

NIH
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INITIATIVE

NIH National Institutes of Health
HEAL Initiative

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Research in Action



NIH • Helping to End Addiction Long-term

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DIRECTOR'S MESSAGE

Now in its fourth year of funding, the NIH Helping to End Addiction Long-term® Initiative, or NIH HEAL Initiative®, is an aggressive effort to find scientific solutions to the nation's opioid crisis. Amid this dangerous and evolving crisis, the need for answers is more urgent than ever. In 2021, [nearly 107,000 Americans](#) lost their lives to drug overdoses. More than 80,000 of those were from opioids, including highly potent synthetic opioids like fentanyl. Simultaneously, we need to vigorously pursue durable science-based solutions to address the needs of the millions of Americans who experience daily pain. That includes better understanding of how pain management can help mitigate multiple public health needs, including the opioid crisis.

As you will see in this year's annual report, HEAL research claims some noteworthy accomplishments with direct implications for policy and practice. These include defining a new standard of care for soothing infants exposed to opioids during pregnancy who are born with neonatal opioid withdrawal syndrome, or NOWS. Through the HEALing Communities Study, researchers have partnered with communities to introduce nearly 1,000 evidence-based interventions into neighborhoods hard-hit by the crisis. Research from the HEAL-funded Justice Community Opioid Innovation Network (JCOIN) showed that when incarcerated individuals receive effective opioid treatment in jail, they are less likely to be-reincarcerated after their release. We are making important progress in the ability to target the underlying biology of the human pain response, through discovery and use of several cutting-edge technologies. These include [improved cell models](#), [tissue chips](#), and [advanced imaging tools](#). We've made important incremental advances too; this is vital progress in the scientific process.

Bringing a new drug target from the initial stage of discovery to a safe and effective treatment for use in people requires many iterative steps. We are making significant strides toward moving several potential new treatments for pain and addiction into the clinical testing phase (see **On Ramp for Clinical Impact**, p. 10).

Data sharing is one major area of cross-cutting progress that doesn't often make headlines but is essential currency for science. HEAL is making steady progress to leverage and maximize the power of data that can build a bridge across research disciplines and is independent of any one creator or user. This past year, HEAL launched the [HEAL Data Platform](#), a free, secure, user-friendly cloud-based search interface. This powerful system can be used by HEAL investigators, other

EXTERNAL DATA SETS

LEVERAGED BY HEAL RESEARCH

- [Centers for Disease Control and Prevention \(CDC\) WONDER](#)
- CDC's [National Vital Statistics System](#)
- CDC's National Electronic Disease Surveillance System (NEDSS)
- CDC's Prescription Drug Monitoring Program
- [Substance Abuse and Mental Health Services Administration's \(SAMHSA\) National Survey on Drug Use and Health \(NSDUH\)](#)

researchers, and a broad range of stakeholders including advocates, clinicians, and community organizers to easily find HEAL research results and data. HEAL is also reaching outward to identify and leverage additional sources of data to enrich HEAL research. This past year, HEAL launched several studies that will leverage existing epidemiological datasets related to pain and substance use that are collected and managed by HEAL's federal agency partners. These datasets can be used to test innovative approaches for more accurately assessing, predicting and tracking overdoses, identifying novel illicit substances in hotspots across the country, and mining health data for pain management solutions already in use. This collaborative effort is essential to improve the way communities and government agencies monitor and respond to the dynamically changing opioid crisis.

Given varied challenges posed by the intertwined crises of opioid misuse, addiction, and undertreated pain, HEAL research is diverse in scope. The challenges faced when developing new treatments for pain and addiction are starkly different than those faced when determining ways to increase access to evidence-based strategies, such as through advancing health equity in care systems. To achieve a balanced, yet targeted research portfolio, HEAL centers its efforts around four guiding principles: using a whole-person/patient-centric approach, working with communities to bring research to life, targeting the biology of pain and addiction, and addressing health system challenges and inequities. This past year, HEAL scientists have made inroads in all of these areas, toward providing help and hope for the millions of Americans devastated by this public health challenge.

