by Reynaldo Leal

VA Secretary Robert McDonald (left) presents a Service to America medal to Drs. William Bauman and Ann Spungen.

VA spinal cord injury researchers Dr. William Bauman and Dr. Ann Spungen received the Samuel J. Heyman Science and Environment Medal on Sept. 22, 2014. The Science and Environment Medal is one of several Service to America medals, or "Sammies," awarded each year by the Partnership for Public Service.

In 2001, Bauman and Spungen began the VA's Rehabilitation Research and Development National Center of Excellence for the Medical Consequences of Spinal Cord Injury in the Bronx, N.Y. In recent studies here, Spungen has tested a robotic exoskeleton that enables people with paralysis to stand, walk, and climb stairs. Over their 25 years working together, the team has made huge strides in understanding the effects of spinal cord injury on the body, and advancing therapies to ease complications such as low blood pressure, bone loss, and pressure ulcers. Experts say their work has extended life expectancy for Veterans and others with spinal cord injury, and greatly improved their quality of life.

The researchers received their award from VA Secretary Robert McDonald. "Any research institution would be proud to have these leading scientists," said the Secretary, "but they have chosen to dedicate their careers to serving Veterans at VA, and we are proud to call them our own." ★

To view a video and read more about Bauman and Spungen's work, visit www.blogs.va.gov/VAntage/15467/va-researchers-win-coveted-service-award-for-work-with-paralyzed-veterans/

Experimental drug packs **double whammy against Alzheimer's**

An experimental drug being tested in lab studies at the Bronx VA not only blocks plaque-forming amyloid, but also spurs new brain cells.

A new drug that not only blocks plaque-forming amyloid but also spurs new brain cells may be a potent weapon in the war against Alzheimer's disease, if animal results pan out in humans.

Results from a study in mice appeared online Aug. 12, 2014, in the journal *Molecular Psychiatry*. Lead author Dr. Sam Gandy, with the James J. Peters VA Medical Center in the Bronx and Icahn School of Medicine at Mount Sinai, says the drug is promising for its varied effects and because it has already been shown safe, albeit on a limited basis, in people.

"We are cautiously hopeful that this drug might arrest Alzheimer's disease at an early stage so that patients can remain functional for more extended periods," Gandy said in a news release from the Cure Alzheimer's Fund, which helped support the research.

Gandy's team used an investigational drug known as a BCI-838, from San Diego-based Brain Cells, Inc. The company is a licensee of the Japanese pharmaceutical firm Taisho. The oral drug proved safe in a two-week clinical trial involving young healthy adults, presented at the 2012 Society for Neuroscience meeting. More study is needed, but researchers say the early results suggest the drug is safe and readily absorbed in the body.

Gandy says his group hopes to soon launch a phase 1 safety trial of the drug in older adults who have mild Alzheimer's or its precursor, mild cognitive impairment.

The glutamate connection

Actually, BCI-838 is a "prodrug." It gets converted to its active form, BCI-632, only after being metabolized in the body. BCI-632 blocks proteins in the brain known as Group II metabotropic glutamate receptors. These receptors normally bind with glutamate, a neurotransmitter that is abundant in the brain, to enable memory and other brain functions.

Photo by Lynne Kantor

Drs. Sam Gandy (at microscope) and Greg Elder are studying a neuron-generating compound that shows promise for both Alzheimer's disease and traumatic brain injury.

But the receptors also play a role in Alzheimer's. Gandy's lab showed in past studies that the receptors are central to the production of amyloid. Amyloid—or, more precisely, beta amyloid—is one of the main signs of Alzheimer's. The sticky protein clumps into structures called plaques that build up between neurons like grains of sand.

In the new study, Alzheimer's mice that received daily doses of BCI-838 over three months showed improved learning, as well as reduced anxiety. They

VA review study on Alzheimer's worldwide

Finding
Recent studies show declining age-specific rates of Alzheimer's disease (AD) in the U.S. and parts of Europe
(Overall rates may still rise, because of people living longer, but those at a given age are less likely to be affected)

Possible reason
More education and improved cardiovascular care, leading to better brain health

Key questions
Will rising obesity and diabetes offset the trend? Will lower-income countries also benefit?

Source: "Is the risk of Alzheimer's disease declining? A review of evidence from around the world," presented by Dr. Kenneth Langa (VA Ann Arbor Healthcare System) at the Alzheimer's Association International Conference, July 2014
Infographic by Michael Escalante, VA Research Communications (Aug. 2014)

also showed reductions in the levels of beta amyloid in the brain, and the formation of new brain cells, or neurons, in the hippocampus, a part of the brain crucial for memory.

