

Toxins as therapy

Most people know Botox—the trade name for botulinum toxin—as a trendy treatment for facial wrinkles.

Long before its cosmetic use, though, the toxin became known as a potent muscle relaxant. Neurologists have used it for decades, in tiny doses, to treat spasms in the face or limbs, uncontrolled blinking, and other conditions. It's become standard therapy for the abnormal contractions that often occur in Parkinson's disease or after a stroke, or in a rarer ailment called dystonia.

Toxins may seem unlikely tools for doctors. But to VA researcher Paul Fishman, MD, PhD, they are a treasure trove of therapeutic potential. The neurologist and his group at the Baltimore VA and the University of Maryland are now studying the use of toxins besides botulinum, such as tetanus and diphtheria, to treat disorders involving muscles.

In scientific terms, the toxins studied in Fishman's lab are proteins made by pathogenic bacteria. The diseases they cause are nasty and often lethal.

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A VA patient with severe dystonia receives a Botox injection to relieve neck-muscle spasms.



At a 2007 "Stand Down" held in San Diego by the National Coalition for Homeless Veterans, stylist Maria Jackson puts the finishing touches on a haircut for Navy veteran William Hughes.

Studies seek best ways to draw homeless veterans into primary care

Stefan Kertesz, MD, MSc, vividly recalls a patient he saw at a homeless shelter in the 1990s. The man had a mood disorder and hypertension. Clinical guidelines and performance measures called for aggressively managing the blood pressure. But Kertesz sensed that if he were to go that route during their initial meetings, it would drive the man away and stifle their budding patient-doctor relationship.

"I felt if I pushed my agenda—treating his blood pressure—I would have to *not* focus on the problems that he was presenting to me," says Kertesz. "I would have to minimize the time and energy we put into his mood issues and the concerns he was having about his ability to reside in that shelter."

Kertesz followed his instincts: He held off on attacking the blood pressure issue. As a result, he was gently reprimanded by his medical director. Looking back, though, he doesn't regret his action. In fact, he sees the episode as a cautionary tale about why standard approaches to primary care may not work well for patients who are homeless. Now a physician-investigator at the Birmingham (Ala.) VA, Kertesz was inspired by the encounter—and many similar ones—to study what primary care for the homeless *should*

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Spasm spoiler—Veteran Donald Ruth, who suffers from dystonia, receives an injection of botulinum toxin (Botox) from VA's Dr. Paul Fishman to help control severe spasms in his neck muscles. Ruth's sister Jean Filetti helps stabilize his head during the procedure. The toxin works by blocking nerve impulses to muscles in the injected area.

in patients with severe injuries who are laid up in bed for long periods. Tiny doses of the toxin could also be used to energize muscles weakened by neurological conditions, he believes. "Could you take a small amount of tetanus toxin and amplify an inadequate contraction?" ponders Fishman.

He gives the example of a post-stroke patient whose hand is locked in a fist. Botulinum toxin could help ease the grip. But the patient might still have trouble fully opening the hand and extending the fingers. "Could we use tetanus toxin to enhance their ability to open their hand, activate those muscles? I view it as complementary to botulinum toxin," says the researcher.

Tetanus experiments challenged myth

Given the clinical success of botulinum toxin, why haven't others thought of using tetanus toxin in a parallel fashion, as Fishman envisions? The reason has to do with vaccination. Experts have assumed that since almost everyone in Western society is vaccinated against tetanus, the toxin could have no effect—good or bad—on people's systems. Thus, it would be of no use medically.

Experiments in Fishman's lab showed otherwise. Even in vaccinated rodents, the injected toxin evaded antibodies and found its target: nerve cells that control muscles. The toxin then works its way inside cells, where antibodies can't touch it.

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Botulinum toxin was in Hitler's arsenal. It was loaded into bombs by Sadaam Hussein's regime, according to United Nations reports. It is listed by the Centers for Disease Control and Prevention as a prime potential agent of bioterrorism. Understandably, the debut of botulinum toxin

in health care in the 1970s raised some eyebrows. Even Fishman was skeptical, to put it mildly, when he first heard of it being used to help patients. "I thought people were nuts. In my training, I had seen people with botulism. Everyone knew what a powerful toxin botulinum was. Using it as a therapy seemed crazy and dangerous."

Fast-forward to 2009. After years of injecting minute doses of botulinum toxin into patients' muscles and seeing remarkable benefits, Fishman is a big proponent of its clinical use.

