NIH
HEAL
INITIATIVE

National Institutes of Health
HEAL Initiative

2021 ANNUAL REPORT

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Research in Action

NIH · Helping to End Addiction Long-term

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NIH HEAL INITIATIVE

Director's Message

In 2019, 70,630 people in the United States died of overdose, including 49,860 associated with opioids (70.6 percent of all drug overdose deaths) (1). More than 2 million Americans have opioid use disorder (OUD), while 10 million Americans misuse opioids, taking them differently than prescribed (2,3). An additional 50 million Americans experience chronic pain – 24 million with high-impact chronic pain – exposing them to the risks of opioid medications (4). First announced in April 2018, the National Institutes of Health (NIH) Helping to End Addiction Long-term℠ Initiative, or NIH HEAL Initiative℠, is an expansive agency-wide effort. It spans basic, translational, clinical, and implementation science and promotes collaborations of all types to address the crises of opioid misuse, addiction, and overdose in the United States. We established and continue to pursue an "all hands on deck" mindset and action plan furthered by innovative partnerships with a broad range of stakeholders (5).

In 2021, a solid foundation for the NIH HEAL Initiative is now built, and we are wasting no time to put our results into action. By the end of fiscal year 2020, the NIH HEAL Initiative had invested more than $1.5 billion, representing more than 500 research projects across the United States. These studies aim to identify new therapeutic targets for both pain and opioid use disorder, reduce the risk of opioids through nonpharmacological strategies for pain management, and improve opioid addiction treatment in a variety of settings. Many of these research projects are returning actionable results, and strong partnerships with stakeholders have created valuable channels for dissemination of research findings. In this way, the NIH HEAL Initiative is greater than the sum of its parts – joining the power of science to solve problems with the power of people to share results and put them to use.

Adapting to colliding public health emergencies

The COVID-19 pandemic has fueled increases in opioid use, addiction, and overdose. Overdoses increased 30 percent during the 12 months ending October 2020 compared to the previous 12 months. The COVID-19 pandemic has been associated with increases in opioid misuse and overdose deaths (6), and has also intensified contributors to pain and addiction. Disruptions of treatment and recovery services, limited access to mental health and peer recovery support, altered routines, and increased stress provide new barriers to both effective pain management and addiction treatment and recovery. The pandemic has also delayed research and caused research teams to adjust study plans in a variety of ways.

NIH HEAL INITIATIVE

The NIH HEAL Initiative research community has met this moment in extraordinary ways to adapt existing knowledge toward OUD prevention and treatment, generate therapeutics in record time, and leverage available infrastructure and research capacity. (For further details, see "Adapting HEAL Research for the COVID-19 Pandemic" on page 11.) The pandemic has also revealed many weaknesses in both our healthcare system and social fabric. The NIH HEAL Initiative is facing several of these cross-cutting issues head on: stigma in the treatment of both pain and OUD; equity, diversity, and inclusion in research and healthcare; and polysubstance use and co-occurring conditions. The pandemic-driven rapid ascendancy of telemedicine has opened doors for many people with pain and OUD, but runs the risk of further deepening health disparities for those without access to technology or with limited health literacy. We are continuing to monitor effects of the pandemic on the NIH HEAL community and the intended beneficiaries of this research.

Selected Accomplishments From the NIH HEAL Initiative

The NIH HEAL Initiative is continuing to make progress toward key goals, including 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. Notable advances are apparent along several fronts, as described below.

Repurposing or improving the deployment of existing strategies

The evidence-based therapies for OUD and overdose that are currently available are not helping as many people as they could. Lives can be improved and saved in the short-term with interventions that we have now – if they are deployed more effectively. Research funded by the HEAL Initiative includes numerous studies designed to test the integration of existing treatments into practice and help reach those who experience disparities in access. These ongoing studies have made considerable progress so far, especially in the face of the challenging research environment of the COVID-19 pandemic.

