SPECIAL REPORT

The Role of Science in Addressing the Opioid Crisis

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Opioid misuse and addiction is an ongoing and rapidly evolving public health crisis, requiring innovative scientific solutions. In response, and because no existing medication is ideal for every patient, the National Institutes of Health (NIH) is joining with private partners to launch an initiative in three scientific areas: developing better overdose-reversal and prevention interventions to reduce mortality, saving lives for future treatment and recovery; finding new, innovative medications and technologies to treat opioid addiction; and finding safe, effective, nonaddictive interventions to manage chronic pain. Each of these areas requires a range of short-, intermediate-, and long-term research strategies (Fig. 1).

OVERDOSE-REVERSAL INTERVENTIONS

Every day more than 90 Americans die from opioid overdoses.[1] Overdoses result from an opioid's agonist effects at the mu-opioid receptor (MOR), located on brainstem neurons that control breathing. The MOR antagonist naloxone can reverse an overdose, if it is administered shortly after the overdose occurs. Although naloxone has saved tens of thousands of lives, overdoses frequently occur when no one else is around, and often no one arrives in time to administer it.

Overdose fatalities have also been fueled by the increased availability of very potent synthetic opioids such as fentanyl and carfentanil (50 and 5000 times as potent as heroin, respectively). Misuse of or accidental exposure to these drugs (e.g., laced in heroin) is associated with very high overdose risk, and naloxone doses that could reverse prescription-opioid or heroin overdoses may be ineffective.[2] New and improved approaches are needed to prevent, detect, and reverse overdoses.

Through a successful partnership, the National Institute on Drug Abuse (NIDA) and industry developed a user-friendly intranasal naloxone formulation (Narcan Nasal Spray) that results in blood naloxone levels equivalent to those achieved with parenteral administration; it was approved by the Food and Drug Administration (FDA) in 2015. The NIH will now work with private partners to develop stronger, longer-acting formulations of antagonists, including naloxone, to counteract the very-high-potency synthetic opioids that are now claiming thousands of lives each year.

In the intermediate and longer term, alternative interventions against opioid-induced respiratory depression, such as 5-hydroxytryptamine type 1A (5-HT_{1A}) agonists, ampakines, and phrenic-nerve-stimulation devices, could protect persons at particularly high risk for overdose. Research is also under way to characterize the physiological signals that can predict an impending overdose, which would allow wearable devices to detect an overdose when it is occurring and signal for help, automatically inject naloxone, or both.

TREATMENTS FOR OPIOID ADDICTION

This partnership will also focus on opioid addiction (the most severe form of opioid use disorder [OUD]), which is a chronic, relapsing illness. Abundant research has shown that sustained treatment over years or even a lifetime is often necessary to achieve and maintain long-term recovery. Currently, there are only three medications approved for treating OUD: methadone, buprenorphine, and extended-release naltrexone. These medications coupled with psychosocial support are the current standard of care for reducing illicit opioid use, relapse risk, and overdoses, while improving social function.[3] However, limited access to providers and programs can create barriers to treatment.

The NIH has successfully partnered with industry to help develop new formulations of existing medications to improve compliance and reduce the potential for diversion. To facilitate