SELECTED ACCOMPLISHMENTS

FOCUSING RESEARCH ON THE NEEDS OF THE WHOLE PERSON

HEAL scientists are putting individuals first, connecting people to treatments and services that make sense to them. This whole-person approach recognizes that individuals are unique – with co-occurring conditions and a range of experiences that affect risk and resilience.

Identifying and Understanding Risk

HEAL-funded scientists are looking for ways to identify people who are at increased risk for developing opioid use disorder so they can receive early help to prevent or mitigate those risks. For example, investigators collected longitudinal data from nearly 4,000 young adults and found that risk factors for opioid misuse are mostly correlated with risk factors for other substance use, suggesting that interventions that are already available could be tailored to prevent opioid misuse. Other prevention approaches focus on introducing strategies to reduce or slow the progression of opioid use disorder for people at risk. For example, the [Peer Intervention to Link Overdose](#)



[survivors to Treatment \(PILOT\) intervention](#) employs peer recovery coaches who connect with patients while they're in emergency departments or hospitals after an overdose to help them start treatment.

Prevention is a powerful tool for identifying and reducing risks as well as strengthening protective factors that differ among individuals and environments. For example, identifying potential barriers to staying healthy can help people manage their opioid use disorder long-term and live more safely. Identifying and understanding risks associated with discontinuing medication-based treatment are crucial to informing evidence-based care for people managing opioid use disorder. New [findings](#) from the National Drug Abuse Treatment Clinical Trials Network (CTN) examined health records from 6,550 patients from 2012 to 2018, assessing whether the length of buprenorphine treatment affects death from overdose or other causes. The study results suggest that individuals remained at significant risk of overdose and death after discontinuing buprenorphine, no matter how long their buprenorphine treatment lasted. [Ongoing HEAL research](#) is testing various doses, types, and lengths of treatment toward careful clinical management and support services needed when someone discontinues medication-based treatment. It also aims to identify effective strategies (behavioral interventions, mobile apps) to help people stay in treatment.

Meeting People Where They Are

To be effective and useful, pain management approaches need to meet the diverse needs of patients who experience various types of pain. Meeting people where they are is a significant focus of HEAL's clinical pain research programs, such as the Pain Management Effectiveness Research Network, which evaluates the effectiveness of a broad range of pain therapies to guide clinical practice in real-world settings. Two ongoing trials within this program are giving people more flexible options and encouraging shared decision-making between patients and providers.

The [Tailored Non-Pharmacotherapy Services for Chronic Pain: Testing Scalable and Pragmatic Approaches](#) (RESOLVE) clinical trial is comparing the effectiveness of cognitive-behavioral therapy for chronic pain delivered via two types of telehealth: a web-based application and live, coach-led, virtual sessions (conducted by telephone and/or video conference). These pain management approaches are designed to help older chronic pain patients who may not have easy access to transportation or live in rural areas where medical care is limited. Another example is the [Opioid Prescription After Cesarean Trial](#) (PACT) clinical trial. This study involving 5,500 women who had a cesarean delivery is testing an approach that allows a woman and her provider to co-decide pain management needs. The study is comparing an individualized opioid prescription protocol with a fixed dose of opioid tablets, to see whether a personalized approach will reduce the amounts of opioids prescribed without affecting pain relief.

TRANS-AGENCY COLLABORATIONS

Substance Abuse and Mental Health Services Administration (SAMHSA)

SAMHSA leads public health efforts and the delivery of programs and services to address mental health, prevent substance use, and provide treatments.

- SAMHSA partners with HEAL through the HEALing Communities Study to support research on the use and impact of fentanyl test strips that are used by people who use drugs to identify the presence of this potentially deadly synthetic opioid.
- SAMHSA also helps to ensure that best practices and lessons learned from the HEALing Communities Study reach communities and treatment programs that are part of the broad SAMHSA network.
- Through the Justice Community Opioid Innovation Network's Technical Assistance Center, HEAL has built connections with SAMHSA's Addiction Technology Transfer Center Network to ensure bidirectional communication and sharing of research resources and important research findings.

Centers for Medicare & Medicaid Services (CMS)

CMS provides healthcare coverage through health insurance programs like Medicare, Medicaid, the Children's Health Insurance Program, and the Health Insurance Marketplace.