"It's an enormously powerful and effective muscle relaxant," he says. "It's really been beneficial for conditions where there are no other effective treatments."

That is part of what triggered his interest in another toxin: tetanus. It has the opposite effect on muscles—it activates them—and Fishman believes it could play an equally important role in medicine. He and VA collaborator Chris Matthews, PhD, see the toxin as a possible tonic for muscles that have atrophied from disuse. This is common

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Who's at risk for PTSD? VA-DoD research seeks answers

Two soldiers go off to war and have similar combat experiences. One emerges emotionally intact; the other develops chronic PTSD. Why?

That question is at the core of the Marine Resilience Study. The San Diego-based project involves VA and Department of Defense researchers and three and a half battalions of Marines who are volunteering for the effort.

The researchers are probing dozens of risk factors, from biological to behavioral, that may lower “resilience”—the ability to withstand mental and emotional stress. Not everyone with low resilience will necessarily develop PTSD after a trauma. But the two issues are closely linked.

One goal is to help the military develop new training methods or other strategies to boost resilience and prevent PTSD in the first place. Another is to hone the military’s ability to identify early signs of the disorder and intervene before things worsen.

“The Marines’ approach is, you help someone get better. You don’t send them away,” says Dewleen Baker MD, research director of VA’s Center of Excellence for Stress and Mental Health and the study’s administrative lead.

Some risk factors may be more suited for intervention

Not every risk factor the researchers identify will be amenable to change—genetic make-up, for example. Those that are, such as emotional support or deployment circumstances, are more likely to be the targets of military intervention. One conceivable outcome of the study might be new efforts to help troops “garner and maintain resources for wellness and social connection,” says study co-leader Brett Litz, PhD, of VA’s National Center for PTSD and Massachusetts Veterans Epidemiology Research and Information Center.

As for biological factors such as heart rate, blood pressure or chemical signals in the blood, study co-leader William Nash, MD, a former Navy psychiatrist who deployed to Iraq with the 1st Marine Division in 2004, says these may be more difficult for military leaders to directly address. He notes, however: “The Marine Corps would love for us to find objective, physical markers for PTSD in our study because that would go a long way toward reducing the stigma that surrounds PTSD. There are still



Wired—Marine Pfc. Jesse Sheets of Newark, Del., takes part in a VA-Department of Defense study on biological, psychological and social factors that affect emotional resilience and the risk of PTSD.

too many military service members, including healthcare professionals, who don’t believe PTSD is a real illness resulting from real injuries to the mind and brain, but instead think it is caused by a personal weakness. If we can show them biological markers for PTSD, Marines will better accept that PTSD is no more their own fault than any other wound of war.”

Study includes array of health measures

So far, hundreds of Marines have undergone extensive baseline testing before shipping out overseas. Many are now back on U.S. soil and taking part in follow-up tests over six months. In all, more than 2,000 Marines will take part.

The study is not the first to probe the biological, emotional and social roots of PTSD. But it is probably the largest and most detailed project of its kind to date, says Baker.

The researchers are interviewing the Marines in-depth about issues such as childhood traumas, past alcohol or drug use, marital situation, spiritual life, deployment and combat experiences, support within their unit, and past or current PTSD symptoms. On the physiological side, they are taking cardiovascular measures

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Customized care—Larry Fulgham (left), Gladys Colón (with medical assistant Yolanda Tanguí) and John Carozza are patients at a primary care clinic at the Providence (R.I.) VA Medical Center that is geared to the needs of veterans struggling with homelessness.

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look like. What do patients need and want most? What will draw them into a VA clinic, keep them coming back, and improve their health and social outcomes? Do standard guidelines and quality measures—which often focus narrowly on managing a single disease—work for this population?

His findings so far—from scores of interviews with homeless patients and clinicians and managers involved in their care, both in and outside VA—confirm that one critical factor is trust. Without it, he says, primary care for the homeless is a non-starter.

Veterans and homelessness

- Roughly one in three U.S. homeless adults is a veteran. Some 131,000 veterans, about 97 percent male, are estimated to be homeless on any given night.
- Many other veterans are considered at risk for homelessness because of poverty, lack of social support, and dismal living conditions in cheap hotels or substandard or overcrowded housing.
- About 45 percent of homeless veterans have mental illness, and more than 70 percent suffer from drug or alcohol abuse. There is considerable overlap between the two groups.