Gandy and his coauthors write that the drug, or similar ones that block the same glutamate receptors,

> **"We are cautiously hopeful that this drug might arrest Alzheimer's disease at an early stage. …"**

"may offer a unique package of relevant properties as an Alzheimer's disease therapeutic or prophylactic by providing both attenuation of neuropathology and stimulation of repair."

Drug to be studied for TBI

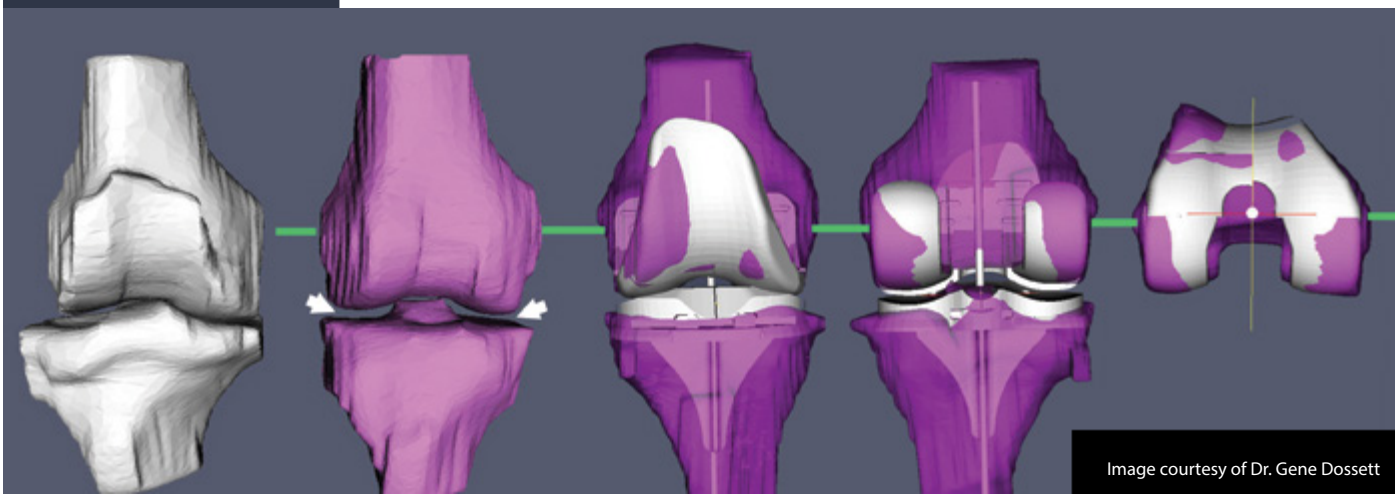
Gandy's group is also now looking at BCI-838's potential to help Veterans with traumatic brain injury. Stimulating the growth of new brain cells might help that condition just as it does Alzheimer's.

Gandy will be working with Dr. Greg Elder, chief of neurology at the Bronx VA, who conducts and has published VA-supported studies on a rat model of traumatic brain injury. Elder developed the model together with Dr. Stephen Ahlers, director of the Operational and Undersea Medicine Directorate at the Naval Medical Research Center in Silver Spring, Md.

To further the research, the Bronx VA expects to install a blast tube that simulates the effects on the brain of improvised explosive devices (IEDs).

The experimental blast system, says Gandy, "will truly concretize our ability to work—and to lead—in this area."

In addition to VA and the Stem Cell Consortium of the Cure Alzheimer's Fund, Gandy's group had research support from the National Institute of Aging, BrightFocus Foundation, the Gideon and Sarah Gartner Foundation, the Louis B. Mayer Foundation, the Alzheimer's Art Quilt Initiative, and several other public and private sources. ★



In kinematic alignment, 3D models of patients' knees, based on MRI scans, are used to create personalized cutting guides that surgeons use to prepare the bones around the artificial knee.

Study: More pain relief with new knee replacement method

A team at the Phoenix VA published promising findings from a clinical trial of a newer method for knee replacement surgery, called kinematic alignment.

Each year, more than half a million patients in the U.S. receive a total knee replacement, and roughly 20 percent of them are dissatisfied with the results, says Dr. Gene Dossett, chief of orthopedic surgery at the Phoenix VA Health Care System.

The main reason? Persistent pain, even after the replacement.

So Dossett and a small team of VA doctors completed a two-year clinical study comparing traditional replacement methods with a newer method in hopes of improving patients' pain levels, function, and range of movement.

