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Nonopioid Approaches to Pain: The Hunt Is On

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As the US opioid epidemic rages on, the need to find safe, effective, nonaddictive, nonopioid approaches to pain management — through both pharmaceutical and nonpharmaceutical strategies — is increasingly urgent.

Current estimates from the Centers for Disease Control and Prevention (CDC) state that, on average, 115 Americans die every day from an opioid-related overdose and that approximately 40% of these deaths involve a prescription opioid.

In 2016, 11.4 million people misused prescription opioids, and 2.1 million had an opioid use disorder, leading the then—acting secretary of the US Department of Health and Human Services in 2017 to declare the opioid crisis a public health emergency.

In addition to the abuse potential, opioids are associated with a myriad of adverse events — and there's no clear evidence that they are effective in the long term.

William Maixner, PhD, president of the American Pain Society (APS) and director of the Center for Translational Pain Medicine at Duke University, Durham, North Carolina, told Medscape Medical News that there are currently two epidemics in progress, one involving opioids, and the other, chronic pain.

"The common variable...is inadequate tools for pain management that are able to replaced opioid exposure in our society. The only way around this problem is through discovery, research, and identification of new therapeutics that are safe and effective and not addictive in nature," said Maixner.

"We are in need of new options. Few studies have evaluated the long-term efficacy of our current treatments. But chronic pain is a life-long sentence," he added.

To get ahead of the crisis, researchers across the country and internationally are investigating new options for chronic pain management.

FDA Calls for Action

During the past year, the US Food and Drug Administration (FDA) has issued several statements reiterating a call for new nonopioid treatment options.

"We don't want to perpetuate practices that led to the misuse of these drugs, and the addiction crisis. At the same time, we don't want to act in ways that are poorly targeted, and end up disadvantaging legitimate patients," FDA commissioner Scott Gottlieb, MD, said in a statement released in July.

According to new data released by the CDC, chronic pain now affects more than 50 million US patients — and "high-impact" chronic pain, which interferes with life or work activities, affects approximately 20 million.

In addition to encouraging the development of opioid prescribing guidelines, the FDA has launched a challenge for the creation of new pain-treating devices.

"We're hopeful that in collaborating with public health-minded innovators, we can identify and accelerate the development of new technologies, whether a device, diagnostic test, mobile medical app, or even new clinical decision support software, that can contribute in novel and effective ways to help reduce the scope of this crisis," said Gottlieb.

The agency is also undertaking a public-private partnership with the National Institutes of Health "to identify areas of opportunity to advance pharmacological treatments," the FDA reported in a press release.

Roger Fillingim, PhD, director of the Pain Research and Intervention Center of Excellence at the University of Florida, Gainesville, and a past president of the APS, told Medscape Medical News that "this is a concerning time" for both patients with pain and the providers who take care of them.

Although there are now "a number of evidence-supported treatments," most lack strong evidence of benefit, especially compared with anything other than placebo. And although combination treatment has been shown to offer more benefit than monotherapy in practice, there have been few systematic comparison studies, he said.

"There is not one treatment that for a majority of patients is transformative — and nothing that is curative," said Fillingim.

However, he noted that "there is hope" that this could change in the near future — especially because the field has learned an increasing amount about the mechanisms of pain and "continues to identify new targets for medications that can successfully reduce pathological pain," he said. For example, progress has been made regarding calcitonin-gene-related peptide (CGRP) antagonists.

The FDA recently approved the anti-CGRP agents erenumab (Aimovig, Amgen and Novartis), fremanezumab (Teva Pharmaceuticals), and galcanezumab (Emgality, Eli Lilly and Co) for migraine prevention.

Maixner noted that ongoing studies are also investigating CGRP-targeting agents for the treatment of other types of pain.

"Classic" Meds Still Useful?

Traci Speed, MD, PhD, assistant professor in the Department of Psychiatry and Behavioral Sciences at Johns Hopkins University School of Medicine, Baltimore, Maryland, told Medscape Medical News that "the more classic medicines," such as the nonsteroidal anti-inflammatory drugs ibuprofen and naproxen, can also offer benefit.

