

VIEWPOINT

Helping to End Addiction Over the Long-term

The Research Plan for the NIH HEAL Initiative

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Extraordinary focus by all segments of society is required to respond to the nation's opioid crisis. Now is the time to channel the efforts of the scientific community to deliver effective—and sustainable—solutions to this formidable public health challenge. Recognizing this opportunity, Congress added \$500 million to the base appropriation of the National Institutes of Health (NIH), starting in fiscal year 2018.¹ The NIH will invest these much-needed resources to support science that advances national priorities for addiction and pain research² with a bold new trans-NIH initiative called Helping to End Addiction Long-term (HEAL).³ In this Viewpoint, we outline the initial components of this cross-cutting, interdisciplinary program.

More than 25 million US adults are affected by daily pain.⁴ More than 2 million individuals in the United States have an opioid use disorder (OUD), most starting with opioid analgesics prescribed to them or procured from diverted medications, but once addicted, often shifting to illicit heroin or synthetic opioids.⁵ The scope of this crisis is staggering, but scientific advances offer strategies that can help the nation overcome it.

At the National Rx Drug Abuse and Heroin Summit in April 2018, leaders from both the public and private sectors affirmed that research is essential to the effort to end this public health crisis. It will take “all hands on deck” to make this happen, which is why HEAL seeks to foster innovative partnerships with other government agencies, academic institutions, industry, communities, and patient advocates. Through a year-long series of engagements with individuals from these groups, the NIH has developed an innovative, action-oriented research plan for HEAL that is focused on 2 primary areas: improving treatments for opioid misuse and addiction as well as enhancing strategies for pain management (Table).

Although there are effective medications for OUD (methadone, buprenorphine, and naltrexone), only a small percentage of individuals in the United States who would benefit receive these medications. Even among those who have initiated these medications, about half will relapse within 6 months. Research to reformulate these medications to improve adherence, as well as to develop new, more flexible therapies, is needed to help those who have OUD. Similarly, although the opioid antagonist naloxone can effectively reverse opioid overdose, its relatively short half-life compared with those of synthetic opioids (fentanyl and its analogues) frequently requires multiple doses to reverse respiratory arrest, and its effectiveness declines when opioids are combined with other drugs (alcohol, benzodiazepines). HEAL will catalyze the development of extended-release formulations of existing medications to treat OUD, longer-acting formulations of opioid antagonists or partial agonists, new therapies to

Table. Research Plan for the NIH HEAL Initiative

Opportunities	Components
Improving Treatments for Opioid Misuse and Addiction	
New treatments for addiction	Identify new targets, develop new medications/immunotherapies; reformulate existing medicines
	Improve overdose reversal medicines
	Develop new therapies for opioid-induced respiratory depression
Optimization of effective treatments for addiction	Enhance NIDA Clinical Trials Network for opioid research
	Establish Justice Community Opioid Intervention Network
	Initiate HEALing Communities Study
NOWS	Expand ACT NOW pilot study; use results to conduct clinical trials to determine best practices for clinical care of NOWS
Enhancing Pain Management	
Better understanding of chronic pain	Establish Acute to Chronic Pain Signatures program
New nonaddictive pain treatments	Identify new targets for pain treatment
	Engineer preclinical testing platforms to profile potential nonaddictive treatments
Public-private HEAL Partnership to speed movement of nonaddictive treatments through clinical pipeline	Enhance data and asset sharing
	Validate biomarkers to inform neurotherapeutic and pain clinical research
	Establish clinical trials network to support and accelerate trials of nonaddictive pain therapies

Abbreviations: HEAL, Helping to End Addiction Long-term; NIDA, National Institute on Drug Abuse; NIH, National Institutes of Health; NOWS, neonatal opioid withdrawal syndrome.

counter opioid-induced respiratory depression, and novel medications and immunotherapies to treat OUD and prevent and reverse overdoses.

HEAL will also support services and implementation research to develop new models of care for OUD within the health care and criminal justice settings that can expand access to medications and improve treatment retention. For example, HEAL will test how integrated evidence-based interventions can improve OUD outcomes through the multisite HEALing Communities Study. This study will be developed in close collaboration with the Substance Abuse and Mental Health Services Administration and other federal partners to avoid duplication and leverage complementary ongoing efforts. HEALing Communities will measure the effect of integrated implementation of a comprehensive set of evidence-based strategies across the OUD cascade of prevention, screening and detection, linkage to care, initiation of medication-assisted treatment, and long-term retention in treatment. The NIH will encourage applications from researchers with linkages to health care and justice systems, fire and police departments, and state and local governments in rural and urban areas highly affected by the opioid crisis. The wealth of data and evidence

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generated from this closely monitored program will define optimum approaches to lower rates of OUD, decrease overdoses and deaths, and increase the number of individuals in recovery. The ultimate goal will be to extend the lessons learned from the HEALing Communities Study to the entire nation.

