

The Wall Street Journal

A New Prognosis for Pain Care

Landro, Laura

February 6, 2019

Innovative ways to measure, understand and treat pain are allowing doctors to ease patients' suffering—without relying on dangerous drugs



CREDIT: EIKO OJALA

A new world of pain treatment is on the horizon.

Advances in measuring pain could show doctors how much pain a patient feels more vividly and help them dial the treatment up—or down—more precisely. Better ability to assess each patient's risk for chronic pain, including identifying the genes that make it more likely, could lead to more personalized and effective treatments. And a deeper understanding of pain's causes and new methods to treat it are starting to improve doctors' ability to ease pain without relying on potentially dangerous and addictive drugs.

The need has never been more urgent. More than 50 million adults in the U.S. are living with chronic pain at an estimated annual cost of \$560 billion in medical care, lost productivity and disability programs, according to federal data. Unlike acute pain—the sharp, instantaneous sensation that alerts the body to injury or trauma—chronic pain can persist long after normal healing, lasting for months or years.



To decrease lower back pain, University of North Carolina researchers are testing electrical currents that stimulate certain brain rhythms. *PHOTO: ALEX BOERNER FOR THE WALL STREET JOURNAL*

Lower-back pain and migraines are among the most common complaints, but chronic pain can affect any part of the body, drastically limit activity and lead to hopelessness and depression.

With few tools to understand what each patient is feeling, and why, doctors have often turned to a blunt, one-size-fits-all treatment: prescription opioids, which can be effective in treating acute pain after surgery or in the advanced stages of cancer.

But there is scant evidence that opioids are effective for chronic, long-term pain outside of end-of-life care, and the sharp rise in opioid prescriptions after 1999 contributed to an epidemic of overdoses and deaths. In 2016, the Centers for Disease Control and Prevention recommended against opioids as first-line treatment of chronic pain. And doctors have become more cautious, leading to a decline in prescribing rates.

Here are some of the advances that are improving the understanding of pain and medicine's ability to treat it.

How much does it hurt?

For decades, doctors have used a simple 1-to-10 numerical scale, and a range of smiley to frowning faces, to assess how much pain a patient is feeling. Now researchers are developing objective measures for pain by monitoring how the brain reacts to it.

This can allow doctors to determine how much pain a patient is feeling when the patient can't communicate, such as infants or Alzheimer's sufferers. It can also help doctors

predict how patients will react to certain medications or procedures, which can make treatments more effective and aid in the development of new drugs.

In a test at Stanford University, volunteers were touched with prods that caused pain or ones that didn't, and their brain activity was tracked with a noninvasive imaging system. Using an algorithm that detects patterns in brain activity, researchers could distinguish between painful and nonpainful stimuli more than 80% of the time. Sean Mackey, chief of the division of pain medicine and director of the neuroscience and pain lab at Stanford, says the real benefit to using brain scans may be in helping to test the effectiveness of new drugs or procedures. Artificial intelligence can take data from brain imaging and use it to make predictions about how patients will respond to treatment.

Follow-up studies have been used to detect whether someone is experiencing chronic pain based on brain activity or the structure of the brain.

His group has developed technology to image the entire central nervous system from the spinal cord to the brain, to better predict treatment response and whether someone with chronic pain will improve or worsen over time.

“If we had a way to use brain activity to predict the response to treatment, that is at the heart of precision medicine,” Dr. Mackey says. He warns, however, there are ethical issues to be resolved, such as whether brain scans could be used to deny treatment to patients if they don't confirm the patient's own description of pain.

Another area of research involves measuring theta waves, a type of brain activity. A study by researchers at Brown University in November found that measuring the power of theta waves in animals using electroencephalograms—a process involving electrodes attached noninvasively to the scalp—is an effective and direct test of pain, as well as the performance of pain medication.

Study co-author Carl Saab, director of the center for pain and neural circuits at Brown University and Rhode Island Hospital, says that in humans pain is more complicated.

But by combining theta-wave data and other information, artificial intelligence can develop algorithms for measuring pain and identifying pain types. The algorithms can accurately predict pain scores on the numerical and smiley-face pain scales used in clinics and emergency departments, Dr. Saab says.

The algorithms under development will be able to predict pain by type, according to Dr. Saab. For example, brain waves are different for acute back pain than they are for chronic back pain, and distinguishing between the two conditions is crucial for determining the best treatment such as opioids or surgery.