Improving delivery of evidence-based treatment

The unprecedented HEALing Communities study aims to reduce opioid-related overdose deaths by 40 percent over 3 years in 67 participating communities across four states. So far, it has established community advisory boards, formed local coalitions, and identified existing local resources; launched intervention activities; engaged at-risk populations and launched three communication campaigns; created data dashboards to help guide community decision-making;

and developed individual community action plans to implement chosen evidence-based practices. Next, research staff, community members, and partnering agencies will collaborate to develop community-specific implementation plans.

The Justice Community Opioid Innovation Network (JCOIN) has launched 13 clinical trials to improve OUD treatment service delivery and timely access for individuals during incarceration and after release. For example, studies are testing the use of peer navigators and other "linkage facilitators" to improve transitions between carceral and community care settings. The program is also testing an evidence-based tool called the "Stages of Implementation Completion," along with a suite of resources to help organizations treating adolescent substance use disorder track the implementation of new programs. Feedback provided by the tool can help ensure a program's success and sustainability – and if successful may help provide a larger evidence base for treatment options by public health agencies.

The Pain Management Effectiveness Research Network (ERN), a multisite research cooperative program, aims to improve pain care by evaluating the effectiveness of a broad range of therapies to guide clinical practice. The ERN is supporting nine clinical trials that compare the effectiveness of existing therapies or novel approaches for prevention and management of pain. The Pragmatic and Implementation Studies to Improve the Management of Pain (PRISM) program is supporting six pragmatic clinical trials conducted within healthcare systems that will evaluate if interventions can improve pain management at the point of care delivery. Since the launch of HEAL, the ERN and PRISM programs have achieved an unprecedented effort on data harmonization, developing a set of pain-unique Common Data Elements to be included across HEAL clinical pain studies in a standardized fashion. Using a standardized set of pain measurements will allow for rigorous measurement of interventions across different pain conditions, allowing researchers to compare them in meaningful ways that can help determine which intervention to use in which situation.

Health professionals rely on research to improve the delivery and outcomes of treatments for individuals, families, and communities. Research must be designed thoughtfully and conducted rigorously to yield accurate and generalizable results that work in real-world settings. Many HEAL programs are completing planning phases to prepare for clinical studies with the goal of increasing uptake of effective pain treatments. The Hemodialysis Opioid Prescription Effort (HOPE) research program is testing the use of buprenorphine for pain management as part of a whole-person, multidisciplinary approach for treating pain in people with end-stage renal disease receiving hemodialysis, whose opioid use rates are significantly higher than that of the general population. Although the COVID-19 pandemic has resulted in some delays in

enrollment across HOPE research sites, those studies that have been able to continue are modifying protocols to increase the use of telehealth where appropriate, as well as use alternative means to collaborate through research projects.

Reformulating and repurposing existing treatments to treat OUD and opioid overdose

Lifesaving treatments are available for people with OUD: medications approved by the U.S. Food and Drug Administration (FDA) include methadone, buprenorphine, and naltrexone, as well as lofexidine for opioid withdrawal and naloxone for opioid overdose reversal. Yet most patients do not stay on these medications long-term. While methadone and buprenorphine are typically administered daily, extended-release formulations can make treatment adherence easier. HEAL research is aiming to expand the number of user-friendly options available to patients through research on extended-release versions of methadone and buprenorphine, a combined dose of buprenorphine and naltrexone, and several types of naltrexone implants. A medical device that can sense the presence of an overdose, automatically inject naloxone, and alert first responders is also under development.

Medications that are FDA-approved to treat conditions other than OUD are also under investigation as methods to enhance existing OUD treatment regimens and offer more options for overdose reversal. Opioid withdrawal can involve a loss of sleep and other unpleasant symptoms that can interrupt treatment and lead to relapse. Suvorexant, a sleep disorder treatment; brexpiprazole, an antipsychotic; and pregabalin, a treatment for neuropathic pain and seizures, are being tested to see if they can improve the outcomes of OUD treatments. Although nalmefene was FDA approved as an overdose-reversal treatment, its use was discontinued. It is being developed as a continuous-release injection treatment and an implant for relapse prevention of OUD. Dexmedetomidine, which is used in clinical anesthesia in part to preserve respiratory function, is being studied as an option to reduce respiratory depression caused by fentanyl.

