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REGULATIONS

Easing the pain

Efforts to restrict opioid prescriptions in the United States are having unintended effects on people with chronic pain.

BY MICHAEL EISENSTEIN

Despite physician Daniel Alford's best efforts, the appointment did not end well. After almost an hour of explaining to a patient why he couldn't increase his already high-dose opioid drug prescription despite his continuing severe pain, the patient stormed out into the crowded waiting room — and never came back. "'Thanks for ruining my life!' were his parting words," says Alford, director of the Clinical Addiction Research and Education Unit at Boston University School of Medicine in Massachusetts.

These difficult conversations have become increasingly common in US clinical practices because regulators, legislators and health insurance providers have introduced stricter controls on the dosage and duration of opioid prescriptions. Most physicians agree that these policies are well-intentioned, with the goal of lowering a patient's exposure to habit-forming medications that often have only minimal pain-fighting benefits. And some have already seen public-health benefits. "The only policies that have reduced opioid mortality are dosing limits," says Mark Sullivan, a psychiatrist who specializes in pain medicine at the University of Washington in Seattle. But there are also serious concerns that these limits are often implemented without considering the needs of individuals or recourse to effective alternative treatments.

People who are grappling with a long history of using high-dose prescription opioids, such as the man who fled Alford's office, already pose a serious challenge for clinicians who are hoping to push back against opioid-use disorders. "You're doing the right thing, but it's really upsetting," he says. Strict top-down directives on prescribing opioids now greatly constrain doctors in this already-delicate situation. And, given the high stakes of both undertreated chronic pain and drug addiction, there is considerable debate about how to manage prescribing opioids in a way that strikes the correct balance for treating pain in routine medical practice.

COURSE CORRECTION

The medical community's perspective on prescription opioids has shifted enormously in the past few decades. Michael Barnett, a physician and health-policy researcher at Harvard T. H. Chan School of Public Health in Boston observes that whereas clinicians in the mid-1990s embraced the drugs wholeheartedly, "Now, we're running away from opioids."

There is little dispute that the early days of the opioid epidemic were fuelled by the aggressive marketing and incautious prescription of the potent analgesics (see page SS10). In the past decade, medical authorities began to issue formal recommendations on the appropriate use of opioids, but these were issued separately by state and federal agencies and offered conflicting guidance.

It wasn't until 2016 that some order was brought to the situation. The US Centers for Disease Control and Prevention (CDC) assembled a panel of experts to formulate a broadly applicable set of guidelines for the opioid-based treatment of pain[1]. They were not intended to be mandatory, but rather to serve as guidance for physicians who lacked expertise in pain care and addiction medicine. "These guidelines were exceptionally important in terms of giving primary care providers some sense of how

to operate in a setting where evidence is incomplete and opioids are being over-prescribed," says Erin Krebs, who studies the outcomes of opioid-mediated pain therapy at the University of Minnesota, Minneapolis, and helped to review the guidelines. The CDC recommended that physicians should use caution when offering opioids at any dose to people with chronic pain, as well as avoid giving such patients daily doses that exceed an equivalent of 90 milligrams of morphine. For people who are already receiving high doses, the CDC suggested working to gradually reduce their treatment through a controlled 'tapering' process. And for acute pain after surgery or injury, three days of opioid treatment should be sufficient.

The guidelines' authors acknowledged that they were working with limited scientific evidence on optimal dosing, and some researchers have expressed concern about drawing lines in the sand without more rigorous data. But most acknowledge that the suggested limits are much better than the uncertainty that came before, and reflect available evidence. "As you go higher than 90–100 morphine milligram equivalents, there's an increased risk for overdose and respiratory depression," says Martin Cheatle, director of research on behavioral medicine at the Penn Pain Medicine Center in Philadelphia, Pennsylvania. And crucially, the CDC proposals were intended to be revisited as fresh evidence emerges.

PRESCRIPTION OR PROSCRIPTION

Sensible prescribing can reduce opioid abuse and overdose risk, and opioids have long been over-prescribed for post-surgical recovery. A study in 2012 of people who were recovering from hand or wrist surgery showed that, on average, they used only one-third of their prescribed pills[2]. Shorter prescriptions could therefore greatly reduce the number of opioid pills that remain in people's homes, where they are available for abuse.

Clinicians are running out of reasons to start people with chronic pain on these drugs. A randomized clinical trial in 2018 by Krebs and her colleagues showed that conventional non-opioid analgesics might be a better choice for chronic pain conditions involving the back or osteoarthritis in the hip or knee that were previously considered to be prime candidates for opioids[3]. Opioids might still be suitable for use in palliative care or in people who cannot take drugs such as acetaminophen (paracetamol) for medical reasons, but Krebs and other researchers think that it would be best for patients to steer clear of opioids even when other options fail.

