Cold pressor tests estimate a person's pain threshold based on how long they can tolerate ice-cold water.

PRIMED FOR PAIN

Do opioids make chronic users more sensitive to pain?

By **Kelly Servick**; *Photography by* **Matthew Rakola**

Mark Hutchinson could read the anguish on the participants' faces in seconds. As a graduate student at the University of Adelaide in Australia in the late 1990s, he helped with studies in which people taking methadone to treat opioid addiction tested their pain tolerance by dunking a forearm in ice water. Healthy controls typically managed to stand the cold for roughly a minute. Hutchinson himself, "the young, cocky, Aussie bloke chucking my arm in the water," lasted more than 2 minutes. But the methadone patients averaged only about 15 seconds.

"These aren't wimps. These people are injecting all sorts of crazy crap into their arms. … But they were finding this excruciating," Hutchinson says. "It just fascinated me." The participants were taking enormous doses of narcotics. How could they experience such exaggerated pain?

The experiment was Hutchinson's first encounter with a perplexing phenomenon called opioid-induced hyperalgesia (OIH). At high doses, opioid painkillers actually seem to amplify pain by changing signaling in the central nervous system, making the body generally more sensitive to painful stimuli. "Just imagine if all the diabetic medications, instead of decreasing blood sugar, increased blood sugar," says Jianren Mao, a physician and pain researcher at Massachusetts General Hospital in Boston who has studied hyperalgesia in rodents and people for more than 20 years.

But how prevalent hyperalgesia is, and whether it plays a role in the U.S. epidemic of opioid abuse and overdose, is unclear. A lack of reliable testing methods and a series of contradictory papers have created believers and skeptics. A few researchers, like Mao, think hyperalgesia is an underappreciated puzzle piece in the opioid epidemic—a force that can pile on pain, drive up doses, and make it harder for chronic users to come off their drugs. Some of those

researchers are looking for ways to turn down hyperalgesia, to help patients function on lower doses of their oxycodone, for example, or make it easier to taper off it altogether. Others see OIH as an oddity in the literature—real, and a powerful clue to the workings of pain pathways, but unlikely to tighten the grip of opioids on most patients. Hutchinson thinks the majority of physicians are either unaware of hyperalgesia or unconvinced of its importance. "I think if you surveyed prescribers of opioids, they would be divided probably 60–40."

PARADOXICAL AS IT MAY SEEM, OIH makes evolutionary sense. "Nature didn't come up with pain just to torture mankind," says Martin Angst, an anesthesiologist and clinical pharmacologist at Stanford University in Palo Alto, California. Pain causes us to recoil from a hot stove and to stay off an injured leg while it heals. And when it's crucial that we temporarily ignore pain—say, when we run on that injured leg to evade a charging lion—the body has a way of numbing it, in part by releasing its own opioids. These natural molecules bind to receptors on neurons to block pain signals and activate reward centers in the brain.

But doses of prescription opioids are orders of magnitude higher than our endogenous levels, Angst says. Confronted by these, "your biology fights back and says, 'I'm blindfolded to pain by all these chemicals. I need to be able to sense pain again.'"

Some studies of hyperalgesia rely on gradually heated probes applied to the skin.

PHOTO: MATTHEW RAKOLA

Mao was among the first to delve into potential mechanisms of OIH in an animal model. In 1994, while at Virginia Commonwealth University in Richmond, he and his colleagues showed that after 8 days of spinal morphine injections, rats were quicker to pull their paws away from a gradually heated glass surface. The animals' baseline pain threshold had changed, and the effect was something more than tolerance, in which the body requires increasing doses of a drug to get the same effect. In this case, a higher dose could actually increase sensitivity to pain.

The researchers found they could reverse the hyperalgesic effect by blocking certain receptors on neurons in the animals' spinal cord. These N-methyl-D-aspartate (NMDA) receptors pick up chemical signals—notably an excitatory molecule called glutamate—released by sensory neurons projecting from the skin and organs, and transmit pain signals up to the brain. Researchers already knew that even without opioids, some people with chronic pain from nerve damage or fibromyalgia, for example, experience hyperalgesia when normal pain signaling gets reinforced and amplified over time. It appeared that, at least in animals, opioids had a similar effect.

By 2000, Mao was turning his attention to patients, and the population of opioid users was expanding. Doctors had begun to consider the drugs relatively safe options for managing chronic pain. With the release and aggressive marketing of the long-acting narcotic OxyContin in 1996, a class of drugs that had largely been reserved for cancer patients was becoming a go-to treatment for conditions such as lower back pain.