Advancing promising therapeutics through the clinical trial pipeline to support FDA approvals

Few new molecular entities advance through the clinical pipeline to become FDA-approved treatments, but the number of experimental therapies supported by HEAL that have reached the clinical trials phase is a promising signal for the future of new medications for OUD and pain.

When researchers have gathered enough evidence from preclinical studies in animals and have determined that an experimental drug or a new formulation of an already available drug would be reasonably safe to test in humans, an investigational new drug (IND) application required to begin clinical trials is filed with the FDA. Among its original goals, the HEAL Initiative aimed to produce 15 INDs for treating opioid addiction or overdose filed with the FDA within 5 years. In the first 2 years of the program, that goal has been exceeded, and 16 INDs have been filed for a diverse group of new or improved interventions to prevent or treat OUD or overdose.

The wide range of the products that have received IND or medical device designations is indicative of the diverse needs of people with pain and OUD. One of the INDs cleared by the FDA was for the first-ever phase 1 clinical trial of a vaccine targeted against oxycodone. An opioid vaccine would harness the immune system to develop antibodies that would stick to opioids once they enter blood and prevent them from entering the brain, which would limit rewarding effects and may lessen the effects of an opioid overdose.

In addition to candidates for treating OUD, a new type of pain treatment for neuropathic pain that is entirely novel received an IND, with a mechanism of action that is distinct from both opioids and common over-the-counter pain relievers like ibuprofen. The experimental treatment targets a regulatory enzyme that modulates the activity of bioactive lipids that can cause inflammation.

Similarly, several medical devices have also received Investigational Device Exemptions, or IDEs, to begin early stages of human testing. Several HEAL studies of new medical devices have also received the FDA's "Breakthrough" designation, for products that have the potential to be dramatically more effective at treatment or diagnosis, granting access to expert FDA staff as well as an accelerated review timeline.

A Breakthrough Device designation was granted to researchers developing a digital health platform (software and hardware) to capture spinal-motion metrics, patient-reported outcomes, and patient preferences to help categorize patient characteristics that may influence their response to treatment, and help providers make decisions about personalized treatments. Another small business funded through HEAL received a Breakthrough Device designation for a bassinet pad that can deliver gentle vibrations to newborns suffering from neonatal opioid withdrawal syndrome. This vibrating technology has been shown to improve relaxation, breathing, and heart beats for the newborns.

The number of projects that have progressed into early human testing so far is just a fraction of what could come in future years: 51 other projects, including 32 new molecular entities, have been funded to develop new treatments or repurpose existing ones.

Building the infrastructure and tools to rapidly evaluate new interventions for pain and OUD

As HEAL invests in research to develop new treatments for both pain and OUD – including behavioral interventions, drugs, and devices – it is also investing in the capacity to test the safety and effectiveness of these interventions through needed infrastructure. HEAL's research investments, combined with the rich body of existing science, provide new avenues for therapeutics, and HEAL-funded clinical trials networks stand ready to test their safety and effectiveness and rapidly bring interventions to people who need them.

Screening platforms of pain and addiction

Before potential drugs are tested in humans, new tools can allow researchers to both identify new compounds with therapeutic potential and to identify potential safety risks. HEAL-supported projects are building on advanced technology that allows researchers to create an "organ-on-a-chip" from cultured cells, creating tiny models of key body systems that can mimic how those systems respond to drugs or toxins.

Several HEAL projects are working on a multi-organ platform that can simulate the way cells from throughout the body – liver, heart, muscle, kidney, immune system, as well as neurons in the brain's breathing center – react during an opioid overdose. The platform can then simulate the way the body responds to overdose-reversal therapies like naloxone. Others are attempting to model the key cells responsible for the rewarding, addictive effects of opioids to identify which compounds might have higher or lower risk of misuse. Models are also being built to simulate the body's pain receptors, including a model of pain sensation in the skin, as well as a tiny "microjoint" to help researchers test potential therapies and complications for arthritis. Another set of studies have constructed cellular models of the blood-brain barrier, which can help researchers determine which potential therapeutic compounds might have an easier time reaching their targets in the brain to have their effects. Together, these projects will provide key tools for identifying new candidates for treating pain and OUD.