Using the algorithms could eventually “help patients convey their pain level with more accuracy and assist the doctor in reaching an objective pain diagnosis,” he says. This

could lead doctors to prescribe fewer opioids, lowering the risk of addictions, and lead to better health outcomes.

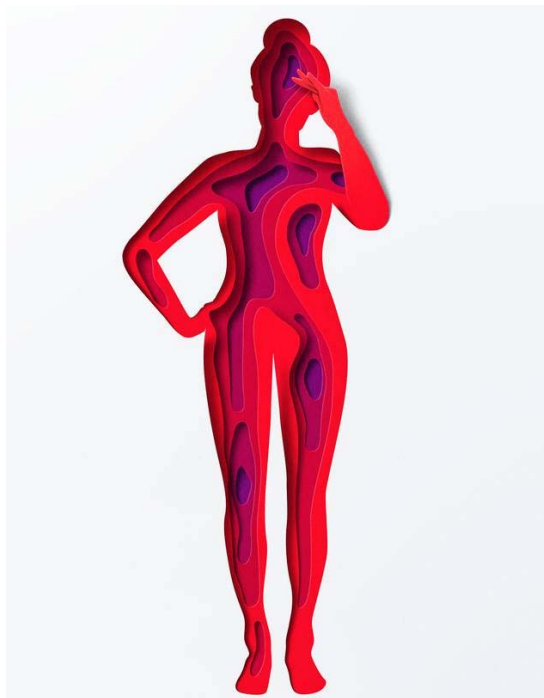
He adds, “This is not going to trump or deny what the patient says, it is simply going to bring in this third perspective that is objective, which would be particularly useful if a verbal report cannot be obtained from the patient.”

Where does the pain come from?

Researchers are developing assessments to provide a fuller picture of how pain affects a patient’s life. That has significant consequences for treatment. So, doctors are starting to examine how a patient’s other psychological and physical conditions can change the subjective experience of pain—such as how pain can be amplified by depression and anxiety.

At the University of Washington Center for Pain Relief in Seattle, researchers developed an online assessment called PainTracker where patients answer a series of questions to determine what impact pain has on their lives and help them better understand their condition and manage their recovery. Questions involve not just pain intensity but issues involving difficulty with sleep, mood, appetite and performing daily activities.

An evaluation of data from over 4,000 patients found that a substantial number were struggling with depression, anxiety and post-traumatic stress disorder and were severely disabled or worse. Many were at moderate to severe risk of opioid misuse.



CREDIT: EIKO OJALA

Learning about such issues through the PainTracker assessments can help busy doctors evaluate the patient's pain experience and help steer them to the most effective treatments, the researchers say. "Many patients with chronic pain get hunkered down into this chronic crisis mode where they are just thinking about surviving into the next day," says Mark Sullivan, a co-author of the study and professor of psychiatry and behavioral sciences. He says the assessments help doctors steer patients to interventions that have been shown to help manage pain, such as developing better sleep habits and behavioral therapy to develop resilience and coping skills.

Follow-up questionnaires are used to create a visual graph showing areas of improvement and engage patients as active participants in their care.

The researchers also incorporated the assessments into a web-based support tool, PainTracker Self-Manager, using concepts from so-called acceptance and commitment therapy, which has been shown to help patients learn to live with pain to limit the control it exerts over their life. In a pilot test, patients could receive coaching from nurses and social workers along with education, and found it helped patients improve their own management of chronic pain and satisfaction with their treatment. "You have to empower patients to do what they can to help themselves," Dr. Sullivan says.

Using Genetics to Understand and Treat Pain

Studies have shown that family history and shared genetic risk factors can play a role in the development of chronic pain. Understanding those risk factors—and identifying people who have them—could let doctors optimize treatments for those patients, and give them a better shot at recovery.

At the University of North Carolina, researchers have found that people with certain genetic variants are more likely to have chronic pain after exposure to trauma, such as sexual assault and motor-vehicle crashes. In a study of 1,500 blood samples of people who had experienced motor-vehicle trauma, published last year in the *Journal of Neuroscience*, the researchers found that those with the risk variant had impaired ability to regulate the stress hormone cortisol, and thus are more likely to experience chronic pain than people without the variant.

"The finding helps us understand why some people develop chronic pain after trauma and others do not, and also helped us identify a possible novel target for drug discovery," says lead study author Sarah Linnstaedt, an assistant professor of anesthesiology and investigator at UNC's Institute for Trauma Recovery. The goal is to develop a therapy that could help the body control cortisol levels after trauma exposure.

Dr. Linnstaedt's lab is also investigating the role of sex hormones in driving increased chronic pain after trauma exposure in women.