Nevertheless, questions remain about the extent to which formal prescription controls have protected public health. The number of new prescriptions of opioids has undeniably decreased, but this trend pre-dates the CDC intervention. A study[4] published in March indicates that such prescriptions dropped by more than 50% between 2012 and 2017, with the decline clearly apparent long before December 2015, when the CDC draft guidelines were released. Meanwhile, deaths from opioid overdose have continued to climb steeply — a trend that can be attributed to the use of cheaper and more dangerous black-market opioids such as heroin and the ultra-potent fentanyl. Stefan Kertesz, a preventive-medicine specialist at the University of Alabama at Birmingham, notes that of 47,600 deaths linked to opioid overdose in 2017, roughly 75% involved heroin or fentanyl.

Restricting the access of people with chronic pain to prescription opioids could send them scrambling for other options. "There is definitely a concern that, as these drugs have become more restricted, then, people have gone on to use other types of drugs like heroin," says Magdalena Cerdá, director of the Center for Opioid Epidemiology and Policy at NYU Langone Health in New York City. There is no decisive evidence for such a shift at present, but a 2018 study showed that the introduction of further restrictions on hydrocodone prescriptions in 2014 was followed by a considerable spike in illegal opioid sales through online black markets[5].

The people who are put at most risk by this response to the opioid crisis are those with chronic pain who receive long-term opioid therapy — generally defined as lasting at least three months. According to the US National Institutes of Health (NIH), 5 million–8 million people in the United States were receiving such treatment for chronic pain in 2014, many at daily doses surpassing 90 morphine milligram equivalents. Unfortunately, since 2016, the CDC's efforts to guide consistent practice have been transformed into an inconsistent patchwork of rigid regulations, fuelled partly by political pressure to tackle the public-health crisis more aggressively — even when such policies go beyond specialist advice. At least 35 US states have laws that regulate opioid prescriptions, most of which were passed after 2016 and formalize strict limits on dosage and treatment duration that differ from each other and from the CDC guidelines. "These states are clearly not listening to any sort of expert consensus — it's all over the map," says Barnett.

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Many pharmacy chains and providers of health insurance have imposed further limits on opioid prescriptions, some of which misinterpret the intent of the CDC guidelines and apply extra pressure on clinicians. According to Kertesz, these limits were often informed by a desire to do something about the crisis while minimizing potential liability for opioid abuse and its consequences. "There were so many congressional committees, federal agencies, state agencies and insurers, all invoking the CDC's authority in the wrong way, at the same time," he says. "Prescribers feel jeopardized and at risk of losing their careers, and they transfer that pressure onto the patients." Such fears might be especially strong in an age when doctors who are suspected of being pill-pushers are increasingly in the cross-hairs of US law-enforcement agencies. Legitimate practitioners therefore seek to avoid any type of guilt by association.

This situation inspired Kertesz, Alford and more than 300 colleagues to send a letter to the CDC in March, to ask the agency to evaluate the consequences of opioid discontinuation and to clarify the intent of its recommendations. In April, the agency responded and clarified that its guidance "does not endorse mandated or abrupt dose reduction or discontinuation", and pledged to continue evaluating its guidelines and their impact.

TUNING THE TAPER

People who receive long-term opioid therapy often succumb to two distinct features of these analgesics. First, such drugs are widely thought to lack a therapeutic ceiling — which means that patients who are acclimatized to high doses can still derive further effects by increasing the dose. By contrast, the efficacy of non-opioid painkillers such as acetaminophen (paracetamol) or ibuprofen has a clear upper bound. Second, opioid use leads to physical dependency (see page S20). This establishes a cycle that can be difficult and dangerous to break. "Physical dependence was initially billed as a very minor problem," says Krebs. "But in the real world, a lot of people have real trouble getting off these medicines."

Ideally, these people would be carefully weaned off opioids, but tapering is a challenging and labour-intensive process and clinicians have minimal guidance in terms of best practice. In 2017, Krebs and her colleagues found only low-quality evidence to support the efficacy of a variety of tapering strategies, including those that are supported by medications such as buprenorphine (Subutex) or by behavioural therapy[6]. Without a clear route to success, physicians who are experienced in tapering generally favour a cautious, collaborative approach to dose reduction. "I describe myself as an advocate of the world's slowest taper," says Krebs. "If someone has been on 200 morphine milligram equivalents for ten years, I may work with that person for three years and reduce their dose by 90%." By contrast, many tapers are conducted over the course of less than one year.