The new method, called kinematic alignment, uses MRI scans and special software to create customized cutting guides that the surgeon uses to prepare the bones surrounding the artificial knee. The result is a more personalized fit.

VA study was first of its kind

The new method is not yet commercially available, and little formal research on it exists. The new VA study was the first randomized, controlled trial comparing clinical results between kinematic and conventional alignment. Dossett's team published the results in July 2014 in Britain's *Bone & Joint Journal*.

"What we found is that kinematic knee replacement provided much better pain relief and was more effective in restoring function and range of movement," says the surgeon.

Among the 88 Veterans who took part in the study, those who received the kinematically aligned knees were more than three times as likely to be pain-free at two years, compared with those whose procedures had used conventional mechanical alignment. They also were able to walk 50 feet further, on average, in the hospital prior to discharge.

In the study, neither the patients nor the clinicians who evaluated them knew which of the two styles of alignment had been used.

Standard method has been in use 30 years

The same knee-replacement procedures have been used by orthopedic surgeons for nearly 30

years, says Dossett: Align the bones in the leg, from the hip to the ankle, and cut the bones at 90-degree angles to allow for the prosthesis.

Kinematic alignment uses a more individualized approach. The bottom of the thigh bone and top of the shin bone are cut using personalized guides, made of hard plastic. The guides are fabricated based on patients' MRI scans and 3D models of the knees generated by special software.

The guides fit the end of the bones to create the cutting angle and resection depth for each patient's knee. The goal is to reproduce a more natural position for the patient's knee—similar to how it was prior to arthritis setting in.

Both types of surgeries use the same cobalt chrome prosthesis.

Veteran Charles Schmidt, the first patient to undergo the kinematic technique as part of the Phoenix VA study, reported that before his surgery, he was in pain every time he tried to walk.

"My new knee is my strongest knee," Schmidt said. "Now I'm totally pain-free and have been since the operation and rehab. The best thing to say about it, I guess, is that I don't think about it anymore."

Veteran Charles Condrotte, now retired, holds a picture of himself from when he was a forest ranger. Still an active hiker, he took part in a Phoenix VA study in which he received a kinematically aligned knee replacement.

"What we found is that kinematic knee replacement provided much better pain relief and was more effective in restoring function and range of movement."

Schmidt said that since the surgery, he's taken extended trips to South America without any problems from his knee. He said he soon will leave for a tour of Spanish cities.

Navy Veteran still hiking

Another recipient of the kinematic knee, Charles Condrotte, has also traveled extensively since his operation in 2009. He said he's been to China, Great Britain, and several countries in Europe, and has taken part in safaris in Tanzania and Kenya. He plans to visit Vietnam, Cambodia, and the Galapagos Islands in the near future.

After retiring from the Navy, he worked as a forest ranger in Flagstaff, Ariz. He said he's logged more than 2,000 miles of hiking mountainous trails.

Before surgery, his knee reached the point where the pain was constant and always on his mind—limiting his work and personal life. Afterwards, Condrotte said, he's been pain-free.

"I still hike a lot up in Flagstaff," Condrotte said, now retired from the Forest Service after 17 years. "We have some wonderful trails."

"I've had fantastic care at the VA," he added. "They do a wonderful job."

Meanwhile, Dossett says he is "using the knowledge gained from this study to continue to help Veterans obtain the best possible results from their knee replacement." ★

Diabetes wound care: Much progress in past 25 years, but challenges remain

Longtime VA clinician-research Dr. Margaret Doucette specializes in wound care and amputation prevention.

For Veterans and others with diabetes, foot care is super-critical.

The disease can damage nerves in the feet, causing a loss of feeling. Minor cuts, scrapes, and blisters go unnoticed, and poor blood flow slows healing. Without careful and frequent attention, these wounds can become infected and worsen to the point of requiring amputation of a foot or leg.

Of the 16 million Americans with confirmed diabetes—including about one in five VA patients—about a quarter will have foot problems related to the disease. People with diabetes account for about two-thirds of lower-limb amputations in the U.S.

Longtime VA clinician-researcher Dr. Margaret Doucette has been in the forefront of providing top-notch wound care to Veterans with diabetes or related problems. Today, she is chief of physical medicine and rehabilitation at the Boise VA Medical Center. *VA Research Currents* interviewed Doucette about a VA study on the topic that she published exactly 25 years ago, and how the field has progressed since then.