To evaluate potential novel therapeutic agents, HEAL has established models to rigorously profile, screen, and validate assets in an optimized Preclinical Screening Platform for Pain (PSPP). PSPP uses a tiered approach to evaluate in vitro and in vivo abuse liability,

pharmacokinetics, and side effect profiles of promising small molecules, biologics, natural products, and devices, and evaluates the asset in models relevant to human pain conditions. About 80 percent of the asset owners are from industry, including a large proportion of start-ups/academic spinoffs.

Once new interventions are ready for human testing, networks of physicians, researchers, and participants across a variety of settings and healthcare systems are needed to carry out efficient clinical trials of potential interventions.

Expanding clinical trial networks

Established in 1999, the National Drug Abuse Treatment Clinical Trials Network (CTN) develops, tests, and implements new addiction treatments. The CTN nodes act as regional hubs for engaging participants, researchers, clinicians, and health systems in a range of settings, including primary care, specialty substance use disorder care, emergency departments, obstetrics/gynecology clinics, hospital settings, and rural locations. HEAL expanded the CTN from 11 nodes to 16, with each node in a particular region of the United States.

Through HEAL, the CTN has also launched 26 new studies, including large, multisite clinical trials to test approaches for optimizing treatment with medications for OUD in primary care and specialty care, emergency department, OB-GYN, hospital settings, and rural locations. This research has led to the finding that the use of 12-step groups can be beneficial as an adjunct to clinical care for opioid use disorder.

Ongoing research includes testing the impact of a model of coordination between primary care clinics and telemedicine vendors on access to and retention in treatment in rural locations. Other studies are evaluating the effect of extended-release buprenorphine formulations on maternal–infant outcomes and testing new protocols for initiating patients on long-term naltrexone. Since the launch of HEAL, a clinical decision support tool to improve clinical practice and patient outcomes in OUD care has been deployed in one of three large healthcare systems participating in the study.

Developing novel interventions in new networks

HEAL has also launched new networks of collaborating researchers, clinicians, and study participants. To identify effective treatment approaches for people who have both an opioid use disorder and co-occurring mental health conditions, HEAL established the Optimizing Care for People with Opioid Use Disorder and Mental Health Conditions program. Investigators in

this program combine strong research–practice partnerships with the expertise of interdisciplinary teams to diagnose and treat OUD and mental health disorders, including addressing suicide. Studies are recruiting participants in rural and urban settings nationwide to determine the clinical effectiveness of multiple collaborative strategies with a focus on primary care settings.

The Advancing Clinical Trials in Neonatal Opioid Withdrawal (ACT NOW) program studies the clinical care of infants who are exposed to opioids in the womb and are at risk for a condition called neonatal opioid withdrawal syndrome (NOWS) or neonatal abstinence syndrome. NOWS symptoms can include tremors, excessive crying and irritability, and problems with sleeping, feeding, and breathing. In 2017, ACT NOW launched a large observational medical-record abstraction study across 30 research hospitals to identify how clinicians currently care for infants with NOWS. The study found significant variation in practice between nurseries (7) and no standard of care exists. Through HEAL, ACT NOW has launched three large-scale trials: one to study ways to soothe infants without medications, one to study the best ways to provide medications and taper them off over time, and one to study the long-term effects and development of individuals born with NOWS.

The Early Phase Pain Investigation Clinical Network (EPPIC-Net) aims to enhance the treatment of high-impact pain conditions and reduce reliance on opioids through early-phase clinical trials of nonaddictive pain treatments at 12 specialized clinical centers. EPPIC-Net is launching its first clinical trial of a novel asset for the treatment of knee osteoarthritis. EPPIC-Net will work closely with another new network established by HEAL, the Back Pain Consortium (BACPAC) Research Program. BACPAC is a translational, patient-centered effort to address the need for effective and personalized therapies for chronic low back pain, a leading cause of disability in the United States. BACPAC has designed a consortium-wide trial using an innovative new precision medicine-based design that allows for patients who were randomized to receive one of four interventions, to be re-randomized to either switch or add treatments if pain persists. Since the launch of HEAL, these two networks and others have harmonized experimental methods and measures, including both self-reported and biological measures of pain and function. They have also defined best practices for designing clinical trials and engaging patients in research.