Neonatal opioid withdrawal syndrome (NOWS), also referred to as neonatal abstinence syndrome, affects up to 10% of infants.⁶ Innovative methods to identify and treat newborns exposed to opioids, often along with other drugs, have the potential to improve both short- and long-term developmental outcomes in such children. To determine the best approaches, HEAL will expand Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome (ACT NOW). This pilot study is designed to assess the prevalence of NOWS, understand current approaches to managing NOWS, and develop common protocols for larger-scale studies that will determine best practices for clinical care of infants with NOWS throughout the country.

Ending addiction long-term will require successful preventive efforts in multiple domains including education, mental health, stigma, childhood trauma, and socioeconomic and effective management of acute and chronic pain. In pursuit of the latter, the second major focus of the HEAL research plan includes a coordinated approach to discover and validate new biologic targets for effective, nonaddictive pain management, as well as accelerate the process of discovery to develop therapies aimed at these targets.

For example, HEAL will mount a research effort to understand the biology and psychosocial factors that lead an acute painful event to transition to a chronic pain disorder. HEAL investigators will collect data over time from people experiencing acute pain after a surgical procedure or musculoskeletal trauma. With the goal of guiding precision prevention approaches, neuroimaging, "omics," sensory testing, and psychosocial assessments will form a comprehensive data set to predict which individuals are likely to develop chronic pain and how to block that transition.

As part of its effort to speed preclinical discovery and development of new nonaddictive pain treatments, HEAL will support the identification and validation of novel targets for small molecules, biologics, natural products, and devices. It will also fund research to discover and validate much-needed biomarkers to help evaluate whether a treatment is working as intended, eg, determining whether a therapy engages the intended molecular target or neuronal circuit in an affected individual. This initiative will also support the development of preclinical platforms to test potential nonaddictive treatments for acute and chronic pain. This will include

animal models that more closely mimic a variety of human pain conditions, as well as human-based screening platforms that more closely approximate human physiology of pain.

HEAL lays the foundation for an innovative therapy-development pipeline through a planned new public-private partnership. In collaboration with biopharmaceutical groups, the Food and Drug Administration, and the Foundation for the NIH, the NIH will collect and evaluate treatment assets from academia and biopharmaceutical and device companies to coordinate and accelerate the development of effective treatments for pain and addiction. The most promising assets will be tested in HEAL's clinical trial networks, which will focus primarily on phase 2 trials. Clinical investigators will develop well-phenotyped cohorts of patients who have specific pain conditions with high unmet medical needs. Organized in a "hub and spoke" model, the network will promote effective training, consistency among clinical sites, streamlined approval of protocols, and recruitment of participants with specific pain conditions. Through its standing infrastructure, the clinical trial network will also reduce startup times to further incentivize testing of nonaddictive therapies for treating pain.

HEAL's initial research plan reflects only a portion of its ambitious vision. Further investments are currently in an active planning stage. Additional resources will be directed toward gaps in current plans, including prevention research, precision medicine for pain and addiction, and nonpharmacological and integrated models of pain management. Information about funding opportunities, expected to be announced starting in summer 2018, will be made available on the HEAL website.³

Like most other pioneering scientific initiatives, HEAL will focus on a range of objectives, from short-term goals to research priorities that will take longer to bear fruit. Yet, all will be aimed at the same ultimate vision: a nation of people with far less disabling pain and opioid addiction. In this future, acute pain will be managed using precision approaches, with individuals at risk for transitioning to chronic pain or becoming addicted to opioids being identified and helped before lasting problems arise. In this future, nonaddictive management strategies for chronic pain, whether pharmacological, device-based, behavioral, or integrated interventions, will be made available to individuals based on objective knowledge of what is likely to work best for them. Those individuals still affected by addiction will be able to take advantage of multiple evidence-based options for treatment, and communities will have the tools and knowledge to effectively bring research advances to patients to treat OUD and prevent overdose. The NIH and its partners are committed to working toward this brighter future.

ARTICLE INFORMATION

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