- The CMS-NIH Opioid Working Group identifies existing evidence and open research questions for which NIH science can best inform CMS coverage decisions.
- For example, findings from a current HEAL-funded study testing different doses of acupuncture will help CMS make decisions about their payment structure for this type of pain treatment. The trial is making great process and just completed enrollment.
- CMS and HEAL developed a website that identifies validated assessment tools that clinicians can use to track pain patient outcomes to simplify treating Medicare beneficiaries with chronic pain.

Food and Drug Administration (FDA)

FDA is responsible for ensuring the safety, efficacy, and security of drugs, biological products, and medical devices.

- HEAL scientific staff and HEAL-funded consultants provide HEAL researchers with feedback, technical assistance, and guidance for navigating the FDA development process for advancing promising new treatment options.

Office of National Drug Control Policy (ONDCP)

ONDCP is part of the Executive Office of the President of the United States and is responsible for leading and coordinating the nation's drug policy.

- Through the HEAL-funded JCOIN study, NIH scientific staff participate in regular briefings with ONDCP regarding JCOIN's research findings, which inform key metrics for ONDCP's National Drug Control Strategy.

Department of Justice (DOJ)

DOJ is responsible for enforcing federal laws.

- DOJ partners with HEAL through the Bureau of Justice Assistance to support research for JCOIN. JCOIN meets periodically with the bureau to share relevant findings and provide technical assistance.
- Through JCOIN, HEAL collaborates with the Bureau of Justice Statistics, such as by coordinating large-scale data collection activities from the nation's jails.

Centers for Disease Control and Prevention (CDC)

CDC is the nation's leading data driven service organization that protects the public's health.

- Through the HEAL Data2Action and Real-Time Opioid and Pain Management Data programs, CDC and NIH staff participate in information-sharing meetings and leverage insights from HEAL research to improve surveillance and health system strategies to address overdose.

Addressing Opioid Use Disorder in Healthcare

Among the millions of people in the United States with opioid use disorder, nearly two-thirds have a mental illness and up to one-fourth have an additional substance use disorder for which they often do not receive appropriate treatment. To address these needs, HEAL research supports innovative strategies to develop, optimize, and test approaches to improve delivery of treatments and services for people with co-occurring opioid use disorder, mental illness, and/or suicide risk. In many cases, this research is conducted in healthcare settings where people can be screened. New HEAL findings include [development and clinical testing](#) of [Opioid Addiction Recovery Support \(OARS\)](#), a health portal and mobile app. Integrated with patient electronic health records, the software platform helps primary care providers improve clinical management of patients with opioid use disorder. The software platform provides a dashboard and real-time measurement of patient achievements toward their recovery. It also provides opportunities for patients to interact with their healthcare providers, increasing opportunities for connection and support.

HEAL investigators are also examining well-known links between mental illness and substance use disorders to identify successful strategies for improving whole-person care. This year, HEAL-funded researchers published a review of 21 studies examining the effects of medication-based treatments for psychiatric disorders on use and misuse of substances. They found that receiving treatment for mental health disorders can reduce the risk for developing a substance use disorder.

WORKING WITH COMMUNITIES TO BRING RESEARCH TO LIFE

HEAL recognizes that meaningful research is relevant to the individuals, families, communities, and populations it is designed to help. HEAL investigators are taking a variety of unique approaches to incorporate guidance and perspectives of community members into their research projects.

Acquiring Diverse Patient and Community Perspectives

The experience of pain is universal, cutting across ethnicity and race. Yet, to be effective and useful, pain management strategies need to address culturally distinct health concerns and preferences. Guided by input from patients and communities, several HEAL programs have customized research study recruitment materials to communicate with specific populations such as Blacks, Arab Americans, Hispanics, healthcare workers, and veterans about participation in research. These efforts have benefited from community-led focus groups and interviews that inform development of clear and culturally appropriate information about research participation. There is limited research about how patient expectations of the effectiveness of a potential treatment might affect both outcomes and participation in a clinical trial. In a small study, HEAL researchers interviewed patients with chronic pain to learn how their individual experiences and

[Advance Practice \(LEAP\) program](#) connects researchers and practitioners who work in the justice system to help them become more familiar with research methods and findings. This work will support more research in justice agency settings and enhance opportunities for collaboration to reduce overdose among justice-involved populations.