Defining non-opioid targets for both pain and OUD

One of HEAL's fundamental goals is to find novel ways to treat pain and OUD, expanding options for treatment beyond the approaches that are currently in use. Achieving this goal requires exploring options for pain management that are less likely to be misused and carry

little or no risk of overdose. Achieving this goal also requires exploring treatments for OUD that engage systems beyond the brain's opioid system, expanding the range of effective medications. As part of HEAL's balanced investment in addressing the opioid crisis, these studies, while often in earlier stages of the translational pipeline, have the potential to make important advances in the management of pain and OUD. As mentioned above, in some cases these medications are novel to OUD, but are already approved for other conditions. In other cases, the researchers in the search for new therapies are exploring entirely new molecules, cells, and circuits.

HEAL's Focused Therapeutics Development program is leading a concerted effort to explore new options for OUD treatment and overdose reversal. The program has funded investigations of 32 different New Molecular Entities, an FDA designation for drugs with active chemical components that have not yet been approved or marketed in the United States. While some of these drugs seek to target the opioid-signaling system in novel ways that are safer or more effective, others explore entirely new pathways. Some of these novel approaches include targeting molecular signaling systems with roles in learning and memory that could help the brain "unlearn" addiction. Others target hormone-signaling pathways known to be involved in craving and withdrawal symptoms. As mentioned earlier (see "Repurposing or Improving the Deployment of Existing Strategies"), this program is also examining 23 repurposed medications, several of which target non-opioid pathways involved in processes known to play a role in withdrawal and craving, such as sleep.

Other HEAL projects are looking beyond creating new drugs and investigating novel device-based treatments for OUD. For example, one HEAL project has filed an IDE with the FDA to begin human trials of deep brain stimulation for OUD. Deep brain stimulation, which involves implanting and stimulating electrodes into key brain areas to restore normal brain activity, has been shown to be safe and effective for treating Parkinson's disease and obsessive-compulsive disorder, and it is also being investigated for a variety of mental illnesses, such as treatment-resistant depression. This study, and others like it, may provide device-based alternatives to medications that expand options for the safe treatment of OUD.

To effectively combat the opioid crisis, treating OUD alone is insufficient. New, non-addictive pain medications are desperately needed. Since its inception, the HEAL Initiative has invested in projects across the pain therapeutics development pipeline, including crucial formative research steps like analgesic target discovery and preclinical drug development. The projects described below represent the progress that is being made in early drug development that will

aid in our effort to overcome challenges to developing non-addictive, effective pain medications.

To advance the discovery and validation of new drug targets, HEAL has funded 34 projects that aim to discover and verify a diverse set of drug target types across multiple pain conditions, and six drug optimization studies on new safe and effective pain treatments. HEAL research is also translating discoveries about pain pathways and circuits into effective devices for managing pain: 11 projects are underway to test the effectiveness of implanted devices and noninvasive stimulation of nerves in the brain or throughout the body to reduce perception of pain. Finally, nine projects are focused on characterizing reliable biomarkers, or biological signatures, of common chronic pain conditions to aid pain diagnosis and speed analgesic drug development.

HEAL's investments in these research areas have already yielded several noteworthy successes. Two teams of HEAL researchers have filed patents for small molecule modulators of pain receptors involved in chronic pain and migraine. One HEAL small business team recently filed a patent for a portable thermoelectric device can block pain signals in two different peripheral nerves in preclinical model systems, and a second team used genetically engineered viruses to test the effects of blocking sodium channels using several model systems.

Early successes in these longer-term investments are part of a balanced investment with short-term projects that explore repurposing approved drugs for pain treatment and changing treatment implementation strategies to mitigate addiction risk. By funding research focused on discovery and optimization of nonaddictive pain targets, HEAL is ensuring that future pain therapies can move beyond our current limited options.

