other medical conditions involving chronic pain. Physicians have an obligation to learn how to diagnose it and develop strategies to address it. Risk-mitigation strategies such as periodic urine drug screening, scrutiny of prescription-monitoring reports, identification of aberrant behaviors, and patient education in safe use and storage of opioid medications are of paramount importance for all patients taking opioid analgesics. Similarly, take-home or coprescription of naloxone for patients taking any opioids should be routine. This strategy could save not only the patient's life but also that of a relative, friend, or bystander unlucky enough to suffer an opioid overdose.

Finally, physicians and advanced care clinicians can undergo brief training (8 and 24 hours, respectively) to obtain an "X" waiver on their DEA license so they can use buprenorphine to treat OUD. Increasing the availability of such treatment could stem the tide of opioid misuse and improve the lives of patients with OUD.

Opioid analgesics are an important part of our therapeutic armamentarium, but they have serious consequences when used improperly. As the pendulum swings from liberal opioid prescribing to a more rational, measured, and safer approach, we can strive to ensure that it doesn't swing too far, leaving patients suffering as the result of injudicious policies.

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Our Other Prescription Drug Problem

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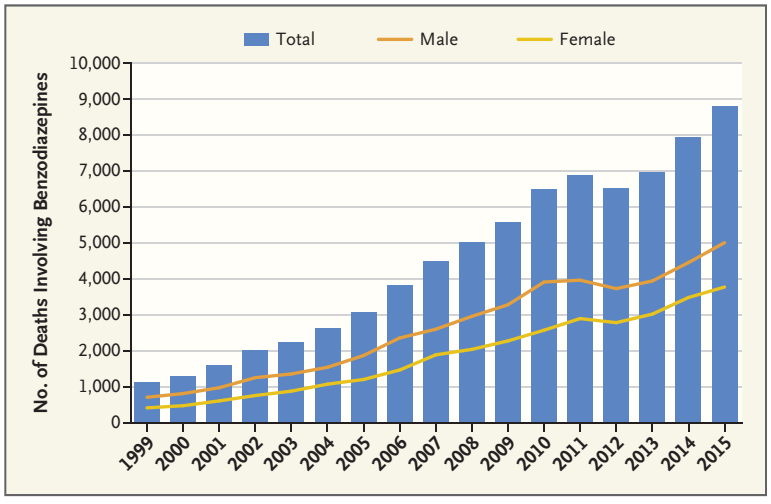
The epidemic of opioid addiction and overdose has appropriately garnered national attention and led to concerted efforts to reduce overprescribing of opioids, a major cause of today's drug crisis. By contrast, there has been little effort to address inappropriate prescribing of benzodiazepines — controlled substances such as alprazolam, clonazepam, diazepam, and lorazepam. The Food and Drug Administration (FDA) has approved benzodiazepines for a diverse set of clinical indications, including anxiety, insomnia, seizures, and acute alcohol withdrawal. These drugs are also prescribed off-label for many other conditions, such as restless legs syndrome and depression.

Between 1996 and 2013, the number of adults who filled a benzodiazepine prescription increased by 67%, from 8.1 million to 13.5 million, and the quantity of benzodiazepines they obtained more than tripled during that period, from 1.1-kg to 3.6-kg lorazepam-equivalents per 100,000 adults.[1] According to data from the National Institute on Drug Abuse, overdose deaths involving benzodiazepines increased from 1135 in 1999 to 8791 in 2015 (see graph). Despite this trend, the adverse effects of benzodiazepine overuse, misuse, and addiction continue to go largely unnoticed. Three quarters of deaths involving benzodiazepines also involve an opioid,[1] which may explain why, in the context of a widely recognized opioid problem, the harms associated with benzodiazepines have been overlooked.

In 2012, U.S. prescribers wrote 37.6 benzodiazepine prescriptions per 100 population. Alprazolam, clonazepam, and lorazepam are among the 10 most commonly prescribed psychotropic medications in the United States. Medicaid expenditures on benzodiazepines increased by nearly $40 million between 1991 and 2009,



Overdose Deaths in the United States Involving Benzodiazepines, 1999 through 2015.
From the National Institute on Drug Abuse.

even as the price of benzodiazepines generally fell, suggesting greater utilization.[2] Despite the increased risk of overdose in patients taking both benzodiazepines and opioids, rates of coprescribing nearly doubled, increasing from 9% in 2001 to 17% in 2013.[3] Use of so-called z-drugs such as zolpidem and eszopiclone alone or in combination with opioids is also associated with increased mortality.

Highly potent new forms of benzodiazepines are increasingly penetrating the illicit market. Manufactured in clandestine laboratories in the United States and elsewhere, these drugs are indistinguishable from prescription benzodiazepines and are potentially as deadly as the synthetic opioid analogue fentanyl. Clonazolam, an analogue of clonazepam that is akin to a combination of alprazolam and clonazepam, is so potent that it needs to be dosed at the microgram level using a high-precision scale to prevent accidental overdose. It can be bought on the Internet as a "research chemical" and shipped virtually anywhere.

