Medical News & Perspectives

Limits on Opioid Prescribing Leave Patients With Chronic Pain Vulnerable

Rita Rubin, MA

Thomas Kline, MD, PhD, refers to 22 of his patients as "pain refugees."

Stable for years on opioid therapy for chronic pain, these patients sought out Kline—well-known for his advocacy on their behalf on Twitter and elsewhere—because their physicians had abruptly cut their dose or refused to refill a prescription.

They had appealed to multiple physicians for treatment with no success before contacting him, said Kline, a Raleigh, North Carolina, physician who practices internal and geriatric medicine. "They give me lists of the doctors, which I would like to make public someday," he said. "They're in this horrible withdrawal, plus pain."

Kline accepts these patients that no one wants because he's trying to keep them off another list, one he has helped compile: a list of US residents believed to have committed suicide because their physicians would no longer prescribe adequate doses of opioids to treat their chronic pain.

As of late April, the list was 40 people long, but it is not inclusive, Kline said. "The problem is a lot of families don't want this public. I have to respect that."

Kline and others blame the desperation of patients with chronic pain in part on the Centers for Disease Control and Prevention (CDC). In 2016, spurred by growing numbers of overdose deaths (27% of which that year involved a prescription opioid) the CDC published an opioid prescribing guideline for adults with chronic pain.

"Chaotic and Brutal"

The CDC guideline recommends that physicians carefully reassess potential benefits and risks when considering whether to increase a patient's dose to 50 or more morphine milligram equivalents (MMEs) per day (MMEs are used to compare doses of different opioids). Physicians should avoid raising the dose to 90 MMEs or more unless they can carefully justify it, according to the CDC.

Although that recommendation relates to patients who have not yet started taking opioids for chronic pain, it has also been widely interpreted as a target for the millions of users who long ago surpassed 90 MMEs a day. Approximate 25 million US residents have moderate to severe chronic pain, and an estimated 5 million to 8 million of them have used opioids for long-term management, according to National Institutes of Health data.

"There's been rampant misapplication" of the guideline in the form of "a snowballing of initiatives, regulations, and mandates from multiple parties," said Stefan Kertesz, MD, MSc, who coauthored a letter in March, signed by 3 former White House drug czars and more than 300 other people, urging the CDC to clarify its guideline. "The effect of the snowball is increasingly chaotic and brutal," added Kertesz, who also served on an expert panel that reported on the challenges of implementing the guideline.

A recently published study by Stanford researchers concluded that many rules limiting opioid prescriptions would increase deaths over a 5- to 10-year period, because they will drive some prescription opioid users to switch to illicit heroin or fentanyl. But, the authors wrote, "over a longer horizon, some such policies may avert enough new addiction to outweigh the harm."

The accompanying editorial, entitled "We Cannot Treat the Dead," questioned whether the marked increase in US suicide rates might be related to inadequate pain treatment, since a CDC study noted that 22% of suicides in 2015 reportedly occurred among people with documented physical health problems.

Kertesz, an internist at the University of Alabama at Birmingham, said he regularly receives reports from patients with chronic pain and their advocates about suicide attempts linked to inadequate opioid therapy.

"In my heart, these are innocent people who are almost in the position of being put to death against their will," he said. "There's a systematic tendency to discount patients' reports of distress," leading some physicians to reduce their dosage even further.

In April, CDC Director Robert Redfield, MD, responded to the letter Kertesz coauthored, noting that "[t]he Guideline does not endorse mandated or abrupt dose reduction or discontinuation, as these actions can result in patient harm."

Two weeks later, the authors of the 2016 guideline echoed Redfield's letter in a Perspective piece published in the *New England Journal of Medicine*.

"Unfortunately, some policies and practices purportedly derived from the guideline have in fact been inconsistent with, and often go beyond, its recommendations," the authors wrote. For example, they continued, the recommendation that physicians avoid increasing dosage to 90 MMEs or more "does not address or suggest discontinuation of opioids already prescribed at higher dosages, yet it has been used to justify abruptly stopping opioid prescriptions or coverage."

Kertesz said he was happy that the guideline authors provided "appropriate clarification" of their intent but added, "the other question for the CDC is, 'What took you so long?'"