For an overview of a five-year plan to end homelessness among veterans that VA Secretary Eric Shinseki announced in November 2009, visit www.va.gov/opa/pressrel/pressrelease.cfm?id=1807.

For more information on VA's current programs for homeless veterans, visit www.va.gov/homeless.

Kertesz: “Homeless patients are very experienced with stigma, and they are accustomed to finding that doctors, social workers and other authority figures tend to discount their concerns and agenda in favor of what the expert clinician judges to be the problem that merits attention. This fosters distrust. We stand a better chance of achieving our clinical goals over the long term if we can first establish a durable and sustainable relationship.”

He is collecting data to guide the design of a survey for homeless veterans about their experiences with VA primary care. He has a “heavy emphasis,” he says, on enlisting homeless patients to help define quality. Eventually, he hopes to compare existing models within the VA system and learn which features work best.

Lack of chronic-disease care shortens lives

An estimated 131,000 veterans are homeless on any given night. Perhaps twice as many are homeless at some point during the course of a year. Many are coping with mental illness or substance abuse, although Robert Rosenheck, MD, who has studied homeless programs for VA for more than 20 years, asserts that “homelessness is clearly a function of two things: low incomes and high rents.”

VA has been a national leader in homeless programs overall since the 1980s, including efforts spanning housing, work rehabilitation, substance abuse treatment, and mental health. But the agency has been less successful at engaging homeless veterans in primary care.

That is crucial, because chronic diseases typically managed in primary care—diabetes, hypertension, heart disease—are widespread among the homeless. And they account, in large part, for a sharp rise

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Visits to Providence VA clinic lead to housing solution

After 25 years in the military—including a stint as a gunner's mate on a Navy destroyer during the Vietnam War and 15 years as an Army cook—John Mitchell hoped he would find a decent civilian job. Things didn't work out that way.

"I just had a bunch of bad luck," is how the 60-year-old veteran describes the rough stretch that began when he left the service in the mid-1990s. One restaurant where he worked went out of business after a fire. Another laid him off. His diabetes got worse and heart disease set in.

In 2004, he found himself on the street. No job. No home.

Surviving with help from shelters, soup kitchens

"If I wasn't staying in shelters, I was in a cardboard box," says Mitchell, of Providence, R.I. To fend off wintry weather, he would huddle between two metal dumpsters and use discarded soda or beer cases to block the wind. He would lay down larger pieces of cardboard to provide at least some insulation between his ailing body and the cold, hard ground.

There was one shelter in particular he would frequent, but space was tight. "Unless you got there early enough, they'd either close the door or put us on the floor, because they had no room."

Mitchell relied on soup kitchens for most of his meals. Because of his diabetes, he tried to buy less starchy foods at the store when he could. "Not having the medicine I needed wasn't helping, either," he says.

"If I wasn't staying in shelters, I was in a cardboard box."

—Navy/Army veteran John Mitchell

Sometimes he panhandled, even though it went against his grain. "I had to do it. It was a question of survival."

Trying to find a job—even at a fast-food joint—could be an ordeal. "I'd have to get a shower and a shave, and then I'd have to work out how fast I could get clean clothes," recalls Mitchell. "We'd go to shelters and use the bathroom sink to wash our clothes, or hop in the shower and soap up our clothes, and then soap up ourselves." If he had managed to buy himself a new pair of pants or a warm coat, it might get stolen at a shelter.

After more than five years on the streets, Mitchell found his way to a free clinic VA had set up as part of an outreach event. "I

was so sick, and I figured if it's free, it's for me," he says.

That initial contact led to Mitchell's becoming a regular patient at the Providence VA's walk-in clinic for homeless veterans. Eventually, he was referred to the transitional housing facility where he now lives, sharing a three-bedroom apartment with five other men.

Still coping with health challenges, but grateful

Mitchell is still coping with a variety of health problems. He gets flashbacks that trigger depressive episodes and has arthritis in both hips—on top of his other chronic conditions. But he feels grateful that he has the VA clinic to turn to for medical care. And that he is no longer on the street, but on the road, he hopes, to better days.

"Nothing's easy," says Mitchell. "I'm still struggling. But at least I have a roof over my head." →



In good hands—John Mitchell (right) meets with social worker Sean Lonergan, MSW, at the Providence VA primary care clinic where Mitchell is now a regular patient.

