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RETHINKING RELIEF

Doctors are breaking away from opioids to treat chronic pain with nondrug remedies and psychological interventions instead

By Stephani Sutherland

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The United States is in the grip of an unprecedented public health crisis—

one in which well-meaning doctors have played a part. Between 1999 and 2014 sales of prescription opioid drugs nearly quadrupled. In 2012 alone, physicians issued 259 million opioid prescriptions—enough to give a bottle of pills to every adult in the country. And in 2015 more than half of all overdose deaths in the U.S. involved opioids—either pain medications, such as OxyContin and Vicodin, or illicit substances, such as opium and heroin. To put that statistic in perspective, opioids claimed roughly as many lives that year as car crashes.

Addiction is undoubtedly part of the problem, but experts now agree that the real driver behind the opioid epidemic is chronic pain. According to a landmark study published in 2011 by the Institute of Medicine, an estimated 100 million American adults live with persistent or chronic pain. Many rely on opioids just to keep moving.

Chronic pain is defined as lasting more than six months but involves thought, emotion, attention, sleep, memory and social interactions.

There is no question that these drugs provide the best defense against acute, short-term pain, which alerts us to an injury or disease and subsides during recovery. But chronic pain is fundamentally different. It lingers long after an injury has healed and can produce a variety of symptoms, from headaches to body aches to crippling fatigue. It may stem from an underlying condition, such as osteoarthritis or multiple sclerosis, or have no obvious source. For some, chronic pain begins with nerve damage from diabetes, chemotherapy, a virus, a car accident or some other insult. In these cases, injured nerve fibers mistakenly continue to send pain signals to the brain, causing what is known as neuropathic pain.

No matter how chronic pain starts, it often increases and spreads, leaving many people reaching for more pills. Unfortunately, higher doses of opioid drugs do not guarantee relief—and can actually make matters worse. For starters, patients build tolerance to these medications, so that over time, it takes more opioids to blunt the same levels of pain. Higher doses increase the risk of dangerous side effects, including addiction, coma and death [*see box on page 33*]. And recent research shows that even relatively low doses of opioids can also cause hyperalgesia, or an increased sensitivity to pain: sometimes these drugs intensify the very pain they are meant to suppress.

For these reasons, a significant number of chronic pain sufferers eventually find themselves caught in a delicate—and deadly—balancing act: They need to take more opioid medications to keep their disabling pain in check while somehow dodging the drugs' serious and life-threatening side effects. Some succeed for decades. But those who lose their footing are

FAST FACTS

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1. Opioid drugs work well for acute pain but not chronic pain, which is fundamentally different and requires a broader, multipronged treatment approach.
2. Complementary therapies—including yoga, mindfulness-based stress reduction, biofeedback and acupuncture—have all shown promise against chronic pain.
3. Psychological interventions targeting anxiety and the tendency to catastrophize are also helping people to reduce their experience of chronic pain.

flooding emergency rooms and hospital beds, battling withdrawal, accidental overdose and a host of other opioid-related complications.

Last year medical authorities began to respond on several fronts. In March 2016 the Centers for Disease Control and Prevention issued stricter guidelines for prescribing opioids. Contrary to what has been common practice, it advised against treating chronic pain with these drugs unless the benefits clearly outweigh the risks. Surgeon General Vivek H. Murthy amplified that message five months later, when he wrote directly to all the nation's health care providers—the first time any surgeon general has done so—urging 2.3 million professionals to commit to "turn the tide on the opioid crisis." Around the same time, the Food and Drug Administration required stronger warning labels on all opioid medications. The Department of Health and Human Services joined the fray by issuing a new *National Pain Strategy,* emphasizing the need for greater prevention, safer drugs and broader approaches to treatment.

The message is being heard. At a handful of state-of-the-art pain centers around the country, clinicians are exploring a range of nondrug alternatives, from psychological interventions to complementary therapies. Researchers are also working on next-generation opioid drugs, along with new nonopioid painkillers [*see box on page 34*]. These initiatives represent the one upside to the opioid crisis: "It's forcing us to revisit how we care for people in pain," says Sean Mackey, who heads the Pain Management Center at Stanford University and co-chaired the committee of experts from multiple U.S. agencies that developed the new HHS strategy. "I'm not pro-opioid. I'm not anti-opioid. I'm pro-patient," he says. "There will be no magic bullet, no pill. Chronic pain requires multipronged treatment."

Many chronic pain sufferers are now caught in a delicate balancing act—taking higher doses of opioids to keep disabling pain in check while also dodging the drugs' serious and deadly side effects.