Patient hesitance is a major barrier for those who could benefit from treatment for opioid use disorder. HEAL research is investigating how community-based approaches can support people to start treatment and continue it. For example, HEAL [investigators in the NIDA CTN](#) worked alongside 19 community pharmacies in Ohio and Indiana to validate a prescription drug monitoring program-based screening tool that identifies risk of opioid misuse and overdose. The [easy-to-use screener](#) provides actionable data to identify at-risk patients and connect them with help.

TARGETING THE BIOLOGY OF PAIN AND ADDICTION

For decades, scientists have studied how the human body reacts to and processes psychoactive substances, including opioids. This work has led to a detailed understanding of how opioids can cause harm through addiction. Through other fundamental research, we also know a lot about which nerve paths transmit pain, and as a result we have safe and effective treatments for acute, short-acting pain. Yet there is a lot we still don't know, since many chronic and acute pain conditions do not respond to available treatments. Using cutting-edge tools like single cell biology, tissue chips, computational biology, and others, HEAL is advancing ways to accurately test benefits and risks of potential new medication treatments for pain and addiction.

Models and Screening Tools

Although the ability to measure pain and its effects on everyday life is essential for finding effective ways to manage chronic pain, measuring these effects validly and reliably remains difficult. Different conditions can produce similar feelings of pain. HEAL-funded researchers have shown that the novel [KnowPain wearable sensor](#) that measures pain effects corresponds well with how people report pain effects, suggesting this tool can help to improve the accuracy of pain assessments. Using a combination of imaging and computer algorithms, [another HEAL-funded project](#) identified a biological signal that can help diagnose a type of chronic eye pain and distinguish it from dry eye disease – an advancement in diagnostics that is a step forward in improving care for eye pain. The ability to precisely monitor recovery from pain and disability is essential for developing patient-specific treatment strategies. The HEAL-funded [Signature for Pain Recovery IN Teens \(SPRINT\) project](#) collected a large amount of data from children with musculoskeletal pain, including brain function and imaging, genetic and underlying molecular profiles, psychological, general functioning, and disease outcome data (e.g., pain, disability,

symptoms). The depth and breadth of this rich data resource is significant and means the information can be used by the scientific community to learn more about pain progression and recovery in children.

Device-Based Treatments

Beyond helping develop and test new medications, technology also plays an innovative role for treating pain and opioid use disorder. HEAL's targeted investments to develop new devices have yielded considerable progress this past year. Two examples developed by HEAL-funded small businesses are novel ways to help infants born with NOWS. These newborns experience tremors, excessive crying and irritability, and problems with sleeping, feeding, and breathing. One technology still in testing is a [hospital bassinet pad](#) that applies gentle, soothing vibrations to newborns dependent on opioids. The device is undergoing an expedited FDA review process for novel medical devices that have no comparable devices approved on the market. Approval would make this product the first available medical device to treat newborns diagnosed with NOWS. Another device [being tested in infants with NOWS](#) is a hearing aid-like device placed around a baby's ear. The device delivers non-invasive neurostimulation through the skin to prompt the release of the body's own version of opioids that can help ease their withdrawal symptoms.

HEAL research has also made progress developing devices for pain management. This past year, researchers completed a clinical study of a [non-invasive brain stimulation technique](#) to treat chronic pain from carpal tunnel syndrome. In addition to showing the device was safe, the results of this early-stage clinical trial suggested improved physical function and reduced anxiety in patients receiving stimulation. The findings are especially promising since past attempts to treat neuropathic pain have not been successful. Other HEAL-funded scientists developed [an approach](#) to measure muscle activity from a woman's pelvic region, allowing clinicians to pinpoint regions of painful muscle overactivity in women with chronic pelvic pain. This device has the potential to help address health disparities and can help researchers better understand pelvic pain.