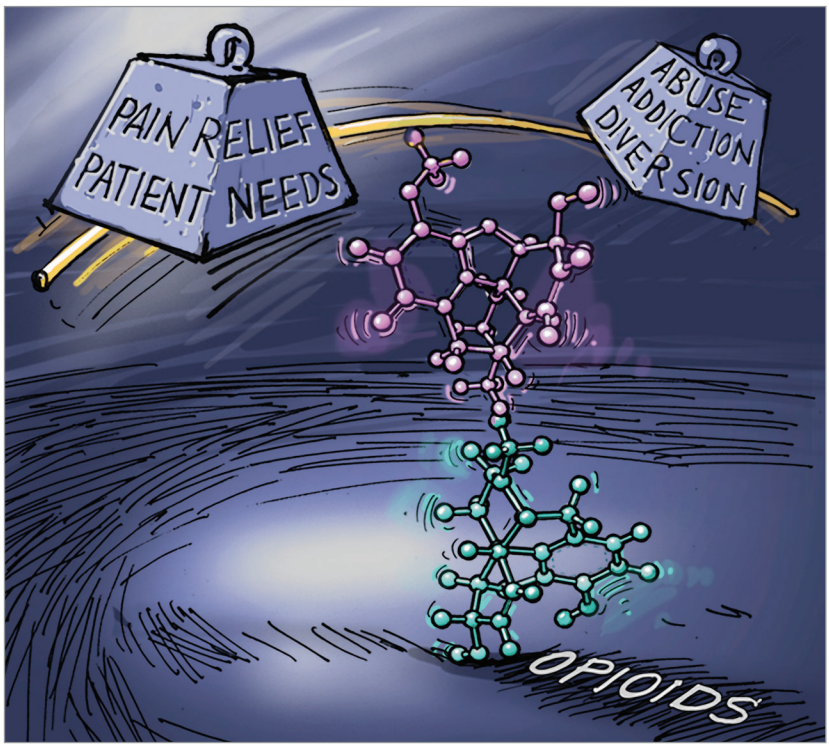
Noncancer vs Cancer Pain

While the CDC's opioid prescribing guidelines were intended for noncancer chronic pain, physicians report that it has been used to block treatment of patients with cancer pain.

The 90-MME threshold "is being used as a blunt instrument by third parties such as insurers," said Paul Chelminski, MD, MPH, an internist at the University of North Carolina, Chapel Hill.

Recently, one of Chelminski's patients, whose cancer had metastasized to her bones, experienced a rapid worsening of her disease. "The pharmacy had informed us that the insurer had put limitations on her opioids, and I could not increase the dose as quickly as necessary," he said. "That used to not happen. The doctor's word was usually adequate in the cancer scenario. These restrictions were never intended to be applied to cancer patients."

At the time, he said, his patient was not quite ready for hospice, which has fewer



restrictions on opioids. "She did not have a peaceful exit."

In a February letter, a CDC official responded to 3 medical organizations that had expressed concern over how misinterpretation of the agency's guideline was affecting patients undergoing cancer treatment, cancer survivors with chronic pain, and people with sickle cell disease.

"The Guideline was developed to provide recommendations for primary care clinicians who prescribe opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care," wrote Deborah Dowell, MD, MPH, chief medical officer of the CDC's National Center for Injury Prevention and Control and a coauthor of the guideline and the recent Perspective piece. Dowell's letter was addressed to officials of the National Comprehensive Cancer Network, the American Society of Clinical Oncology, and the American Society of Hematology.

Patients who don't have cancer are also being adversely affected by the guideline, Chelminski said. He had to cut one patient's 30-day opioid supply from 360 tablets to 180 after the insurer stopped covering more than that. "It's arbitrary, and the reasoning behind it is opaque and not scientifically substantiated," Chelminski said of the 90-MMEs dose threshold. The CDC guideline notes that that "there is now an established body of scientific evidence showing that overdose risk is increased" at higher opioid dosages, but the guideline doesn't cite evidence specifically supporting the 90-MMEs cutoff.