A Different Kind of Pain

In August 2016 David,* a former school worker, wheeled himself into pain psychologist Beth Darnall's office at the Stanford pain clinic, one of the nation's few multidisciplinary pain centers. He and his wife had traveled for three hours that morning from their home by medical transport. David had undergone minor surgery on his right foot just one day before and was still wearing a hospital-issued blue paper bootie, but nothing was going to stop him from keeping this appointment, which he had waited weeks to get.

Darnall started by taking a detailed medical history. David described ongoing pain in his back and body, which had started in 1995, the last time he had felt well enough to work full-time. That year had been devastating for him medically: he had contracted meningitis from a tick bite and was diagnosed with cancer. The diseases, plus chemotherapy, had ravaged his nerves, causing constant pain, which led to further challenges, both physical and psychological.

Many experts now view chronic pain as a disease in its own right. Over time it engages and changes patterns of activity in brain areas associated not only with physical sensations but with sleep, thought and emotion. No wonder that studies show that chronic pain is associated with higher rates of mortality, sleep disorders, depression and anxiety. For 20 years David had been taking ever escalating doses of opioid drugs, including methadone, a long-acting opioid painkiller, and fast-acting Dilaudid, occasionally supplemented with Demerol, yet another opioid. But in addition, he depended on Valium to tamper his anxiety and Ambien to help him sleep.

For most people, this drug cocktail would be deadly. For David, it had become a daily routine. Darnall listened to David's story and then asked if anyone had ever spoken to him about how dangerous this drug combination was. "No," he replied, although he did have firsthand experience: on three separate occasions, he had been rushed to the hospital near death. "This is really the only tool you've

more than an enduring physical sensation. It can affect
It is also associated with higher rates of mortality.

**The patients' names have been changed to protect their privacy.*

ry therapy that has garnered the most attention in recent years is mindfulness-based stress reduction (MBSR), a clinical and secular adaptation of Buddhist meditation practices. Jon Kabat-Zinn, now a professor of medicine emeritus at the University of Massachusetts Medical School, developed MBSR in the 1970s. Since then, MBSR classes have cropped up in every U.S. state and in more than 30 countries. A growing body of evidence suggests that MBSR—which encourages nonjudgmental awareness of the present moment and fosters greater mind-body awareness—can mitigate a variety of ailments, from cancer and depression to drug addiction and chronic pain.

In 2016 senior investigator emeritus Daniel C. Cherkin of the Group Health Research Institute in Seattle and his colleagues tested three treatments for chronic low back pain in 342 young and middle-aged adults: MBSR, cognitive-behavioral therapy—designed to change pain-related thoughts and behaviors—and standard pain care. They found that compared with participants who received standard pain care, more patients receiving MBSR or CBT showed a significant drop in "pain bothersomeness" after 26 weeks. In addition, the MBSR and CBT groups improved more in their functional abilities.

Other chronic pain sufferers are making gains with biofeedback. Using sensors to monitor bodily signals such as muscle tension and heart rate, they build awareness of physiological processes and learn to modulate their own pain. A 2017 meta-analysis evaluated biofeedback for chronic back pain in 1,062 patients and found that it not only lowered pain intensity but also improved patients' coping abilities and reduced the incidence of pain-related depression. Mackey and others have also tested a more sophisticated technique called neurofeedback, which provides patients with images of their own brain activity using electroencephalography or functional MRI. This kind of training can teach patients to control brain regions associated with pain processing.

Additional evidence suggests that acupuncture might help ease chronic pain in some cases—perhaps, some scientists speculate, by stimulating anti-inflammatory signals in the skin or influencing activity deep in the brain. The practice remains controversial, in part because it is difficult to study. But a 2014 analysis of 29 clinical trials of acupuncture for chronic pain in nearly 18,000 patients showed that compared with treatment with no needles or misplaced needles, the traditional form—with needles placed according to centuries-old Chinese practice—produced greater pain relief. At the same time, a significant number of people in the control groups also saw benefits, suggesting a strong placebo effect.

That finding reinforces the idea that when it comes to pain, simply being under the care of a receptive health care professional can be palliative. Researchers are investigating how all these complementary treatments work, "but we are not waiting for basic science to tell us the optimal way to treat pain," Shurtleff says. There is broad agreement that mindfulness, yoga, biofeedback and acupuncture may succeed by changing patients' relationship to their pain rather than actually lowering the intensity of the physical sensation. At the NCCIH, Shurtleff and others are trying to figure out how to best apply ex-

Relief at a Cost

Opioids' Side Effects

Opioids work so well in the short run because they mimic our brain's own morphinelike molecules, called endogenous opioids, which are released to drown out incoming pain signals. Endogenous opioids are released only where they are needed, in the brain's pain circuitry, but opioid drugs go everywhere and activate receptors throughout the body. As a result, the drugs cause a range of side effects:

- **In the brain's pain circuits:** opioids dampen pain, but tolerance develops quickly, so higher doses are needed to achieve the same effect.
- **In the gut:** opioids slow movement in the digestive tract, leading to constipation.
- **In the spinal cord:** some people develop intense itching in response to opioids.
- **In the brain's reward pathway:** the drugs produce highly pleasurable sensations, often leading to addiction.
- **In the brain stem:** most dangerous of all, opioids can drown out signals from the neurons that control breathing, leading to death by respiratory depression.