"Those still have evidence that they can be helpful for chronic pain. When used in combination and under the advisement of a physician, they can be used for durations of time," said Speed.

She noted that new studies show that one dose of higher-dose acetaminophen has equal efficacy in reducing pain in emergency department (ED) settings as one dose of codeine.

Maixner added that "there's evidence that some old medications, such as beta blockers, could potentially be repurposed in some populations."

Michael R. Clark, MD, chair of psychiatry at Inova Health System in Virginia and director of the Chronic Pain Treatment Program in Johns Hopkins' Department of Psychiatry and Behavioral Medicine, chimed in to report that anticonvulsants have also shown promise.

"Particularly in neuropathic pain syndromes, antidepressants and its different subclasses, including serotonin and norepinephrine reuptake inhibitors, and anticonvulsants all have pharmacologic mechanisms that are fairly well understood and match up with what we now have as pretty good evidence for why people are experiencing this type of pain," said Clark.

"So if you connect the dots, you begin to see that you can put together a logical recipe of combinations and pharmacologic mechanisms to address different pathophysiologic mechanisms and normalize the situation," he said.

Low-Dose Ketamine

Although a recent study showed benefit from using low-dose ketamine in the ED in place of opioids to mitigate addiction risk, ketamine has had its own problems, including that it too is possibly addictive and has been associated with several side effects.

"Could this be another agent with abuse potential? Maybe. But under regulations and good clinical practice, it could have utility, especially for perioperative pain," Maixner commented.

However, he noted that clinicians should warn patients about the proliferation of ketamine clinics. "Ketamine can be quite dangerous if not administered in the right hands under the right conditions. And one needs to be careful with any clinic that overpromises and relies on one method," Maixner said.

Speed said that in another 10 years, "I think we'll have a lot more promising options for treating pain, including those that target the opioid receptor — but without risk of addiction."

She added that there's also been a move toward understanding more about sodium and calcium channels; and the National Institute on Drug Abuse will be looking into immunotherapy through its HEAL initiative.

"Funding, such as through HEAL, can begin to help our community develop evidence-based, personalized approaches," said Maixner. "I'm actually very optimistic about the track that we are now taking, both from a research and a health delivery perspective."

"I suspect that if we were much better at matching treatment to individual patients, we could transform many more lives, which is the goal of precision medicine. We're not there yet in treatment chronic pain, but there is hope," added Fillingim.

Device Approvals

As for nonpharmaceutical approaches to pain management, there has been optimism in the field for some noninvasive neuromodulation and spinal cord stimulation products, as well as other devices.

As reported by Medscape Medical News, results from a meta-analysis that were reported at the 2018 annual meeting of the American Academy of Pain Medicine showed that spinal cord stimulation was associated with greater pain reduction than medication in patients with intractable spine or limb pain.

"Opioids don't work very well for patients with nerve-related pain, and yet many patients are treated with these drugs. On the other hand, spinal cord stimulation has been shown to work quite well for many types of neuropathic pain," investigator Tim J. Lamer, MD, professor of anesthesiology, Mayo Clinic College of Medicine and Science, Rochester, Minnesota, said at the time.

In addition, the FDA approved SPR Therapeutics' SPRINT endura (single lead) and extensa (dual lead) peripheral nerve stimulation (PNS) system for pain management in August. It is currently the only percutaneous PNS system cleared by the agency.

Fillingim also noted that there is good evidence for reducing pain and its subsequent side effects, such as depression, with various forms of talk therapy, including cognitive-behavioral therapy, meditation and mindfulness, and acceptance-based therapies.

"There has also been a lot of interest in so-called 'resilience' interventions, although it's very early days," said Fillingim. "It's training patients in certain resilience strategies; for example, increasing positive affect, increasing pleasant activity level, increasing cognitive flexibility, and savoring positive experiences."

