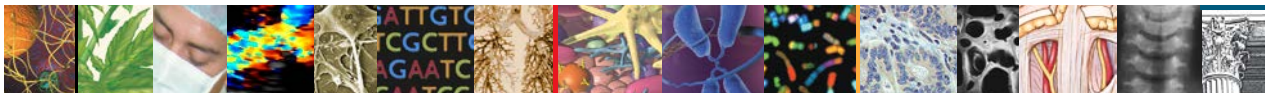

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Perspective

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Chronic Pain, Addiction, and Zohydro

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The recent approval of the long-acting opioid Zohydro ER (hydrocodone bitartrate) by the Food and Drug Administration (FDA) has brought into sharp relief the tension between the twin challenges of chronic pain and addiction.

Chronic pain, which affects tens of millions of people in the United States, is associated with functional loss and disability, reduced quality of life, high health care costs, and premature death. U.S. physicians are now more likely to recognize and treat chronic pain than they have been historically, with the number of prescriptions written for opioids having increased 10-fold since 1990.[1]

Over the same period, however, the rate of overdose deaths in the United States has more than tripled.[2] This is not a coincidence. Many doctors have prescribed opioids for chronic pain without following best practices, understanding the risk for the development of substance-use disorders, or recognizing the red flags that can emerge in clinical practice. There is now evidence from states including our own, Maryland, that some individuals whose path to addiction may have started with a prescription for pain are progressing to heroin.

Enter Zohydro. A single-entity formulation of hydrocodone, Zohydro joins a category of extended-release and long-acting oral opioids that includes Oxycontin (oxycodone hydrochloride), three different versions of extended-release morphine sulfate (MS Contin, Avinza, and Kadian), Exalgo (hydromorphone hydrochloride), Opana ER (oxymorphone hydrochloride), Nucynta ER (tapentadol), and Embeda (morphine sulfate and naltrexone hydrochloride).

Zohydro is a high-potency opioid agonist sold in capsule form, without features to deter crushing and injecting. The FDA explained that it approved Zohydro on the grounds that it is safe and effective for pain when used as directed and may reduce the risk of toxic effects on the liver because, unlike other hydrocodone preparations, it does not contain acetaminophen. But in December 2012, the agency's own advisory committee had voted 11 to 2 against approval, calling for additional safeguards against inappropriate use and diversion. Attorneys general from 29 states have requested

that the FDA reconsider its approval of Zohydro. Declaring a public health emergency over the loss of life from overdose and citing the lack of abuse-deterrent features, Massachusetts Governor Deval Patrick recently took the extraordinary step of banning the prescribing and dispensing of Zohydro in his state. Zogenix, the manufacturer of Zohydro, quickly and successfully challenged the governor's action in federal court. In striking down the ban, Judge Rya W. Zobel acknowledged concerns about the possible misuse of Zohydro but found that the FDA's federal authority preempts state law and that banning the medication would deny appropriate access for patients in pain.

Other states are taking different actions. After his state's health commissioner expressed "dismay" over the FDA approval of Zohydro and called for "getting ahead" of potential problems, Vermont Governor Peter Shumlin announced emergency rules requiring patients to provide informed consent and requiring prescribing physicians to follow a range of specific practices, from drug testing to follow-up care. Failure to do so could lead a physician to lose his or her medical license.

During a recent multiagency call with stakeholders, FDA Commissioner Margaret Hamburg attempted to move the discussion past Zohydro to the agency's broader attempts to address the risks of addiction and overdose.[3] She noted that the agency has supported moving hydrocodone preparations to the more restrictive Schedule II, is relabeling certain prescription opioids with new warnings and narrower indications, is promoting education of prescribers and patients about long-acting opioids, and is seeking to accelerate development of effective nonopioid treatments for pain. The FDA recently approved an autoinjector for the opioid antagonist and reversal agent naloxone.

A new strategy need not prioritize chronic pain over addiction or addiction over chronic pain. Rather, it must recognize that both will remain significant and interconnected clinical and public health challenges for the foreseeable future.