1989 study

Title: "Amputation prevention in a high-risk population through comprehensive wound-healing protocol"

Journal: *Archives and Physical Medicine and Rehabilitation* (October 1989)

Authors: Doucette MM, Fylling C, Knighton DR

VA site: Minneapolis

What was studied: The study included 24 Veterans with diabetes or vascular disease, or a combination. All had received a recommendation for amputation from a surgeon. The study tested an aggressive, comprehensive wound-care protocol that used a number of therapies: restoration of blood flow, infection control, wound debridement [cleaning away of dead or infected tissue], orthotics, and a special wound-healing gel based on the patient's own blood. The result? All but four of the Veterans in the study were able to avoid amputation.

What was learned: Doucette and colleagues concluded that "an aggressive, comprehensive amputation intervention program can prevent the emotional, functional, and economic costs of limb loss in most high-risk patients."

2014 Q&A with Dr. Doucette

Back in 1989, was the assumption that not much could be done to prevent amputation in high-risk patients? Did this study help change that view?

This was one of the first studies using advanced therapies to try and stimulate healing. Along with

other methods, we used platelet-derived growth factors [proteins that trigger cell growth]. At the time, it was a novel intervention to enhance healing. Until then, the best we could do was maximize the body's ability to heal by trying to control variables that influence healing—blood-sugar management, revascularization, off-loading of diabetic ulcers. The use of a topical application of growth factors was an early attempt to actually stimulate the healing process. In the ensuing years, there have been many advanced therapies developed. These include products that involve the use of live cells harvested from neonatal foreskin [also known as "skin equivalents"]; matrixes, such as pig gut, which provide a "ladder" for cells to migrate across wounds; and various growth factors, which have been well-researched.

Among the approaches you used in 1989, which are still used today?

The basic principles of wound healing remain very much the same: Identify and treat infection; address vascular insufficiency; prepare the wound bed with debridement; improve glucose control; and off-load, or protect, the wound.

In the world of infection, we have come to better understand the presence and role of biofilms—these are communities of bacteria that form an impermeable barrier in the wound or on an implant. This reduces the effectiveness of antibiotics.

Techniques of revascularization have become more sophisticated, though they are similar in concept to 25 years ago. Hyperbaric oxygen therapy has gained some traction. We still struggle with how to effectively off-load a plantar diabetic foot ulcer, as this relies considerably on the patient's buy-in. The total contact cast remains one of our best tools, but it is one of the least utilized by clinicians, partly because it is not well-accepted by patients.

Importantly, the field of wound healing has become a specialty in and of itself. There is certification and more training available, so our practitioners are better-versed in treatment options.

The greatest area of development has been with the techniques and products available to enhance healing. There are many more products and techniques available today than there were 25 years ago, partly due to the research that has been performed in VA and elsewhere.

Overall, compared with 25 years ago, how has the outlook improved for those with diabetes who may be at risk for amputation?

Sadly, the risk of amputation still remains high for those with poorly controlled diabetes. Much of the damage has been done before they develop an ulcer, and patients often delay seeking care or have difficulty fully participating in a care plan focused on limb salvage.

One of the greatest tools for successful intervention continues to be that of the interdisciplinary team, a model which VA embraced early on. Successful limb salvage always starts with the interdisciplinary team, and the VA model has this as its foundation. New areas of research can be integrated into this model. VA has a large population of patients at risk for amputation, making it critical that we continue to examine how we can reduce amputation rates★

★ ★ ★ ★

"This was one of the first studies using advanced therapies to try and stimulate healing."

Photo courtesy of John Krumbholz

John Krumbholz of Iowa took part in a VA-led study on walking for Parkinson's disease patients.

A walk a day may keep the Parkinson's symptoms away

In a study by VA researchers and colleagues, patients who walked briskly for 45 minutes, three times a week, showed improvements in their Parkinson's symptoms. They were also less depressed and less tired.

Experts agree exercise is good for Parkinson's patients. But they are still studying how much is needed, and in what forms, to achieve significant results.

In a new study by VA researchers and colleagues, patients who walked briskly for 45 minutes, three times a week, showed improvements in their Parkinson's symptoms. They were also less depressed and less tired.

"The results suggest that walking may provide a safe and easily accessible way of improving the symptoms of Parkinson's disease [and improving quality of life]," says study leader Dr. Ergun Uc, a neurologist with the Iowa City VA Health Care System. He is also an associate professor of neurology and neuroscience at the University of Iowa Carver College Of Medicine.

The study was published July 29, 2014, in *Neurology*.

60 people took part in study

Previous research has suggested exercise could improve the symptoms of Parkinson's, and doctors do often advise patients with the disease to exercise. Common choices include walking, jogging, dancing, or bicycling. The key is to ensure the activity is

moderately strenuous. According to Uc, the new study shows that even moderate walking can make a significant difference.