THE AUTHOR

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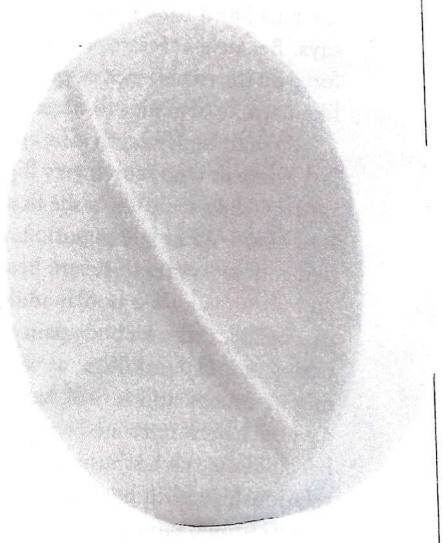
Next-Generation Painkillers

Researchers are working to create opioids that can blunt pain without their nefarious side effects. For instance, extended-release opioids, which are already available, produce less reward than a single blast, reducing the likelihood of addiction. But more sophisticated efforts are also under way. It turns out that the activation of opioid receptors triggers two signaling pathways within cells. Broadly, one pathway leads to pain relief, and the other leads to side effects. Researchers are now focused on creating compounds that can selectively turn on one without the other.

For example, clinical trials are now being conducted to test oliceridine, or TRV130, an agent produced by Pennsylvania biopharmaceutical company Trevena. And in September 2016 researchers described another compound, called PZM21, that produced analgesia in mice without side effects. "The principal goal for both PZM21 and TRV130 is to reduce opioid respiratory depression, which has been shown to be possible both in preclinical [animal] studies and in clinical studies," says William Schmidt, a pharmaceutical consultant at NorthStar Consulting in Davis, Calif. "In addition, both [drugs] appear to show reduced abuse liability and reduced effects on the GI tract, hence less risk of constipation."

To find the new compound PZM21, researchers used computer modeling to test how three million different "virtual molecules" interacted with the structure of the opioid receptor. Based on those interactions, they zeroed in on 23 compounds, which they further tested in cells in a dish. In these cells, PZM21 strongly activated the pathway for pain relief but not the pathway that produces side effects. In mice, PZM21 was more effective than morphine at dampening pain. Future clinical trials of PZM21 and ongoing trials of TRV130 will determine whether these agents will deliver on their promise. —S.S.



isting complementary treatments. "Patients are suffering, and we want to find what really works. We take that pragmatic approach," he says.

The NCCIH recently conducted an extensive review of published clinical trials for a variety of complementary therapies with the aim of finding out which treatments might work best for which patients. It found that acupuncture and yoga benefited people with chronic back pain the most. Acupuncture and tai chi proved most helpful for those with chronic pain resulting from osteoarthritis. Massage therapy provided short-term benefits for neck pain, and relaxation techniques were most effective in those with severe headaches and migraines [see "Can Anything Stop My Migraine?" on page 36].

Feeling Your Pain

There is another reason why individualized care makes sense for chronic pain: different people can experience the same kind of pain in very different ways. In particular, researchers are discovering that how much chronic pain affects any one person depends heavily on so-called biopsychosocial factors—how someone reacts to pain emotionally, what other sources of stress exist, how much social support surrounds the person. Targeting these influences can not only reduce patients' experience of pain but dramatically improve their quality of life. Indeed, chronic pain–related disabilities often leave people isolated and cut off from friends, which can, in turn, make the pain more intense.

To identify biopsychosocial factors up front, patients at the Stanford clinic fill out an extensive online questionnaire, capturing everything from work histories and adverse childhood experiences to sleep habits and anger levels. Mackey believes that collecting this type of data holds the key to matching patients with effective treatments. The questionnaire is part of a free, open-source repository that he and his colleagues at Stanford have created, together with researchers at the NIH. The system, called the Collaborative Health Outcomes Information Registry (CHOIR), is now in use at medical centers around the U.S. and soon will be in several other countries. It contains data from more than 15,000 patients. Health care providers can use the system to track patients' progress over time and to compare their trajectories with similar cases.