The magnitude of harm caused by illicit, high-potency benzodiazepines has yet to be documented. Overprescribing of benzodiazepines may be fueling the use of illicit analogues, just as overprescribing of opioids has fueled increases in heroin and illicit fentanyl use.

Benzodiazepines have proven utility when they are used intermittently and for less than 1 month at a time. But when they are used daily and for extended periods, the benefits of benzodiazepines diminish and the risks associated with their use increase. Many prescribers don't realize that benzodiazepines can be addictive and when taken daily can worsen anxiety, contribute to persistent insomnia, and cause death. Other risks associated with benzodiazepines include cognitive decline, accidental injuries and falls, and increased rates of hospital admission and emergency department visits. Fortunately, there are safer treatment alternatives for anxiety and insomnia, including selective serotonin-reuptake inhibitors and behavioral interventions. Just as with opioids, some patients benefit from long-term use of benzodiazepines. But even in low-risk patients, it is best to avoid daily dosing to mitigate the development of tolerance, dependence, and withdrawal.

In August 2016, the FDA issued a black-box warning regarding the dangers of coprescribing benzodiazepines and opioids and implemented classwide changes to drug labeling. Although such moves were sensible, benzodiazepines carry serious risks in their own right, especially when taken long term. In September 2017, the FDA advised clinicians treating opioid use disorder not to withhold medication-assisted treatment with buprenorphine or methadone in patients concurrently prescribed benzodiazepines, arguing that the benefits of opioid-agonist therapy outweigh the risks of combining these opioids with benzodiazepines. That said, we believe providers should aspire to taper off benzodiazepines in patients who have been stabilized using opioid-agonist therapy, taking into account each patient's preferences, the risks and benefits of benzodiazepines, and possible alternatives.

Despite the many parallels to the opioid epidemic, there has been little discussion in the media or among clinicians, policymakers, and educators about the problem of overprescribing and overuse of benzodiazepines and z-drugs, or about the harm attributable to these drugs and their illicit analogues. We believe national efforts to reduce overprescribing of opioids and to educate the medical and lay communities about their risks should be expanded to target benzodiazepines. Educators and policymakers could address the overprescribing and overuse of benzodiazepines in

tandem with current efforts to curb the opioid epidemic.

For example, prescribers could be encouraged or required to check their state's prescription drug monitoring program (PDMP) before prescribing benzodiazepines, as is often required with opioids. Though their quality and usability vary, PDMPs are now available in every state and typically allow prescribers to see federally controlled and addictive medications prescribed to a particular patient within a given period (usually the past 12 months). Such databases allow the prescriber to check for dangerous drug combinations (such as combinations of opioids and benzodiazepines) and to determine whether the patient is "doctor shopping." Requiring physicians to consult the PDMP before prescribing opioids has been shown to reduce opioid prescribing, doctor shopping, and overdose deaths related to prescription opioids.[4,5] Many, but not all, states have PDMP laws that require physicians to query the database before prescribing opioids, benzodiazepines, or both.

We believe that education about safe opioid prescribing — which is already being implemented at all levels of medical education — should also include information on benzodiazepine prescribing. Health insurance companies could review coverage and payment policies that contribute to overprescribing of benzodiazepines. Efforts should also be made to shut down illegal online pharmacies and other drug-trafficking networks where people obtain illicit benzodiazepines, particularly superpotent analogues.

It would be a tragedy if measures to target overprescribing and overuse of opioids diverted people from one class of life-threatening drugs to another. We believe that the growing infrastructure to address the opioid epidemic should be harnessed to respond to dangerous trends in benzodiazepine overuse, misuse, and addiction as well.

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Federal Right-to-Try Legislation — Threatening the FDA's Public Health Mission

Steven Joffe, M.D., M.P.H., and Holly Fernandez Lynch, J.D., M.B.E.

The Food and Drug Administration (FDA) is the gatekeeper of the country's drugs and medical devices. Originally created to prevent the misleading of patients, it was later tasked with ensuring the safety of medical products. In 1962, Congress expanded the FDA's mandate again, requiring it to determine that medical products are effective for their intended use and that their benefits outweigh their risks. Access to products that are not yet FDA-approved is typically restricted to participants in clinical trials. Consequently, some patients who might benefit from investigational drugs cannot obtain them.

Recognizing this problem, the FDA created "expanded access" pathways to give desperate patients without other options access to promising products before approval, while still providing oversight. The agency received more than 5000 requests under those pathways between 2010 and 2014.[1] But in August 2017, the Senate passed the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act, which would sharply curtail the FDA's oversight of access to investigational drugs for patients with life-threatening illnesses.[2] Though popular with the public and supported by politicians from both parties, the legislation has