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Ironically, Fishman's early tetanus experiments were done with no intention of using the toxin itself therapeutically. In fact, his team was using only a segment of the tetanus molecule—the part that targets and enters motor neurons—in hopes of using it to ferry other therapeutic agents into the cells. The toxic part of the protein was irrelevant—or so they thought. Once they realized how good the toxin was at targeting nerve cells, they decided to repeat their animal experiments with the whole, toxic form of tetanus. They noted with great interest its activating effect on muscles.

Natural toxins becoming hotter topic for researchers

Fishman says natural toxins are becoming a hotter topic among researchers. “There’s lots of precedent recently in the medical literature showing that we can harness the power of natural toxins,” he notes. He cites the example of diphtheria toxin, which spurs the production of antibodies that kill some tumors.

Fishman's team is using diphtheria toxin in a different way: They are combining it with the part of the tetanus molecule that targets nerve cells. The goal is a hybrid toxin that, like botulinum toxin, could be used to selectively kill motor neurons.

Fishman is also collaborating with Homeland Security researchers to develop antidotes to botulinum toxin. The project is important for national security, but there may also be a routine clinical benefit, he explains.

“I tell patients all the time, I’m going to be very careful with dose, I’m going to stay in the lowest ranges, because if I overdose you, there is no antidote. I’d like to be able to rephrase that and say, if I overdose you, I can give you something that will terminate the action of the toxin.” —

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in mortality. Life expectancy for homeless people is 30 years less than average.

The VA health system as a whole is working toward a care model to brighten that picture. As of today, most VA medical centers still deliver primary care to homeless veterans through mainstream primary care clinics. Veterans are usually referred from other VA homeless programs. Some VA sites have added primary care providers to their mental health clinics, to speed up access to primary care.

Meshing primary care with other homeless services

Several VA medical centers have gone further. Their goal is to integrate primary care with a fuller network of homeless services. Rather than having to navigate through a maze of various services at different locations on different days, homeless veterans can see an internist, social worker and psychologist, for example, all in one morning. Missed appointments—a particular problem for the homeless—are minimized. Primary care becomes the hub of treatment, rather than one element to be coordinated with others.

One of the best-known examples of this approach is the Mental Health Outpatient Treatment Center on the VA campus in Los Angeles—a city sometimes called the homeless capital of America. The center was funded by VA in 2002 as a demonstration project. An 18-month study published last year by a team including Rosenheck and James McGuire, PhD, of the Los Angeles VA showed the clinic has increased access to primary care and curbed emergency-room use. The researchers are continuing to study the benefits on patients' long-term health.

Thomas O’Toole, MD, runs a similar clinic at the Providence (R.I.) VA. Homeless

veterans are welcome without an appointment. They can see primary care doctors as well as mental health providers, social workers, and benefits and housing counselors. Referrals to VA substance abuse programs are made as necessary. It’s one-stop service for people with multiple, complex health and social needs. “We try to have open-access and sensitive care,” says O’Toole.

His research focus is motivating veterans to visit the clinic in the first place. “They are a treatment-resistant population,” he says. “But if we can somehow increase their motivation, they will seek out care.”

O’Toole has designed a protocol to complement existing outreach efforts. A nurse will accompany the clinic’s social worker, who does outreach in a mobile van and at local shelters and soup kitchens. The nurse will do personalized health assessments for homeless veterans, identify issues of concern, and then conduct a motivational interview. This counseling technique honors patients’ autonomy and elicits and builds on their own internal motivation to make positive changes.

Claire Bourgault, RN, describes one of the initial encounters she had as part of the study, which is just now getting under way. “I talked with the veteran about what I found—the potential problem he may face in regard to his health. I said to him, it’s your choice, but it may be in your best interests to continue to see us. He said OK, but we didn’t know if he would come back. Sure enough, he did.”

Measuring results based on health and housing

O’Toole, Kertesz and other experts have little doubt at this point—though hard evidence from studies is still being compiled—that primary care for homeless veterans works best when it’s integrated

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with the other homeless services that VA offers—housing, work, mental health, addiction treatment. “These are crucial pieces for the homeless, and they are obvious strengths of VA,” notes Kertesz. But how exactly all the pieces should fit together remains to be determined. The Los Angeles and Providence VA models seem fairly successful, but researchers are intent on pinpointing the optimal approach and replicating it across the entire VA system.