This data set has revealed that one factor in particular—a mindset called catastrophizing—predic

the impact of chronic pain on a person's life far better than any other measure. At its core, catastrophizing is a tendency to exaggerate or magnify the threat of pain, to fear the worst and remain focused on the experience of pain. For people trapped in this way of thinking, their pain feels overwhelming. They hold little hope that they will ever be well again. "That leads to a very strong desire to escape the pain, and they reach for the meds," Darnall says. Because catastrophizing is such a powerful force on the experience of pain, she says, "it seems like a stroke of genius to target it."

Darnall took exactly this approach with Angela,* a patient who scored very high on CHOIR's catastrophizing scale when she first came to the Stanford clinic. After a traumatic brain injury, Angela had endured years of severe headaches, neck pain and fibromyalgia, a poorly understood syndrome that includes all-over body pain and fatigue. She was taking opioid painkillers, as well as various potent migraine medications. Still, her pain often left her in a wheelchair. It interfered with her ability to care for her children, run her business, and maintain healthy relationships with her husband and parents. Like many chronic pain patients, Angela also mourned the loss of her life before the pain. She used to enjoy a variety of fast-paced sports—activities that now, she says, exasperated, "I can't even imagine!"

Angela's sense of powerlessness is common—and doctors who dismiss chronic pain because they cannot explain it only compound that feeling. When surgeries or other treatments fail to help, patients learn to expect failure. "Patients come to us so demoralized—they have been through the mill," Darnall says. "Our job is to 'remoralize' them first." The initial step is giving patients back a sense of control, no matter how small. "People need to know that their pain is real, it's not their fault, and here are some ways that we can address it," Darnall says.

As with all her patients, Darnall invited Angela—along with her family—to a free two-hour educational seminar to learn about how pain and biopsychosocial factors interact. Angela also received a relaxation CD like the one David was given. Darnall explains to patients in her care that the auditory experience recorded on the CD works to calm the nervous system and that they should think of listening to it as taking a dose of mind-body medicine. "Do it regularly—establish a new pattern," she emphasizes. "Even if you can't do 20 minutes, do five. Doing something is better than nothing. Always, always."

Angela started using the CD right away. She also took up yoga, began regular massage therapy and pursued a specialized pain-focused talk therapy with Darnall. Now, several months later, she has made measurable gains. She has learned to keep her emotions in check during stressful times, which has improved her relationships. Her catastrophizing score is way down. She no longer takes opioids but instead only a very low dose of naltrexone, a drug that blocks opioid receptors and is thought to reduce inflammation. And she can walk again for several miles at a time, pain-free. Perhaps most significant, she has started to set goals for her future. "I can't dance like I used to, but I can move a little bit," she says with a sly smile. For Angela, who spent years in a wheelchair, thinking she would never move freely again, to dream of dancing is a triumph. M

One factor—a mindset called catastrophizing—predicts the impact of chronic pain on a person's life far better than any other measure. It is the tendency to magnify the threat of pain, fear the worst and remain focused on the experience of pain.

MORE TO EXPLORE

- **Acupuncture for Chronic Pain.** Andrew J. Vickers and Klaus Linde in *JAMA*, Vol. 311, No. 9, pages 955–956; March 5, 2014.
- **The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop.** Roger Chou in *Annals of Internal Medicine*, Vol. 4, No. 162, pages 276–286; February 17, 2015.
- **National Pain Strategy: A Comprehensive Population Health-Level Strategy for Pain.** Interagency Pain Research Coordinating Committee. U.S. Department of Health and Human Services, 2016. https://iprcc.nih.gov/National_Pain_Strategy/NPS_Main.htm
- **Effect of Mindfulness-Based Stress Reduction vs Cognitive Behavioral Therapy or Usual Care on Back Pain and Functional Limitations in Adults with Chronic Low Back Pain: A Randomized Clinical Trial.** Daniel C. Cherkin et al. in *JAMA*, Vol. 315, No. 12, pages 1203–1299; March 22, 2016.
- **Evidence-Based Evaluation of Complementary Health Approaches for Pain Management in the United States.** Richard L. Nahin et al. in *Mayo Clinic Proceedings*, Vol. 91, No. 9, pages 1292–1306; September 2016.
- **Efficacy of Biofeedback in Chronic Back Pain: A Meta-analysis.** Robert Sielski et al. in *International Journal of Behavioral Medicine*, Vol. 24, No. 1, pages 25–41; February 2017.

From Our Archives

- **A Painful Descent into Addiction.** Daniel Barron; Cases, March/April 2017.