Many clinicians lack the expertise, time or will to make such a commitment. Others find themselves at the mercy of health insurers or pharmacies who enforce an abrupt downsizing of patients' prescriptions. "You may have a patient whose dose is at 500 morphine milligram equivalents, and now these people are saying you need to be down to 90 tomorrow," says Alford. This could put patients in considerable jeopardy, according to a 2019

Physician Daniel Alford at the Clinical Addiction Research and Education Unit at Boston University.

observational study[7] by Jason Glanz and his colleagues at the Kaiser Permanente Colorado Institute for Health Research in Aurora. "We showed that patients who are on a stable dose were at a lower risk for overdose than those whose doses fluctuated," says Glanz. The cause of the overdoses remains unclear, but Glanz notes that they could potentially result from people's mismanagement of their medication or turning to illicit drugs as a substitute.

Suicide is also a concern. A 2017 study[8] of people being treated by the US Veterans Health Administration found that rates of suicidal ideation more than doubled within one year of terminating long-term opioid therapy, and that there was a sixfold increase in suicide attempts compared with a control cohort of military veterans. "These are already brittle patients with significant psychiatric comorbidities," Cheatle says. "We're sort of pushing people to the edge."

AFTER ALTERNATIVES

Concern over tapering prescriptions is not a defence of the status quo. Some people who take high doses of opioids for long periods can achieve remarkable stability and a good quality of life, but many more are taking on further health burdens while failing to manage their pain. Another study of US military veterans found that high doses of opioid are also associated with a greater risk of suicide[9] — possibly because the drugs have failed to control chronic, severe pain. "Usually, opioids aren't necessary or aren't the best choice," says Krebs. According to Kertesz, a general lack of education and awareness among medical professionals has led to a free-wheeling approach to prescribing opioids. "We had terrible training, without in-depth attention to either pain or addiction," he says.

Tools that enable clinicians to identify people who are vulnerable to opioid dependence — or already in its grip — could help to contain the spread of opioid abuse. Each US state except for Missouri has set up a prescription-drug monitoring programme (PDMP), which doctors must consult before prescribing an opioid. These databases are designed to highlight potential cases of dependence or overdose risk, as well as to detect people who are visiting several physicians to obtain an excessive number of prescriptions, or who are being prescribed medicines that might interact badly with opioids. A 2018 analysis by Cerdá and her colleagues found that there was no clear evidence that PDMPs meaningfully reduce the risk of overdose[10]. However, she notes that conducting such evaluations across the United States has been difficult because of the heterogeneity of state PDMPs and the data that they collect, although these programmes are becoming more harmonized.

Cheatle notes that PDMPs are helpful for starting tough conversations about overdose risk with patients. With colleagues, he has been working on alternative strategies that might help clinicians to home in on patient-specific factors that might predispose a person to opioid abuse. For example, his team demonstrated that a questionnaire that considers factors such as family history and psychiatric health was effective in predicting which people receiving opioids would go on to develop an opioid-use disorder[11]. If validated, such a tool could prove valuable in planning treatment for these most vulnerable patients.

Although the debate about the benefits of prescription controls is set to continue, there is broad agreement that the US health-care system as a whole has failed people with chronic pain. "The focus on prescribing is an easy win for politicians," says Barnett. "But it doesn't address the gaping chasm that is the complete failure of our mental-health system in this country." Treating chronic pain and its consequences is a multidisciplinary problem, which often combines medical treatment, psychiatric care and exercise, as well as addiction treatment for those with an established dependency. Sullivan contends that the failure to treat it as such is probably a big reason why prescription opioid abuse has exacted a much greater toll on the United States than it has on Europe, where national health-care programmes tend to offer alternative treatments for, and closer oversight of, people in pain. "In Germany, for example, they have psychosomatic clinics and pain clinics that integrate a lot broader range of therapies," he says. By contrast, US health insurers favour simpler pharmacological solutions over more effective, longer-term alternatives, so that the abrupt discontinuation of a prescription could leave patients out of options. "We tend to blame clinicians and patients, but we really need to look at the insurance companies and the paucity of education on pain and addiction medicine in medical schools," says Cheatle.

Some progress is being made. Alford notes that in Massachusetts, universities have been bolstering medical education on treating pain, and that hospitals are expanding their resources for combating addiction. He also cites a constructive meeting this year with Blue Cross Blue Shield Association, a federation of health-insurance companies that collectively provide coverage to one-third of people in the United States, which focused on effective, non-opioid protocols for treating chronic pain. But achieving a lasting victory will probably require a thorough rethinking of how pain treatments are designed, managed and paid for at the national level. "You can't have it all ways," says Cheatle. "You can't claim to be plagued by what to do about pain patients and opioids and this epidemic if you're not going to transform the system from top to bottom." ■

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