Hamburg is right that the FDA is doing more than ever before to respond to the overdose epidemic. However, the agency's list of assorted actions is not likely to reduce pressure from elected officials and distraught families who are grappling with an alarming loss of life from overdoses. A more comprehensive and coherent strategy, cutting across the breadth of U.S. health care, is urgently needed.

This strategy need not prioritize chronic pain over addiction or addiction over chronic pain. Rather, it must recognize that both will remain significant and interconnected clinical and public health challenges for the foreseeable future. Millions of people with chronic pain are at risk for addiction or overdose when treated with opioid medications. At the same time, many people with addiction also have chronic pain. Approaches to managing these clinical situations effectively should be a significant focus of research funding, a subject for education in medical and dental schools, and a topic for training in accredited residency programs. A new specialty fellowship in chronic pain and addiction could be developed to foster expertise for consultation to both clinicians and policymakers.

Professional licensing boards can better balance their support of high-quality pain management with effective care for opioid-use disorders. To date, 45 state medical boards have adopted policies on best practices for managing chronic pain with prescription opioids, as recommended by the Federation of State Medical Boards. However, only four of those states have adopted the model policy that encourages ambulatory care physicians to treat opioid-use disorder in their offices with buprenorphine.[4]

The federal government can do more to promote the concurrent treatment of chronic pain and addiction among patients who are at greatest risk for both disorders. For example, we believe that the Substance Abuse and Mental Health Services Administration should provide guidance to physicians practicing in opioid-treatment programs on appropriate ways of using methadone or buprenorphine to treat concomitant opioid-use disorder and chronic pain. Specially designated opioid-treatment programs should be allowed to incorporate compre-

hensive approaches to chronic pain into their scope of services.

Health care systems can incorporate nonjudgmental screening, brief intervention, and referrals for further assessment and treatment of addiction into all clinical settings where opioids are prescribed. Conversely, addiction-treatment providers can screen patients for pain, recognizing that inadequately treated pain is a risk factor for relapse.

Payers, including Medicare and state Medicaid programs, can use data-analysis tools to spot the red flags of inappropriate prescribing and refer prescribers to medical boards or other state agencies for further review, education, and oversight. Prescription-drug monitoring programs can also identify prescribers in need of assistance. Coherent, evidence-based review of clinical practice can be conducted with the aim of supporting high-quality care for both chronic pain and addiction — and avoiding the unintended consequence of deterring physicians from caring for patients with complex needs.

An audio interview with Dr. Olsen is available at NEJM.org

Public and private insurers can provide as generous coverage for treatment of opioid-use disorder as they do for management of chronic pain. This standard is infrequently met — for example, it is long past time for Medicare to begin covering the effective care provided in opioid-treatment programs.

It is also time for the FDA to address the intertwining of chronic pain and addiction farther upstream in the drug-development cycle. The agency might consider creating a pathway for development and review of new products and indications for simultaneous treatment of chronic pain and opioid-use disorder. Building on its own work to advance the science of abuse-deterrent formulations, the FDA should also require that prescription opioids meet basic deterrent standards and should facilitate the gradual reformulation of existing products to meet such standards. In declining to apply such a standard to Zohydro, the agency noted that existing deterrent mechanisms have had minimal impact by themselves. However, even modest safeguards have been shown to reduce the potential for inappropriate use.[5] As part of a comprehensive strategy, a set of reasonable requirements for opioid medications is well in line with the FDA's public health mission. Taking such action will deter others with less expertise from filling a perceived void.

In the end, pointing the finger at Zohydro is not going to resolve the tension that exists today between chronic pain and addiction. All concerned about the treatment of chronic pain and all responding to the rise in overdose deaths need to come together to promote high-quality and effective prevention and treatment for both conditions.

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Medication-Assisted Therapies — Tackling the Opioid-Overdose Epidemic

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The rate of death from overdoses of prescription opioids in the United States more than quadrupled between 1999 and 2010 (see graph), far exceeding the combined death toll from cocaine and heroin overdoses.[1] In 2010 alone, prescription opioids were involved in 16,651 overdose deaths, whereas heroin was implicated in 3036. Some 82% of the deaths due to prescription