As prescribing skyrocketed, so did overdoses. U.S. deaths from prescription opioids have roughly quadrupled in the last 2 decades, reaching 21,000 in 2014. Making things worse, abundant prescription opioids have been diverted for recreational use, which has driven up rates of heroin addiction as users have sought cheaper or more accessible alternatives. Both prescription and illegal opioids kill when high doses slow breathing, especially when combined with alcohol or antianxiety drugs called benzodiazepines.

"I'm not sure you could find an example of physicians doing more harm to human beings than we have achieved in our liberal opiate prescribing," says David Clark, an anesthesiologist at Stanford.

Mao and others wondered whether hyperalgesia was another important opioid side effect. People might be seeking a higher dose as drug-induced pain compounded the original pain, he thought. If so, doctors who ignore hyperalgesia might bump up the dose when the right decision was to reduce it. And when a patient tried to taper off a drug, a temporarily lowered pain threshold might make it harder for them to manage without it. "If they're hyperalgesic, they can just go back to the drug again to feel okay," says Jose Moron-Concepcion, a neuroscientist at the Washington University School of Medicine in St. Louis in Missouri.

The evidence for hyperalgesia is clearest in people taking extreme doses—for instance, in opioid abusers or terminal cancer patients managing severe pain. Surgical patients given large amounts of the opioid remifentanil have shown signs of hyperalgesia; they have larger areas of soreness around their wounds and seem predisposed to chronic pain following surgery. But what about patients who take lower doses of opioids daily over months or years to manage chronic pain? As a pain specialist at a large teaching hospital, Mao frequently encounters patients who can't find relief from increasing opioid doses and who tell him that their pain has become worse—diffuse, nagging, and harder to pinpoint.

But just how many people experience OIH, and at what opioid dose, is hard to say. The phenomenon can be very hard to distinguish from tolerance, when pain increases as the drug loses its effectiveness over time. (It's also possible that a patient's underlying condition has changed, or that the chronic pain itself has kicked their pain signaling into high gear.)

Because diagnosing hyperalgesia can be a guessing game in the clinic, some researchers have turned to the lab. They have tried to document changing pain thresholds with quantitative sensory tests, like the so-called cold pressor test Hutchinson witnessed in the methadone patients in Australia, or contraptions that apply heat or pressure to the skin. But the studies have been small and the results inconsistent. "Nobody has actually shown that that particular stimulus in a human being is a valid way to say, 'Yes, this person has become hyperalgesic,'" Angst says.

In 2006, for instance, a team that included Angst and Clark gave the cold pressor test to six people with chronic lower back pain before and after a monthlong course of morphine pills. After the drug treatment, the team found signs of hyperalgesia: On average, the subjects registered pain from the ice water about 2 seconds earlier, and removed their hands about 8 seconds earlier, than they had beforehand. But those results didn't hold up in a larger group of 139 patients randomized to take opioids or placebo, nor did they appear in a different pain test that applied a gradually heated probe to the forearm. Then in 2013, a study with a different methodology seemed to confirm the effect. A research team in Israel reported evidence of hyperalgesia in 17 of 30 patients with radiating spinal nerve pain by asking them to rate the intensity of heat pain on a numerical scale before and after a 4-week course of hydromorphone.

If you can't reliably diagnose hyperalgesia, it's hard to predict its long-term effects, says Michael Hooten, an anesthesiologist at the Mayo Medical School in Rochester, Minnesota. His group found evidence in 91 patients tapering off opioids that those whose doses were higher at the start, forcing them to make greater reductions over the 3-week program, had worse measures of heat pain hyperalgesia. But the team wasn't able to track these patients long-term to ask the bigger questions: How long until their pain thresholds bounced back to normal? Do hyperalgesic patients who manage to quit taking opioids ultimately see improvements in pain? Are hyperalgesic patients more or less prone to addiction or relapse?

For some, this lack of evidence makes research into hyperalgesia look like a dead end. "When I go to work every day, I don't think about opioid-induced hyperalgesia," says Gary Bennett, a pain researcher at the University of California in San Diego. "We know that it's real. We don't know how important it is, and it's really, really hard to answer that question, so let's move on."

MAO ISN'T READY to move on. He believes the risk of hyperalgesia should motivate doctors to try tapering patients off their opioids when their pain worsens without an obvious cause. But in his experience, only about a third of chronic pain patients are willing to try that. So he's hoping for a different solution: a drug that targets the mechanisms behind hyperalgesia and that might be given alongside an opioid, either when it's first prescribed or when a doctor suspects OIH.

Mao is recruiting patients for clinical trials to test two candidate drugs. One is ketamine, an anesthetic that blocks NMDA receptors. The other, guanfacine, is currently used to treat high blood pressure and is thought to keep sensory neurons from releasing glutamate into the spinal cord. A team led by Peggy Compton of Georgetown University in Washington, D.C., meanwhile, is investigating a pain and antiseizure drug called gabapentin that may block neural transmission to reduce excessive pain signals.