Parkinson's disease is a chronic movement disorder. Classic symptoms involve a tremor, stiff limbs, slowness, and gait and balance problems. There is no known cure. According to the Centers for Disease Control and Prevention, Parkinson's is the 14th leading cause of death in America. The CDC estimates between 500,000 and 1.5 million Americans currently live with Parkinson's.

Parkinson's disease gained wide attention when celebrity Michael J. Fox was diagnosed with it in 1991. More recently it was revealed that prior to his death, comedian Robin Williams had also been diagnosed with Parkinson's.

The disease is most common in people over 50. Though researchers suspect genetics may play a role, it is unclear exactly what causes the disease.

Up to 15 percent improvement

For the study, researchers recruited 60 participants with mild to moderate Parkinson's. All of the patients could walk without a cane and had no other major health problems. The participants walked for 45 minutes at an average of 2.9 miles per hour, three times a week for six months. The sessions began at 15 minutes and gradually increased to 45 over six to eight weeks.

"The regimen was moderately strenuous," says Uc. "Patients walked at 47 percent of their heart rate reserve or 70 percent of their age-estimated maximal heart rate."

Of the 60 participants who started the study, 49 completed it. Only three of those who quit did so for reasons related to the exercises, such as knee pain. For those who did complete it, the results were encouraging. "We observed 7 to 15 percent improvement in various symptoms," says Uc.

Participants' motor function and mood improved by 15 percent, on average. Tiredness was reduced by 11 percent, and attention and response control improved by 14 percent.

Uc suspects the improvements could be due to any of a number of factors, such as an improvement in the brain's neuroplasticity as a result of exercise, increased oxygenation and metabolism, or an increase in dopamine, a neurotransmitter. Parkinson's involves a loss of dopamine-producing cells in the brain.

While Uc cautions that exercise and medication work in different ways and should not necessarily be compared, he does believe exercise can play a role in treating Parkinson's disease.

"Aerobic walking may represent an accessible, low-risk supplemental treatment for fatigue and depression, and [a way to] improve quality of life in Parkinson's disease," he says. "If patients are in good enough health to exercise, even moderately, they should." ★

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"If patients are in good enough health to exercise, even moderately, they should."

Photo by Senior Airman Daniel Hughes/USAF

U.S. Army soldiers from the 1st Armored Brigade Combat Team, 3rd Infantry Division, listen to a pre-mission brief in August 2014.

Unit cohesion could be key to **PTSD resiliency**

A VA study of nearly 800 National Guard and Reserve troops found that soldiers reporting more unit cohesion tended to be more resilient to mental health problems, including PTSD.

A VA study of nearly 800 National Guard and Reserve troops found that soldiers reporting higher levels of unit cohesion tended to be more resilient to mental health problems, including posttraumatic stress disorder. The results, presented at the American Psychological Association annual meeting in August 2014, could help explain why some soldiers seem more resilient than others to PTSD.

"We defined resiliency as having better mental health function. Veterans should have the ability to fulfill their usual roles and conduct normal activities on a regular basis," said Dr. Lisa McAndrew, a researcher with the VA New Jersey Healthcare System and VA's War Related Illness and Injury Study Center. "What is interesting is that when soldiers come back from combat, most of them are very resilient. They're able to go about their daily lives, but we don't know why that is."

According to VA's National Center for PTSD, between 11 and 20 percent of Iraq and Afghanistan Veterans develop PTSD. Symptoms can include flashbacks, avoidance, negative changes in behavior, and hypervigilance. Treatment often involves long-term therapy aimed at developing coping mechanisms, something McAndrew believes may be more likely to take place informally in soldiers with high unit-cohesion.

'Almost a natural intervention'

"Basically it's almost a natural intervention where soldiers have the support of their fellow military personnel. They can talk to them about their

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"It's almost a natural intervention where soldiers have the support of their fellow military personnel."

problems almost immediately instead of dealing with them on their own, and that may help them learn strategies to cope during the deployment and afterward," says McAndrew, who is also an assistant professor in the division of counseling psychology at the University at Albany-State University of New York.

As part of their research, McAndrew and her team assessed the mental health and coping methods of 767 soldiers before deployment, immediately upon their return, and then three months and one year later. In addition, the participants were asked to rate three statements about unit cohesion immediately after their return:

The members of my unit are cooperative with each other.

The members of my unit know that they can depend on each other.

The members of my unit stand up for each other.