Since the CDC published its guideline, at least 33 states have adopted guidelines, limits, or other requirements for prescribing opioids, according to data compiled last fall by the National Conference of State Legislatures (NCSL). Nearly half the states with limits specify that they apply to treating acute pain, and most states set exceptions for chronic pain treatment. Maine is the only state whose law, which sets a limit of 100 MMEs for up to 30 days, applies to both acute and chronic pain, according to the information compiled by the NCSL.

Although the state laws target prescribing for acute pain, they could affect prescribing for chronic pain, the authors of a recent review article wrote. For example, some North Carolina patients with chronic pain have said their physicians stopped prescribing opioids and, by way of explanation, handed them a copy of the state's 2017 Strengthen Opioid Misuse Prevention (STOP) Act, which limits initial prescriptions for acute pain to 5 or 7 days. The STOP Act specifically states that the limits do not apply to chronic pain. And yet, a quarter (663) of the 2661 physicians who responded last fall to a survey by the North Carolina Medical Board said they had stopped prescribing opioids for chronic pain.

"The effect of that intense collision of regulatory efforts is a final message that says the patient you think needs this medication is a professional and legal liability to you, the physician," Kertesz said. For that reason, patients receiving long-term opioid therapy live in "utter terror" of their physician dismissing them, he said. "They understand that they're seen as a liability. It's very analogous to the early HIV epidemic."

The Pendulum Swings

The US rate of opioid prescribing peaked at 782 MMEs per capita in 2010 and then declined to 640 MMEs per capita in 2015, according to a 2017 report by CDC researchers. However, the amount prescribed in 2015 was still about 3 times as high as in 1999. The rate decreased 20.1% from 2015 to 2017, to 512.6 MME per capita—still more than double that in 1999—according to a recent research letter in *JAMA Internal Medicine*.

Prescribing increased in the first decade of the 21st century for 2 main reasons: the concern that chronic, noncancer pain was not being adequately treated and the downplaying of opioids' risks and overstating of their benefits by manufacturers such as Purdue Pharma and 2 widely cited articles—one a 1-paragraph research letter and the other about a study involving 38 patients.

"Starting in the '90s, there was kind of a coalition of forces that came together to prioritize a simple medication-based solution-...for complex pain," Kertesz said, referring to the US Food and Drug Administration (FDA), pharmaceutical companies, and organizations such as the Joint Commission, which has been blamed for promoting aggressive pain treatment in its 2001 pain management standards. "They pushed opioids obsessively, optimistically," Kertesz added.

Management of pain became a quality measure, incentivizing physicians to prescribe large doses to stomp it out. The Joint Commission "created a mindset that we needed to abolish pain, but that's not even what patients would expect," Chelminski said. Instead, patients simply want to reduce their pain to a level that allows them to function.

"The whole initiative to better manage chronic pain occurred without the sobering influence of good science," he added, noting that high-quality clinical trials to determine how best to manage chronic pain have

enrolled fewer than 1000 patients in total. In addition, Chelminski said, more liberal prescribing of opioids for chronic pain was supposed to be accompanied by robust psychological support for patients, but that has been missing.

Many patients probably would have fared better on treatments other than opioids, research suggests. "These medicines are not really great," Kertesz said. "They are often deeply problematic as a treatment for pain, long-term pain especially." For example, a randomized clinical trial published last year in *JAMA* concluded that opioids were not superior to nonopioid medications—acetaminophen and nonsteroidal anti-inflammatory drugs—for improving pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain.

Today, in light of the rising toll from opioid overdoses, a new advocacy coalition is saying, "We erred. We erred grievously," Kertesz said.

"Legacy Patients"

Multiple factors account for why patients with chronic pain have ended up taking high doses of opioids.

"Tolerance is certainly one of them," said Joanna Starrels, MD, MS, an internist and addiction medicine specialist at the Albert Einstein College of Medicine and Montefiore Medical Center. "Overly aggressive treatment of pain with opioids for the past 2 decades is another." Patients' pathology might have changed over time, and they might have new pain sites, she added.

"In addition, we're learning about opioid-induced hyperalgesia," Starrels said, referring to a little-understood phenomenon in which long-term opioid exposure is thought to increase pain sensitivity, possibly leading to higher doses.