Overall, "there are a variety of talk-therapy approaches to pain treatment that have been supported by really well-conducted randomized controlled trials," he noted.

Other nonpharmaceutical options that have shown effectiveness for acute and/or chronic pain include acupuncture; distraction therapy, such as playing games, doing puzzles, or counting; and virtual reality (VR) programs.

In fact, a small study published earlier this summer in *Neurology* showed that heartbeat-enhanced VR reduced pain and improved motor limb function in patients with complex regional pain syndrome.

"Exercise Beats Everything"

Beneficial evidence has also been shown for exercise of all types, including yoga and tai chi.

"Exercise, in my view, beats everything else out there, including any medication on the market. In terms of pain reduction, in terms of improving function and quality of life, exercise works," said Fillingim. However, he noted that the challenge is getting patients to do it.

As for diet, he noted that a preclinical study showed that a group of rodents that consumed a typically American diet on a daily basis and a group that ate it only during the weekends both showed greater sensitivity to pain than a group that ate a healthy-type diet. "So there's some preclinical evidence there and every reason to believe there's some connection," said Fillingim.

"There are also some examples where dietary changes could have a significant effect on, say, the inflammatory profile," he said. "There's a lot of potential there, but diet is probably the only thing we're worse at than exercise."

"There's emerging evidence for most of these noninvasive methods, but it's really matching the right patient to the right modality. If it doesn't do any harm, you can give it a try," added Maixner.

"Signals of efficacy from small studies give us hope for usefulness in our clinical populations — but substantial trials of sufficient duration will help move us on from just 'give it a try.' "

Role for Cannabis?

Fillingim noted that a future possibility might include cannabis and various cannabidiol (CBD) products. "There's at least a story there," he said.

The FDA recently approved the CBD product Epidiolex for the treatment of seizures in two rare forms of epilepsy. Now that the Drug Enforcement Administration has rescheduled the product from its previous Schedule 1 classification, could similar products become treatment options for pain?

"The effect size for relieving pain with cannabinoids is not that high right now, and we haven't really done studies where we've stratified patients into subgroups. But this is definitely a pathway of interest for the treatment of pain," noted Maixner.

Imaging findings from a small randomized, crossover study published earlier this month in *Neurology* showed how tetrahydrocannabinol (THC), the psychoactive component of cannabis, may work to treat chronic neuropathic pain.

THC-induced pain relief was associated with reduced functional connectivity between the anterior cingulate cortex and the sensorimotor cortex.

"This effect seems to involve a breakdown in functional connectivity between brain regions that process different dimensions that construct the experience of pain," study author Haggai Sharon, MD, Sagol Brain Institute, Tel Aviv, Israel, told *Medscape Medical News* at the time.

"Patients are already using [cannabis] legally or illegally," said Fillingim. "As a society and as a healthcare profession, we're going to have to deal with this and try to understand what its effects are, and to what degree it's a viable intervention for patients with chronic pain."

However, he emphasized that in the absence of large-scale, long-term evidence of pain relief, which is the case right now, "it's all just snake oil. We need the evidence in order to know what to recommend to patients, assuming they have access to it, and what to caution them against."

Different Toolboxes, Different Strategies

Overall, treatment for chronic pain "needs to be multimodal, meaning we need to use several approaches," noted Speed. "Everyone's toolbox might be a little different, and oftentimes it takes trying different strategies."

Fillingim noted that it's also important to ask a patient with chronic pain what their goals are, because "moving their pain rating from a high number to a low number is certainly not their only goal — and it might not be their primary goal.

"We need to think about improving their quality of life, reducing their pain to the extent that it interferes with daily activities, and increasing their hope and optimism," he said.

"It's very important to have a dialogue with patients, and a trust," agreed Maixner. "In many cases, we can't promise to completely alleviate pain, but we can help manage expectations."

"I think clinicians should ask whether or not a patient's function has improved. If not, ask, 'Is this the best I can do for my patient?' If the answer is no, think about what more can be done. Ultimately, that's what society deserves," concluded Clark.