Scores ranged from 3 to 15, with higher scores indicating higher perceived unit cohesion. The average score was 9.3.

"We hypothesized that participants with higher scores would also have better mental health functions post-deployment," says McAndrew, "and that's what we found." There was also a direct correlation between unit cohesion and more effective coping techniques.

Less 'avoidance coping' in cohesive units

McAndrew believes much of it may have to do with a decrease in avoidance coping—that is, the tendency to avoid or ruminate over a problem rather than address it head on. The alternative, approach coping, tends to require a healthy social network. "Seeking support and advice are part of approach coping," says McAndrew, "and it is generally thought to be more effective in dealing with problems."

"It's not always possible to do 12-week individual interventions, or in the case of National Guard troops or reservists, to even ensure they have the same level of support when they come home that active-duty soldiers may have," says McAndrew. "If we can do things to encourage unit cohesion and build relationships within the units, it might be feasible to build resilience to PTSD and other mental illnesses associated with combat trauma."

The next step for McAndrew is to explore whether soldiers who feel understood when they get home are more resilient than those who do not. "It's all about answering these questions," says McAndrew. "If we understand [these factors], then we can help everyone to become resilient."★

Photo courtesy of www.jenx67.com

In a survey of homeless Veterans in Massachusetts, nearly all owned a mobile phone, and nearly all expressed interest in receiving calls or texts about appointments and other health matters.

Mobile phones offer hope for reaching homeless Veterans

A VA study of homeless Veterans found that nearly all owned a mobile phone and were interested in receiving calls or texts about appointments and other health matters.

Homeless. The word evokes images of sleeping on broken-down cardboard boxes, of struggling to stay warm on winter nights and panhandling for food money. Mobile phones and Internet, not so much. Yet research shows that not only do people who are homeless often have access to mobile technology, but that in many cases they are making it a priority.

Among people who are living on the streets, estimates of mobile phone ownership hover around 50 percent, says Dr. Keith McInnes, a research health science specialist at VA's Center for Healthcare Organization and Implementation Research in Bedford, Mass. McInnes, who cautions that it is notoriously difficult to capture the full range of people who are homeless, recently reported his findings from a survey on mobile phone use, conducted in a sample of Veterans experiencing homelessness.

The results, published in the journal *Telemedicine and e-Health* in September 2014, suggest that mobile phones may represent a new communications channel for important health data to and from Veterans who are homeless and enrolled in VA.

106 Veterans surveyed

McInnes, also an assistant professor at the Boston University School of Public Health, focused on a population of 106 Veterans in a variety of homeless programs in Massachusetts. "These were people making a concerted effort to improve their lives and reduce the chaos," says McInnes. Surprising to many, 89 percent of the respondents

owned a mobile phone while 76 percent said they used the Internet. Of those with a mobile phone, 71 percent said they used text messaging.

"When you think about it, for people who have very little, if you can have one important possession, why wouldn't it be a phone?" asks McInnes. "It might cost $30 to purchase and $30 per month to keep, but it's portable and it gives you a sense of identity and a method of communicating with the world."

McInnes and his team wanted to see if Veterans would be interested in receiving calls and texts from VA health care providers. The response was overwhelming. Nearly all the participants were interested in receiving mobile phone reminders about upcoming medical appointments, or an outreach call or text for those who had not been seen in clinic for a long time. The findings, according to McInnes, point to another viable method for communicating with an often difficult-to-reach population of Veterans.

"It goes along with VA's increasing emphasis on patient-centered care," says McInnes. "The old model where you're only open from 8 to 5 for appointments is kind of disappearing. That doesn't serve the patient well."

Benefits to Veterans, VA, and taxpayers

Government programs to provide free mobile phones and free minutes to low-income populations, and the emergence of a younger, tech-savvy group of Veterans, mean an increase in communication opportunities for VA. "If a Veteran wants to get phone advice at 9 at night or a text at 6 a.m. to remind them to take their medicine, then why not," says McInnes.

According to McInnes, improved communication benefits not only the Veteran, but also the VA system and the taxpayer. "If we can use these technologies to encourage Veterans to better self-manage their chronic conditions and to come in for care early, as opposed to waiting until things get really bad, then we'll be able to reduce emergency room visits, hospitalizations, and even appointment no-shows."

And McInnes sees more opportunities on the horizon for an integrated mobile network between VA and homeless Veterans. "It could help with isolation, potentially even with addictions, as far as putting people in touch with peer support or reminding them of an AA meeting. It could even help notify Veterans during flu season by indicating where, and what hours, to get a flu shot," he says. "It's not a fix-all by any means, but this could be an important part of the way we communicate with and engage low-income and other vulnerable Veterans." ★

Photo by Robert Turtil

Fostering research on women Veterans' health

VA researchers from across the nation who special-ize in women Veterans' health issues convened this summer to advance the field.