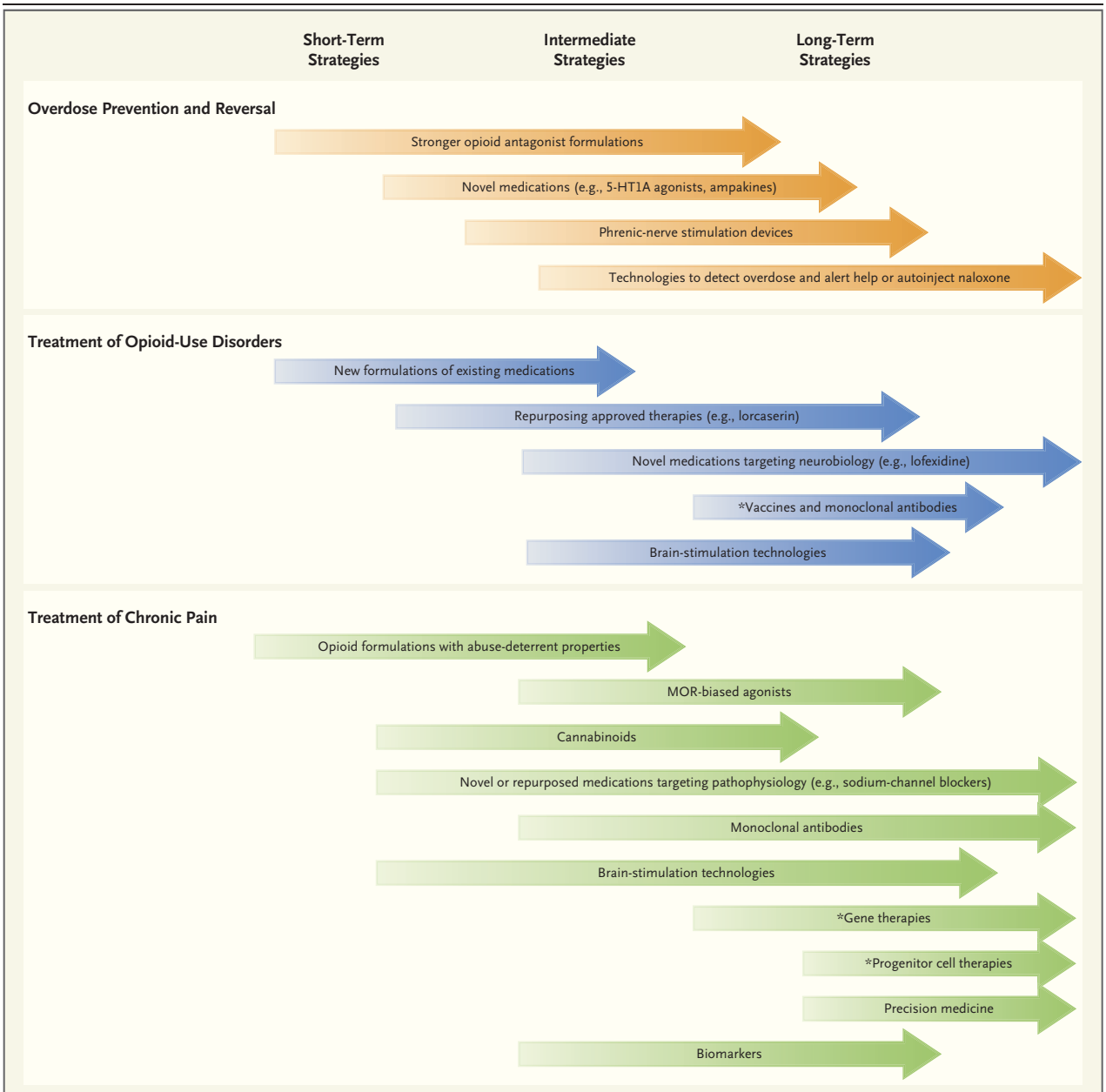

Figure 1. Scientific Strategies for Combating the Opioid Epidemic.
An asterisk denotes strategies that are largely based on preclinical findings, which therefore have more uncertain outcomes and timelines.

compliance with buprenorphine treatment, NIDA worked with Titan and Braeburn Pharmaceuticals to produce a long-lasting (6-month) implant, Probuphine, which the FDA approved in 2016. Initial clinical trials testing the safety, efficacy, and pharmacokinetics of buprenorphine formulations that deliver therapeutic doses over 1-week or 1-month periods have also been completed; such formulations may be particularly valuable for patients in emergency departments after nonfatal opioid overdoses, to facilitate engagement in long-term treatment.

There is a clear need to develop new treatment strategies for opioid-use disorders. New pharmacologic approaches aim to modulate activity of the reward circuit through antagonists

of the neurokinin-1 receptor and counteract the aversive state of withdrawal through antagonists of kappa-opioid receptors. The selective 5-HT_{2C}-receptor agonist lorcaserin, an FDA-approved diet drug, was found to reduce opioid seeking in a rodent model. NIDA has also helped fund clinical trials of lofexidine, an α_{2A}-adrenergic-receptor agonist not currently approved in the United States. Lofexidine was originally developed as an antihypertensive drug and is currently used in the United Kingdom for opioid detoxification, since it controls withdrawal symptoms (although not cravings).

Vaccines against prescription opioids, heroin, and fentanyl, which induce antibodies to opioids in the bloodstream to keep them from entering the brain,[4] have shown great promise in preclinical studies. Similarly, long-lasting monoclonal antibodies against very potent synthetic opioids (e.g., fentanyl and its analogues) have the potential to prevent overdoses and relapses.

NONADDICTIVE TREATMENTS FOR CHRONIC PAIN

The third area of focus is chronic pain treatment: overprescription of opioid medications reflects in part the limited number of alternative medications for chronic pain. Thus, we cannot hope to prevent opioid misuse and overdose without addressing the treatment needs of people with moderate-to-severe chronic pain. Though more cautious opioid prescribing is an important first step, there is a clear need for safer, more effective treatments.