HEAL-supported projects are using induced pluripotent stem cells (iPSCs), human skin or blood cells that can be transformed into any cell type, to predict potential reactions to drugs before they advance to testing in people. Using this approach, HEAL-funded researchers have [developed reproducible procedures to create pain-sensing cells](#) from human tissues, using an efficient, robotic system to grow cells in the lab. The approach has now been licensed by Fujifilm CDI and is being used to help discover treatments for pain related to diabetes and cancer. Another tool for testing new medications is a "[human on a chip](#)," which contains miniature versions of the liver, kidney, heart, skeletal muscle, and neurons. This powerful technology developed with HEAL funding is being used to test a new drug to treat chronic inflammatory demyelinating polyneuropathy, a painful neurological disorder. Another [HEAL-funded project](#) has developed a

novel way to mimic different brain regions, including areas that control the addictive effects of opioids and craving. This past year, [HEAL researchers developed a large animal model for sickle cell disease](#) by altering the genes of pigs to give them the same genetic mutation that causes misshapen blood cells in humans with sickle cell disease. This model system will be used to measure pain effects and behavioral changes, and the data will be widely available to researchers and companies developing new drugs for sickle cell disease.

Toward identifying unexplored areas of potential, HEAL-funded researchers developed the [HEAL Target and Compound Library](#), which contains nearly 3,000 small molecules thought to be involved in addiction, pain, and overdose. The library is available to the scientific community and provides a platform to support data mining, machine learning, structural modeling, and virtual screening techniques that can boost scientific discovery in the biology of pain or addiction. HEAL research also closed in on a potential new molecular culprit for back pain. Recently, a [BACPAC study](#) showed that certain molecules that change the physical structure of DNA in response to life experiences are involved in chronic low back pain. Because these molecules are linked to the development and maintenance of pain, they may help researchers develop new treatments for back pain.

THE ON RAMP FOR CLINICAL IMPACT

Drug development is an extended process focused on two main goals: showing that a potential new treatment has its intended effect in the human body and that it is safe. Critical steps along the way include obtaining permission from the U.S. Food and Drug Administration (FDA) to begin clinical testing. The start of this process is an investigational new drug (IND) application (for drugs) and an investigational device exemption (IDE) application for technologies or devices. HEAL programs focused on accelerating treatments for all aspects of the opioid addiction cycle have made significant steps toward clinical development this past year. Several INDs have been cleared by the FDA, and first-in-human clinical testing will begin for the following indications:

- [Testing a molecule](#) that could treat neuropathic pain by reducing incoming signals to pain pathways in the spinal cord
- [Testing drug-drug interactions](#) caused by a molecule that affects levels of the neurotransmitter glutamate for treatment of opioid use disorder
- Testing a new [opioid-like pain treatment](#) that doesn't have dangerous opioid side effects
- Testing a new treatment for [opioid withdrawal](#)
- Testing a [spinal cord stimulation technology](#) to treat neuropathic pain

The FDA's Breakthrough Devices Program speeds up development, assessment, and review of new medical devices. This past year, two HEAL-funded projects were accepted into this program:

- [A digital health platform](#) that combines a wearable sensor to measure spinal motion with patient reported outcomes and preferences to better diagnose chronic low back pain
- [A near infrared light-based therapy](#) for reducing cravings, anxiety, and depression in patients with opioid use disorder

ADDRESSING HEALTH SYSTEM CHALLENGES AND INEQUITIES

The conditions in which people live, learn, work, and play (often termed social determinants of health) affect people's lives in many ways. Social and environmental factors such as poverty, lack of access to care, systemic racism, stigma, and provider bias set the stage for a wide range of health-related disparities – especially in the diagnosis and treatment of pain and addiction. HEAL research is addressing these structural inequities in many ways to increase awareness, access, and use of treatments known to be effective but that remain underused.

Health Needs of Children and Families

Preventing harmful outcomes, such as risky substance use, is simple in principle but can be very difficult in real life, where many children and adults live with numerous social and structural risk factors. The [child welfare system](#) represents an underused source of prevention opportunities. Past research has shown that parental use of substances is a risk factor for children being referred for social services. Since these children are at risk for ongoing child abuse or neglect, [HEAL researchers hope to learn if offering services to parents can ultimately protect children](#). HEAL research is looking at the multiple needs of families referred to the child welfare system for severe substance use (methamphetamine or opioids) and child neglect. The goal is not only to prevent further substance use among parents but also to prevent harm to their children by addressing social determinants of health and stabilizing the family unit.