Read more at www.research.va.gov/currents/summer2014/summer2014-17.cfm

Photo by Robert Turtil

A counselor in action at VA's Center of Excellence for Suicide Prevention, which houses the Veterans Crisis Line and other services. The center will play a role in a VA clinical trial of the drug lithium for suicide prevention.

Can lithium help stem suicide rate? VA study aims to find out

Some studies have suggested that lithium, used widely to treat bipolar disorder, may help prevent suicide. A new trial, expected to involve more than 1,800 Veterans at 28 VA sites, will test the theory.

As a drug, lithium has been around since the 1800s. Made from a whitish mineral found in rocks, the drug is widely used today as a mood stabilizer, especially for those with bipolar disorder.

Some studies suggest it may also be useful for preventing suicide. But the theory needs further testing.

Enter VA's Cooperative Studies Program (CSP). The program is gearing up to launch a major trial involving more than 1,800 Veterans from 28 VA medical centers. The study will include only those with bipolar disorder or depression who recently survived a suicide attempt, or were hospitalized to prevent one.

Some 12,000 VA patients with bipolar disorder or depression survive a suicide attempt every year. Experts say such patients remain at increased risk of suicide for the rest of their lives.

The new study will enroll Veterans for three years and follow each patient one year. The study team will look at outcomes such as repeat suicide attempts and hospitalizations to prevent suicide, as well as deaths from suicide. Half the study volunteers in the randomized, double-blinded trial will get a form of the drug known as lithium carbonate, in an extended-release tablet to minimize side effects. The other half will get a placebo.

All will get VA's standard mental health care, plus extra care coordination: The study team will follow up with each patient throughout the study, and give regular updates to other care providers.

VA Research Currents spoke with three members of the study team to learn more about the research effort, which was announced by President Obama at the American Legion national convention in August 2014.

Study chair **Dr. Ira Katz**, a psychiatrist based

in Philadelphia, is a senior consultant for VA's Office of Mental Health Operations.

Study director **Dr. Matt Liang** is a "trialist" at the Boston CSP Coordinating Center who has led close to 30 clinical trials in his career, some with VA but most through the National Institutes of Health and the Centers for Disease Control and Prevention. He is also an internist with Brigham and Women's Hospital and a professor at Harvard Medical School.

Study project manager **Natalie Morgenstern** is a health science specialist for the Boston CSP Coordinating Center.

Why study lithium?

Katz: The observation that patients on lithium were less likely to die from suicide has been around at least since the 1980s or early 1990s. It's been seen mainly in studies in which lithium was being used to treat bipolar disorder or depression. There have also been epidemiologic studies in different parts of the world that have found a correlation between lower suicide rates and higher levels of lithium in the drinking water.

This has all helped lay the groundwork for our study. We're looking directly at whether pharmacologic doses of lithium do indeed have an anti-suicide effect.

This has been a confusing and difficult issue from a research standpoint because lithium has a substantial number of side effects, and it is dangerous in over-dosage. In fact, it can be fatal. So the question has always been this: When we see that patients on lithium are less likely to commit suicide, is it because lithium really does have anti-suicide effects, or is it because doctors don't dare give lithium to anyone who is at risk for suicide, for fear they might intentionally overdose?

That sort of puzzle, in which it looks like lithium has anti-suicide effects, but it may be because the people who are prescribed the drug are at less risk to begin with, is called an indication bias. That's been the major problem in interpreting the observational studies.

To the extent researchers have been able to tease out the answer from database studies, they've argued that the drug probably does have anti-suicide effects. But the gold standard to know about causality and to establish the effectiveness of a treatment is a randomized clinical trial, and that's what we're doing.

What is the study team doing to ensure lithium is used safely?

Liang: Lithium has a narrow toxicity-efficacy ratio. That means there's a relatively small difference between the effective therapeutic dose and the higher dose that would be toxic. So we've tried very hard to minimize the possibility of harm. We're being extremely careful about who we include, and how we monitor the lithium levels and potential side effects. We have two central consultants, Dr. Malcolm Rogers, a psychiatrist, and Dr. Chester Conrad, a cardiologist, who will be available 24/7 to assist the sites. The protocol meets or exceeds any published guideline on safe usage, and is probably over and above what is done in normal clinical practice, in VA or the general psychiatry community.