The CDC guideline is reasonable for patients who are just starting opioid therapy for chronic pain, but it's not meant to be retroactive, noted internist Margaret Lowenstein, MD, a National Clinician Scholar at the University of Pennsylvania who focuses on policy and delivery of behavioral health and addiction treatment. In other words, Lowenstein said, the recommended dosage limits do not apply to those she calls legacy patients, whose daily dose long ago surpassed 90 MMEs a day.

"The problem is not the guideline," said Starrels, who served on the expert committee that helped develop the document. "If you read the text of the guideline, it is very nuanced and avoids being overly prescriptive. The problem is the way that the guideline has been used to justify blanket practices for all patients."

Tapering as Opposed to Chopping

The CDC guideline also advises physicians on how to treat patients who have long been stable on high doses of opioids, said agency spokeswoman Courtney Lenard, MA. The CDC is supporting 4 extramural research projects examining the unintended consequences of tapering and discontinuation, according to an enclosure accompanying Redfield's letter to Kertesz and colleagues.

Physicians should review the risks and benefits of continuing high-dose opioid therapy and offer patients the option of gradually tapering their dose, according to the guideline. If patients decide they want to try, physicians need to collaborate with them on a tapering plan that is slow enough to minimize opioid withdrawal, such as a 10% monthly dose reduction, Lenard said. Since publishing the chronic pain prescribing guideline, the CDC has released a pocket guide to tapering for physicians and, more recently, a free mobile app to help physicians apply the guideline in clinical practice.

Although limiting the dose and duration of opioid therapy has proven to be a "seductive target" for policy makers and regulators, efforts to achieve that goal have "inaugurated a tide of nonconsensual tapers in otherwise stable patients, for which evidence of benefit is lacking and reports of harm are concerning," Kertesz and his coauthor wrote last summer in a *JAMA Network Open* editorial.

Such tapers could have the opposite effect of their intended goal, according to a case-control study published in April in *JAMA Network Open*, which found that dose variability is a risk factor for opioid overdose independent of dose alone in patients receiving long-term therapy.

Spurred by reports of serious withdrawal symptoms, uncontrolled pain, and suicide in patients whose opioid doses were abruptly stopped or cut, the FDA announced new opioid labeling changes in April to better inform physicians how to properly taper patients. "This information is intended to be used when the health-care provider and the patient have determined together that a decrease in dose or discontinuation of the opioid is appropriate," Douglas Throckmorton, MD, deputy director for regulatory programs in the FDA's Center for Drug Evaluation and Research, said in a statement.

It's unclear whether these new changes will address clinicians' biases that might be contributing to inappropriate tapers. In a recently published study, Starrels found that physicians were more likely to taper female or black patients. "The factors associated with tapering were sociodemographic, not clinical factors" such as high doses of opioids or concurrent benzodiazepine use, she said.

If she thinks stable patients might benefit from tapering, Starrels said, "we talk about the studies that have been done where people who've reduced their doses have improved function and no worse pain."

However, she emphasized, "there are times when it [tapering] does need to be the clinician's decision. The degree to which we can make a shared decision with patients is related to how high the risk is at continuing at the same dose." Risk factors include a nonfatal overdose and alcohol use disorder, she said. If the patient has opioid use disorder (OUD), though, "tapering alone is insufficient and could be dangerous," Starrels said. "In that case, we want to connect the patient with treatment…with methadone or buprenorphine, for example."

Reduce Doses, Reduce Overdoses?

Intuitively, it makes sense that limiting opioid prescriptions would help reduce overdose deaths, Lowenstein said. However, she said, "the evidence is mixed at best." While studies show that state prescription monitoring programs appear to have reduced potentially inappropriate opioid prescribing, that hasn't necessarily translated into fewer overdose deaths, in part because most opioid overdoses are due to illicit fentanyl or heroin, not prescription opioids.

"With our therapeutic impulse in the '90s, we used this medicine without sound science, and now our reaction is without sound science," Chelminski said.

And that's a problem, Kertesz says.

When it comes to opioid therapy for chronic pain, "we have set aside ordinary customs of both health and medical practice," he said. "There's a very understandable reason: People are trying to respond to extraordinary tragedy caused by overprescribing. The tragedy is truly gargantuan, and everybody feels accountable for that, as well they should." ■

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