Partnerships to Help End the Opioid Crisis

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The escalating rates of opioid misuse and addiction in the U.S. have many causes, including overprescribing of opioid analgesics starting in the late 1990s and later an influx of high-quality heroin and now fentanyl. But the epidemic of deaths that has resulted from this crisis is partly a symptom of our society's sluggishness to recognize substance use disorders as medical conditions and people with these disorders as patients needing and deserving of medical care rather than punishment. A positive effect of the enormous attention now being given to the opioid crisis — however belated — is that these attitudinal barriers are finally breaking down, and medical treatments for opioid use disorders are becoming more accepted and understood and utilized in a wider range of healthcare contexts (such as emergency departments) as well as in the criminal justice system.

Unfortunately, the range of available treatments for opioid addiction remains limited. Buprenorphine, approved in 2002, has proven extremely successful, with numerous studies showing effectiveness on par with the only medication available until then, methadone. And because buprenorphine is a partial rather than full agonist at the mu-opioid receptor, it has a slightly better profile for safety and misuse risk: it is hard for an opioid-tolerant individual to obtain euphoria from this drug. But as with methadone, many factors have made it hard to administer and utilize, especially for people in rural areas without frequent access to a health-care provider who is waivered to prescribe it and who can continuously monitor the treatment.

The approval in 2016 of Probuphine, a buprenorphine implant, was a first step toward greater versatility of buprenorphine treatment, although it delivers a low dose and thus is not appropriate for the majority of patients. In November 2017, the FDA approved Sublocade, a once-monthly buprenorphine injection that delivers a sufficient dose to treat patients with moderate to severe opioid use disorder; other depot formulations of buprenorphine are also in the drug-approval pipeline. These medications could potentially greatly extend the reach of maintenance treatment.

Naltrexone, the third currently approved medication for opioid addiction, faces its own challenges in proving itself, in part because of compliance issues — unlike methadone and buprenorphine, it does not minimize cravings or withdrawal symptoms but instead blocks the effects of opioids at the mu-opioid receptor. The approval of extended-release naltrexone (Vivitrol) in 2010 went a long way to address compliance, as the patient only needs to make the right decision once a month, instead of once a day. Still, a lack of head-to-head comparisons with other medications left uncertainty in providers' minds as to its effectiveness. Two recent trials however, one in Norway[1] and one in the United States[2], compared extended-release naltrexone to buprenorphine and found the drugs equally effective at preventing relapse and retaining patients in treatment once they could be successfully inducted. The "detoxification hurdle" — the need to detoxify the patient initially and thus face the risk of noncompliance with the treatment plan in the induction phase — needs to be addressed, but from these trials we now have reason to believe that extended-release naltrexone is as effective as buprenorphine once this hurdle is cleared. However, more research is needed, including research on the safety of naltrexone during pregnancy.

Even though three effective medications are FDA approved to treat opioid use disorders, new medications as well as non-pharmacological interventions are needed. Not all opioid-addicted patients respond to the medications currently available, and each of the medications has drawbacks associated with it. Thus, a broader treatment toolkit comparable to the range of treatments available for other chronic conditions is essential. Likewise, a wider range of overdose-prevention tools is needed, partly because overdoses on new powerful synthetic opioids like fentanyl are requiring multiple naloxone administrations. And because opioid addiction is so entangled with pain, addressing opioid addiction and overdose means developing new, non-addictive pain treatments.

To these ends, the National Institutes of Health (NIH) has embarked on an ambitious strategy of leveraging public-private partnerships to find and implement solutions to the crisis. At the National Rx Drug Abuse and Heroin Summit in Atlanta last April, NIH Director Francis Collins announced an initiative to cut in half the time it takes to develop new therapeutics, and since then NIDA has convened several meetings bringing together experts and representatives from government, the pharmaceutical

industry, and academia[3]. The partnership is still taking shape, but initial action steps will likely include accelerating the development of new formulations and combinations of existing opioid-addiction medications and overdose-reversal tools, as well as identifying ways to repurpose existing or abandoned medications for addiction or pain or to reverse overdose. Over the longer term, the partnerships will work toward goals that may include the development of new, safer and more effective treatments for pain and the development of new, objective pain assessments and biomarkers.

There are many areas where our efforts could produce novel drugs and treatment strategies in a shorter-than-usual timeframe; NIDA Director Nora Volkow and NIH Director Francis Collins outlined several possibilities in the *New England Journal of Medicine* last July[4]. Within a few years, we could see stronger formulations of naloxone for addressing fentanyl overdoses, for instance, as well as additional depot formulations of approved addiction medications and misuse-resistant formulations of existing pain medications. Also, various existing medications show potential to be repurposed to treat addiction. For example, lorcaserin, an FDA-approved diet drug that acts at a serotonin receptor, has been found to reduce opioid seeking in rodents and could be studied in humans; lofexidine, a hypertensive drug currently being used in the UK for opioid detoxification, is being studied for its ability to control opioid withdrawal symptoms.

In addition, our rapidly increasing scientific understanding of the mechanisms of pain and addiction point to a wide range of novel pain treatments that could appear over the longer term. One of the many drug development strategies that looks promising is the use of so-called biased agonists at the mu-opioid receptor. Studies of that receptor have shown that the signaling pathway that causes pain relief is conveniently distinct from the one that causes reward and respiratory depression, raising the possibility of a compound that could decouple the desired effects from the harmful side effects. Phase 2 trials of one *biased agonist* successfully produced pain relief without producing reward and respiratory depression, and thus this could, if successful in further trials, spur accelerated development of a new, truly safe generation of opioids.

Compounds that target other receptor systems such as the endocannabinoid system are also actively being studied for possible therapeutic benefit both in pain and in addiction treatment. Alternative approaches such as vaccines that recruit the body's immune system to neutralize drug molecules and transcranial magnetic stimulation for pain and addiction are other areas for research, as are technologies such as wearable devices that might detect an overdose and automatically administer naloxone.

Of course, new medications and technologies alone will not cure opioid addiction or solve the overdose epidemic. We also need better delivery of existing evidence-based treatments (both behavioral treatments and medications) to people with opioid use disorders, most of whom currently do not receive any form of care. NAADAC members are well-poised to ensure that quality treatment is supported by evidence and is delivered with fidelity. As addiction treatment becomes increasingly integrated with the general healthcare system, many of these challenges can be addressed.

NIDA has always supported research on addressing opioid addiction; partnerships between NIDA and industry led to the development and approval of buprenorphine and some of the newer tools poised to make an impact on the problem. We are currently taking, as Volkow and Collins put it, an "all scientific hands on deck" approach[5], and the combined will of government and industry to work together to end this health crisis provides much reason for optimism. Science can and will provide solutions.

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