Other groups are attacking opioid side effects, including hyperalgesia, from a very different angle. In the early 2000s, researchers began exploring the role of glia, star-shaped immune cells in the brain and spinal cord, which were traditionally thought to function as mere "housekeepers," offering structural support for neurons and removing debris. But when the immune system becomes activated in response to an illness or injury, glia in regions associated with pain processing seem to take on another role: They release inflammatory molecules that interact with nearby neurons to amplify pain signals.

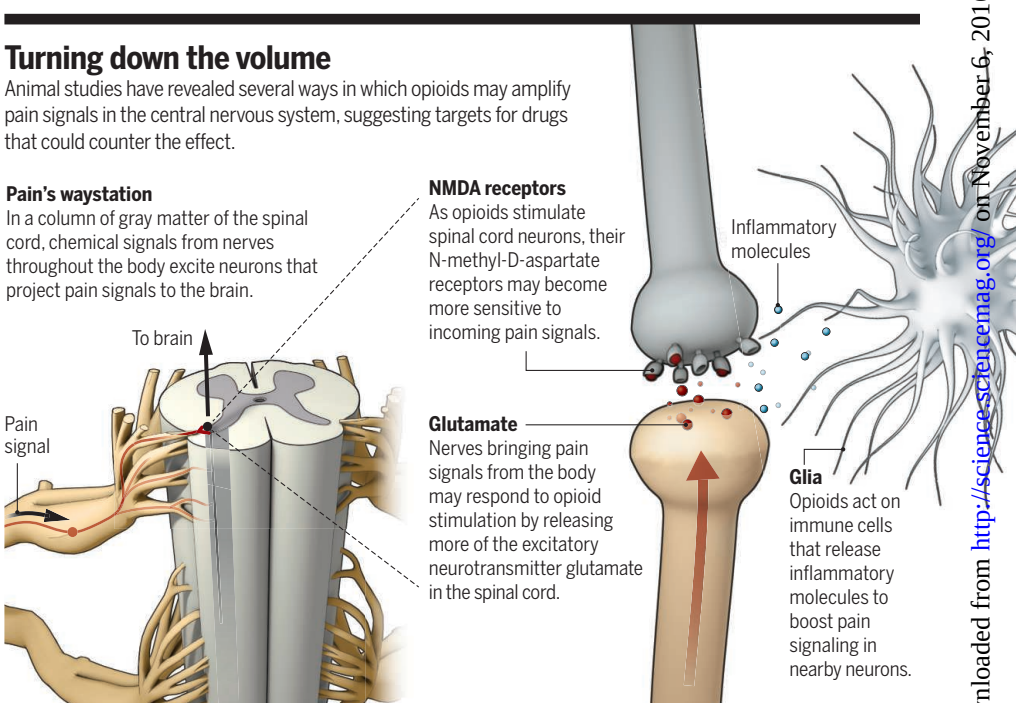
In 2001, researchers at the Chinese Academy of Sciences in Shanghai reported that chronic morphine administration in rats activated glial cells called astrocytes in the spinal cord. Subsequent studies showed that inhibiting the inflammatory molecules released by glia could reverse hyperalgesia and tolerance in the rats. The results suggested that opioids may trigger glia to set off system-wide pain signaling that both counteracts the pain relief from the drug and makes the body generally more sensitive to pain.

Many see dampening this inflammatory response as a promising way to fight hyperalgesia, because it would not interfere with opioids' pain-relieving activity on neural receptors. Several efforts are underway. The San Diego, California–based biotech company MediciNova recently completed a phase II trial of a glia-inhibiting drug called ibudilast, already approved as an asthma treatment in Japan, to relieve pain and treat withdrawal in opioid abusers. A study led by researchers at Yale University is testing the antibiotic acne medication minocycline, which is also thought to block glial activation in the brain. And research spun out of neuroscientist Linda Watkins's group at the University of Colorado in Boulder is testing a new pain drug that may tame glia in the spinal cord by blocking a signaling protein on their surface.

If inflammation turns out to be a key driver of OIH, it might also point the way to a better test for the effect, says Lesley Colvin, a pain researcher at the University of Edinburgh. Markers of inflammation in the blood might correlate with clinical signs of hyperalgesia or declining pain thresholds on sensory tests. Colvin says she already sees strong evidence of hyperalgesia in high-dose opioid users at the clinic where she works. With so much at stake, she is eager to understand the phenomenon and how it might affect them long term. "Although it's complicated," she says, "that doesn't mean we shouldn't try and work out the details." ■

Turning down the volume

Animal studies have revealed several ways in which opioids may amplify pain signals in the central nervous system, suggesting targets for drugs that could counter the effect.



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