Other researchers are investigating how to manipulate the body's pain pathways—the interactions between molecular-level parts of the body that lead to different types of pain.

At St. Louis University, Daniela Salvemini, director of its center for neuroscience and professor of pharmacology and physiology, discovered pain pathways that are dependent on two particular molecules. In animal studies, scientists have been able to block or reverse pain with drugs that targeted those molecules.

Dr. Salvemini is now investigating whether those molecules can serve as biomarkers—measures of biological processes or interventions—for pain associated with a number of different health conditions. If so, doctors can optimize treatments for specific groups of patients that have those biomarkers. “Not everyone develops pain in the same manner or responds to drugs in the same manner, so the goal is to select patients who might be the best candidates for a drug,” Dr. Salvemini says.

Her team is working with doctors at university-affiliated medical practices who treat patients with conditions such as endometriosis, bladder pain and nerve pain caused by chemotherapy, to test for high levels of the molecules in their blood. That in turn would help confirm that a pain pathway is activated and determine whether patients would benefit from a drug that specifically targets the molecules.

Going directly to the brain

To replace the need for drugs that can lead to addiction, researchers and device companies are also making advances in neuromodulation—the use of technology such as surgically implanted spinal-cord stimulators to interrupt pain signals with electrical pulses to the brain.

A new spinal-cord stimulator from Boston Scientific, the Spectra WaveWriter SCS System, allows patients to control how much of a sensation they feel in areas with pain. Maulik Nanavaty, president of the neuromodulation division, says that this choice allows doctors and patients to deliver therapy most comfortable to them, and help with chronic pain from failed back surgery and other intractable pain conditions.

First introduced in the 1960s, neuromodulators now include advances such as the ability to provide more personalized therapies to patients.

These devices, which are implanted into the patient, carry the risks of other invasive surgeries, such as infection, and cost \$25,000 or more. But they are becoming more common and are generally covered by insurance for patients with difficult-to-treat pain syndromes or failed back surgeries.

Jim Davis, a retired Marine in North Carolina, had one of the devices implanted last August. Mr. Davis, 48, suffering chronic back pain after a truck accident, tried a number of other options including back surgeries and alternative therapies, but the pain returned. Prescription opioids “weren’t even taking the edge off, and I was more stoned than relieved of pain.” Neuropathy in his feet made it impossible to walk, and he even considered having both amputated.

The Boston Scientific device, he says, has allowed him to stop using a wheelchair and start swimming and scuba diving. He tweaks his setting on the device so he doesn't have sensations at night because it's easier to sleep without it. He sometimes turns it off for 20 minutes at a time.

"I'm not worried anymore about not being near my morphine pump or leaving the house without my pain pills," Mr. Davis says.

Researchers are also testing neurostimulation approaches that don't require surgery or implanted devices. Flavio Frohlich, director of the Carolina Center for Neurostimulation and associate professor of psychiatry at University of North Carolina, says that chronic pain disrupts normal patterns of brain activity in regions associated with pain, "so you get a persistent pain signal to the brain."

With a treatment known as transcranial alternating-current stimulation, Dr. Frohlich and other researchers delivered weak alternating currents of electricity, imperceptible to study subjects, through electrodes on the scalp. In a study published in November in the *Journal of Pain*, they showed that by targeting one brain region, they could enhance naturally occurring brain rhythms known as alpha oscillations and significantly decrease symptoms of lower-back pain in just one session.

A holistic approach to pain

Some pain-medicine experts are returning to an idea originally conceived in the 1970s—combining modern technology with holistic approaches. According to the National Institutes of Health, a growing body of evidence suggests approaches such as acupuncture, hypnosis, mindfulness meditation, spinal manipulation and yoga may help to manage chronic pain. Research also supports cognitive behavioral therapy, which teaches patients skills to overcome negative thoughts and behaviors, as a cost-effective way to manage some chronic pain.

The NIH last year doubled its budget for pain and addiction research to \$1.1 billion. In addition to research on nonaddictive pain medicines and new biomarkers that might predict who is more likely to transition from acute to chronic pain, it is funding studies to identify the most effective nondrug and integrated therapies for specific pain conditions.

"There are appropriate uses for opioids for pain management, but the risks when they are used over the longer term have to be balanced with the benefits," says Linda L. Porter, director of the Office for Pain Policy at the National Institute for Neurological Disorders and Stroke, part of the NIH. "We need to offer people with chronic pain something else, because they are desperate to get better and get back to their lives."