This past year, HEAL researchers defined a new standard of care for infants with neonatal opioid withdrawal syndrome (NOWS), addressing a major system barrier. Researchers from the Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome (ACT NOW) project first identified [significant treatment variation across the nation](#). They then compared the traditionally used NOWS screening method with a new approach that tests whether an affected baby can eat or sleep for at least an hour after eating, and be consoled within 10 minutes of starting to cry. New HEAL findings show that this Eat, Sleep, and Console screening approach cut the duration of hospital stays and the use of opioid medications to ease withdrawal compared to the traditional approach. [Parallel HEAL research](#) from the HEALthy Brain and Child Development Study (HBCD) is monitoring brain health and function of children from birth to age 10 to assess effects of pre- or postnatal exposure to substances like opioids, tobacco, alcohol, and life experiences. HBCD is identifying factors that enhance resilience or risk for future substance use, mental disorders, and other behavioral and developmental problems.

Overcoming Treatment Barriers

While some patients with pain and/or addiction may have access to primary care, access to a specialist remains out of reach for many. Across the country, HEAL researchers are trying to help



people who live in “treatment deserts” with little care available. [Launched in 2021, an opioid treatment program in Holyoke, Mass.](#), has helped more patients access treatment in a region where availability is limited. As part of the HEALing Communities Study, the facility has dramatically decreased travel time for people who take daily methadone. The treatment center has also established strong referral partnerships with local medical centers, recovery centers, and courthouses. These alliances are building a strong foundation for seamless treatment access in an underserved community. [As part of one study](#), researchers have learned that referring patients in rural primary care clinics to an external telehealth source of medications for opioid use disorder can [increase access to care](#).

Even though access to opioid treatment is generally higher in urban environments compared to rural regions, untreated addiction and overdose remain major problems. [In Washington, DC, HEAL researchers](#) worked with their community advisory board to evaluate and understand barriers to starting medications for opioid use disorder in neighborhoods with the highest overdose rates and low treatment use. [Working within Federally Qualified Health Centers](#) that serve low-income residents, the researchers developed and tested a model that uses peer recovery coaches and telepsychiatry services to improve uptake and effectiveness of opioid treatment. Preliminary findings show that people with untreated opioid use disorder were interested and willing to consider patient-centered treatment offered through a faith-based community center.

Despite a range of efforts to reach people with poorly treated pain and opioid use disorder, many people still do not get treatments that could help them. One contributor to this gap is lack of representation in clinical research to understand treatment needs and variation among individuals and populations. [HEAL scientists who are evaluating pain management in women who have received a mastectomy](#) are currently trying to understand why patients are hesitant to participate in this type of research. Potential factors include race and ethnicity, geographic location, and socioeconomic status. Another example is the [HEAL-funded Hemodialysis Opioid Prescription Effort \(HOPE\) consortium trial](#), a large, multicenter study testing the use of telehealth-delivered pain coping skills to reduce opioid use in people with severe kidney disease who are receiving dialysis. While [the study](#) has enrolled hundreds of participants, this past year, the group ramped up efforts to recruit a more diverse patient population to ensure the study accurately represents individuals affected by this health condition. The research team tailored educational materials toward expanding recruitment efforts into these rural and isolated communities outside of urban areas where the research is being conducted. In particular, these include American Indians in rural New Mexico, people in remote regions of Washington state, and individuals who are hesitant to use telehealth services.

Working Together for the Future

As HEAL reports another year's worth of research, much remains to be done. We continue to build and grow essential partnerships with communities; federal and state agencies; and professional organizations committed to advancing health options for people with poorly treated pain, opioid use disorder, stimulant use disorder, and mental illness.

Addressing untreated pain and the opioid crisis requires an all-hands-on deck approach and government-wide cooperation. HEAL interfaces with several government agencies to advance research, guide clinical practice, and inform policy (See **Trans-Agency Collaborations**, p. 4). These partnerships are essential to developing and implementing safe and effective pain management strategies and to improve prevention and treatment strategies for opioid misuse and addiction.