Morgenstern: We're also using an extended-release form of the drug. The coating tends to make it more tolerable and decrease the severity and frequency of side effects.

Do scientists understand how lithium might work in the brain to prevent suicide?

Katz: We have some insight on this from looking at what happens in clinical populations receiving lithium. Suicide rates seem to be lower both in patients for whom lithium has worked well to treat the underlying psychiatric symptoms, and in those for whom lithium has worked less well. And that's led to the notion that the drug may have anti-suicide effects that are independent of its effect on depression or bipolar disease.

So while the primary goal of the study is to see if lithium prevents repeat suicide attempts, one of the secondary goals is to determine, if we do have a lithium effect, whether it is due to better control of the symptoms of depression or bipolar disorder.

That's an important secondary analysis.

But we really don't know in-depth the cellular or molecular mechanisms of lithium for treatment of bipolar disorder or depression, and we know even less about what could explain its possible anti-suicide effects. We suspect if this study is positive, and we have definite evidence that a drug can prevent suicidal behavior, it will stimulate a good deal of pharmacologic research trying to look for other medications that may have a comparable effect.

How is the study going to recruit participants?

Morgenstern: One source will be referrals from clinicians. There'll also be some targeted outreach, and limited advertising in the form of flyers around the VA medical centers that are taking part. We chose those centers that had higher numbers of patients with documented past suicide attempts. We determined that by using the SPAN database. [SPAN is VA's Suicide Prevention and Application Network, coordinated out of the Center of Excellence for Suicide Prevention at the VA in Canandaigua, New York.] We'll also have access to the screening logs that the sites use, and then we can supplement them with people that they might be missing, so they can try and target those people as well. SPAN will be an invaluable asset. We couldn't do the study without it.

All VA medical centers have suicide prevention coordinators. What role will they play?

Liang: We're collaborating with the suicide prevention coordinators, but we're trying to do it in the most ethical manner possible. They will let potential participants know about the study but won't explain it in any great detail, or actually enroll them. We didn't want any care providers to be conflicted, or to potentially be coercive to people who are potentially vulnerable after a suicide attempt.

If lithium proves effective for suicide prevention, will patients be able to stay on the drug long- term?

Katz: The study itself is one year. In terms of how lithium might be used if we demonstrate an effect, it's important to note that many people with bipolar disorder have been on lithium for or 10, 20, 30 years and managing quite well. We also know that people who have survived a suicide attempt can be at increased risk for suicide for the rest of their life. On the other hand, there are concerns that long-term use of lithium may lead to decreased kidney function.

So the first question will be whether lithium is effective over the time period of the year. A downstream question will be what the risks versus the benefits are of its use over the long term.

Will the patients in the study be followed longer than one year?

Katz: Because they are in the VA system, we'll be able to keep an eye on these patients over the longer term. VA already has an infrastructure and a system for tracking suicide-related behaviors, mainly through the suicide prevention coordinators, who are funded separately from the study. We have that system of care in place, and it is one of the unique benefits of VA.

What might be some next steps after the study ends?

Katz: This study is looking at the effects of lithium in doses that are used pharmacologically. If this is positive, our next question might be whether you need such high doses, or whether far lower doses might also be effective. However, the most important question is about how we would translate findings from the study into improved care. For this, we would make sure that mental health staff and other care providers in VA are aware of the results, and that all VA psychiatrists know how to use lithium to prevent suicide.

Liang: This is the first real test of lithium for suicidality. If the results are positive, it will open up a number of opportunities for understanding how the finding might be applied to a broader population, both in and beyond VA. ★

RESEARCH WORD SEARCH

Find these terms related to health research. They can read forwards, backwards, up, down, or diagonally. Not all the letters in the grid are used, and some may appear in more than one word.

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C I S F B E D K A R A I O T C
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Q A T P K A C O M P O U N D T

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VA RESEARCH CURRENTS

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

Photo: National Library of Medicine

In 1971, Army Veteran and VA researcher Dr. Edward Freis received a Lasker Award for his "exemplary demonstration of the potential of preventive medicine." Before Lasker's work, most physicians did not understand that high blood pressure, except in extreme cases, was a problem for their patients. The trial that Lasker led through VA's Cooperative Studies Program showed otherwise, and would help save many people from falling victim to strokes or other complications of high blood pressure. The study, which ran from 1964 through 1969, was one of the first randomized, placebo-controlled, double-blind, multisite clinical trials in the U.S., with 523 patients and 17 VA sites participating.

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varesearchcurrents@va.gov 410-962-1800, x223

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