One short-term goal is the development of formulations of opioid analgesics with abuse-deterrent properties that are more difficult to manipulate for snorting or injecting, the routes of administration most frequently associated with misuse because of their rewarding effects. Such formulations, however, can still be misused orally and still lead to addiction. Thus, a more promising longer-term avenue to advancing pain treatment is developing a new generation of powerful, nonaddicting opioid analgesics. Recent x-ray crystallography studies of the MOR have provided insight into two separate intracellular signaling pathways: a pathway originating with the G_i protein is believed to underlie analgesia, while a separate pathway involving β-arrestin is believed to underlie the rewarding and respiratory-depressing effects of opioid agonists.[5] One MOR-biased agonist (TRV130) has successfully completed phase 2 clinical testing. If the trials show that TRV130 is not associated with rewarding or respiratory effects, it could energize industry to accelerate development of other MOR-biased agonists.

Ongoing research is also exploring compounds that target other opioid receptors. Through the NIH Blueprint Neurotherapeutics Program, a team of researchers is working to optimize a recently discovered series of selective and orally available kappa-opioid antagonists as nonaddictive medications for stress-induced pain disorders, such as headache and fibromyalgia. Antagonists of the kappa-opioid system are also therapeutic targets for OUD. Encouraging pharmacokinetic studies suggest that these compounds have the potential to be safe and effective drugs for pain, and perhaps also for opioid addiction.

Compounds that target nonopioid pain pathways, such as the endocannabinoid system, are also being evaluated for chronic pain management. There is strong evidence of the efficacy of cannabinoids, including tetrahydrocannabinol (THC), in treating pain. Medications that target the endocannabinoid system without producing the cognitive impairment and rewarding effects of marijuana could provide a powerful new tool. Other targets being investigated include a dopamine D3 antagonist, which was shown to reduce morphine tolerance and dependence without inhibiting analgesia when administered in conjunction with morphine, making this a potentially promising approach to enhancing the safety of existing opioids.[6] Genetic mutations in the sodium channel $Na_v1.7$ in humans modulate pain; loss-of-function mutations result in congenital insensitivity to pain, and gain-of-function mutations cause pain syndromes. Several $Na_v1.7$ antagonists are being explored as analgesics.[7]

Therapeutics that antagonize inflammatory signals involved in pain have led to FDA-approved treatments for specific pain conditions, such as tumor necrosis factor inhibitors for rheumatoid arthritis and monoclonal antibodies to nerve growth factor for osteoarthritis; researchers are exploring their value in other pain conditions. In parallel, clinical trials are testing the efficacy of antibodies to calcitonin gene–related peptide for treating migraine.[8]

Nonpharmacologic approaches including brain-

stimulation technologies such as high-frequency repetitive transcranial magnetic stimulation (rTMS, already FDA-approved for depression) have shown efficacy in multiple chronic pain conditions. At a more preliminary stage are viral-based gene therapies and transplantation of progenitor cells to treat pain.[9] NIH researchers are investigating the use of gene therapy to deliver a potent anti-inflammatory protein to painful sites. Preclinical studies show powerful and long-lasting effects in reducing pain without side effects such as numbness, sedation, addiction, or tolerance.[10]

Development of new pain treatments builds on a foundation of basic research on the complex pathophysiology of chronic pain and the mechanisms underlying the transition from acute to chronic pain. The NIH is committed to working with industry partners to advance basic research in this area and to identify and validate biomarkers for pain and pain relief. Biomarkers can move the field away from reliance on subjective pain assessments, and will facilitate medication development and individualized clinical management. Precision-medicine research is expected to help identify the pain-management interventions likely to be most effective for specific patients.

PUBLIC–PRIVATE PARTNERSHIPS

Recent NIH–industry partnerships, such as the Accelerating Medicines Partnership, demonstrate the power of public–private collaboration in speeding the development of new medications. Ending the opioid crisis will require this kind of collaboration. In April 2017, the NIH began discussions with pharmaceutical companies to accelerate progress on identifying and developing new treatments that can end the opioid crisis. Some advances may occur rapidly, such as improved formulations of existing medications, opioids with abuse-deterrent properties, longer-acting overdose-reversal drugs, and repurposing of treatments approved for other conditions. Others may take longer, such as MOR-biased agonists, opioid vaccines, and novel overdose-reversal medications. For all three areas, our goal is to cut in half the time typically required to develop new safe and effective therapeutics.

As we have seen repeatedly in the history of medicine, science is one of the strongest allies in resolving public health crises. Ending the opioid epidemic will not be any different. In the past few decades, we have made remarkable strides in our understanding of the biologic mechanisms that underlie pain and addiction. But intensified and better-coordinated research is needed to accelerate the development of medications and technologies to prevent and treat these disorders. The scope of the tragedy of addiction and overdose deaths plaguing our country is daunting. With our partners, the NIH will take an "all hands on deck" approach to developing and delivering the scientific tools that will help end this crisis and prevent it from reemerging in the future.

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