Most critical is the housing piece. O’Toole measures outcomes at his clinic based not only on how many veterans come in for primary care, and how their health metrics change, but also on how many eventually end up with housing. “We’re trying to connect people to resources so they’re able to go, say, from an emergency shelter into per diem housing or a domiciliary. Those environments are going to be more conducive to better chronic disease management.”

Another key element, perhaps less tangible, is the attitude with which care is provided. This may be harder to measure, but it will likely be captured in the patient survey Kertesz’s group is designing.

“We need to convey expectations about high quality and patient engagement—the same humanity and dignity that would be afforded any other patients. Patients who are homeless clearly respond to that,” says O’Toole. On a similar note, he echoes Kertesz’s view on the importance of building relationships and respecting homeless veterans’ concerns and needs—even when they seem to compete with medical goals per se. “Unless we spend time understanding what the patient’s priorities are and meet them halfway, our agenda will be dead in the water.”

As VA’s primary care for the homeless evolves, says O’Toole, it could come to play a key role in the vision—shared by VA Secretary Eric Shinseki, the National Coalition for Homeless Veterans, and other advocates—to end homelessness among veterans altogether.

O’Toole: “My working philosophy has always been that most people were not born homeless, and that we should do everything in our power to make sure they don’t die homeless.” —

VA Research Week set for April 26–30

VA Research Week 2010 will be held at VA medical centers nationwide April 26-30, with kickoff events taking place in Washington, DC, April 21–23. The theme of this year’s events will be “85 Years of Discovery, Innovation, and Advancements.”

For details and supporting materials, visit the VA Research website at www.research.va.gov.

CAREER MILESTONES

Karen Ashe, MD, PhD, was elected to the Institute of Medicine. Membership in the organization is considered one of the highest honors in medicine. Ashe, with the Geriatric Research, Education and Clinical Center at the Minneapolis VA and the University of Minnesota, studies the molecular basis of memory loss in Alzheimer’s disease.



Ashe

Matthew Friedman, MD, PhD, and Paula Schnurr, PhD, co-founders of VA’s National Center for Posttraumatic Stress Disorder, were honored by the International Society of Traumatic Stress Studies.



Friedman

Friedman, executive director of the NCPTSD, received the Public Advocacy Award for advancing society’s understanding of trauma. Schnurr, deputy executive director of the center, was given the Robert S. Laufer Award for her scientific achievements—for example, leading a large clinical trial of psychotherapy for women with PTSD. The researchers are also with Dartmouth Medical School.



Schnurr

John Raymond, MD, of the Charleston VA and the Medical University of South Carolina, received the 2009 Marcy Speer Outstanding Reviewer Award from the Center for Scientific Review at the National Institutes of Health. The award recognizes extraordinary commitment—in terms of leadership and volunteer hours—to the peer review process at NIH, which helps the agency assess some 56,000 applications each year and invest more than \$20 billion in the most promising proposals. Raymond, a nephrologist, studies kidney cell function. —



Raymond

Inside: Homeless veterans and primary care

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and collecting blood, urine and saliva samples to check the levels of stress hormones. They will also scan DNA for gene variants possibly linked to stress and resilience. In yet other tests, volunteers are shown different images—some pleasant or neutral, others showing combat casualties or other disturbing scenes—while researchers record eyeblinks and changes in heart rate. They are also looking at how the Marines filter out extraneous stimuli and react to sudden noises.

Most past studies have looked only at a cross section of combat veterans at a single point in time and identified traits more common in those with PTSD—for instance, a brain region that appears smaller, or a larger-than-normal heart response to sudden loud tones. But that leaves unclear whether the trait is a risk factor that existed before the PTSD, or a result of the condition.

Some insights have come from studies of twins. If a trait is found in combat veterans with PTSD but not in their genetically identical brothers, it is considered a probable result of PTSD, not an inborn risk factor. But according to Baker, studies have yielded mixed findings and more research is needed. By collecting



Photo by Col. Aron Shorobeg

The resilience factor— Navy corpsmen tend to a Marine wounded in a firefight in Afghanistan. In the Marine Resilience Study, VA and Department of Defense investigators hope to zero in on the factors that enable troops to withstand and recover from the emotional stress of war.

baseline data and tracking changes over time, the Marine Resilience Study may help pin down answers.

Overall, the researchers say they hope the study will not only build understanding of why some people develop chronic PTSD

while others don't, but also show how physical, mental, social and spiritual factors interact to aid recovery. Nash: "If we can build better models of recovery, the military may be able to turn those models into more effective programs for prevention." —