Looking Ahead—Developing Tools to Facilitate Data Sharing: The HEAL Data Ecosystem

The breadth and depth of HEAL's research portfolio is unparalleled – over time, generating an extensive collection of findings and datasets that will be the basis of future research in many different biomedical domains. HEAL data are highly diverse and include imaging/microscopy; behavior; genomics, transcriptomics, and proteomics; pharmacokinetics; public records; biometrics; biosamples; electrophysiology; actigraphy; and more. The complexity will present data-related challenges, yet data sharing is a high priority to ensure HEAL-funded research investments best address this urgent public health crisis.

A platform under development for accessing HEAL research data will make studies across HEAL and other NIH datasets accessible for investigators and the public, while protecting the privacy and confidentiality of research participants. This platform will form the foundation for an ecosystem for data management, analysis, and interaction through the NIH HEAL Initiative, and accelerate scientific solutions to the opioid crisis. The platform will disseminate findings and results from HEAL studies to patients, providers, institutions, and organizations so that they can rapidly put them into practice across the United States. Sharing HEAL-generated results and associated data as rapidly as possible will allow the broader community to ask and answer new research questions; conduct secondary analyses; and address fast-evolving challenges that surround pain management, opioid use and misuse, and overdose.

ADAPTING HEAL RESEARCH FOR THE COVID-19 PANDEMIC

Pandemic-related mitigation strategies such as social distancing and stay-at-home orders have changed the way people live, work, and receive medical care. In many research settings, from the laboratory to the clinic, pandemic-related changes have been required to ensure the safety of participants and personnel. While this has slowed progress in some areas, HEAL studies have used a variety of strategies to creatively adapt and ensure that their research can safely continue as much as possible.

With COVID-19 mitigation in mind, JCOIN, the HEALthy Brain and Child Development Study (HBCD), HEALing Communities Study, NIDA CTN, ERN, PRISM, and the Biomarkers, Signatures and Endpoints for Pain programs enabled virtual recruitment, patient consenting, and data collection methods, and several engaged in virtual community engagement to improve participant retention. The Pain Biomarkers program facilitated biospecimen collection by including it with other clinical blood draws, and JCOIN supplemented projects to include pooled biospecimen collections in jails and prisons. Finally, HEAL Prevention, NIDA CTN, JCOIN, PRISM, and Behavioral Research to Address Medications for the Treatment of OUD (BRIM) adapted behavioral interventions for virtual delivery, and some integrated telemedicine for clinical decision-making.

To address the effect of COVID-19 on research, HEAL researchers are also working to disseminate updates, impacts, and best practices to the field. For example, HEALing Communities Study researchers issued an update in the *Journal of Drug and Alcohol Dependence* clarifying that the study's goals and hypotheses will remain the same, but the research period will be extended by 12 months to account for pandemic-related disruptions. HEAL Prevention researchers are planning a special issue of *Prevention Science* to highlight effects of the COVID-19 pandemic on SUD and overdose. Finally, researchers from JCOIN are compiling emerging best practices for criminal justice agencies on addressing OUD in the context of COVID-19. Together, the tremendous efforts by researchers across HEAL have helped the initiative continue momentum during a pandemic whose effects have made finding solutions to the opioid crisis even more urgent.

Conclusion

Since its inception in 2018, the HEAL Initiative has made substantial investments in addressing the dual crisis of pain and OUD. Herein, we have described a tangible return on those investments, bringing researchers closer to turning back the nation's intersecting crises of pain, addiction, and overdose by developing several novel strategies for managing pain, preventing and treating OUD, and reversing overdoses. At the same time, the COVID-19 pandemic has exacerbated existing barriers to treatment for pain and OUD and has brought new challenges to the nation's public health infrastructure. The initiative has begun to realize the promise of expanding pain and OUD research despite these challenges – and with continued support, HEAL will move further toward achieving its goals in the coming years.

The above report details high-level areas of progress and accomplishments, with a few selected illustrative examples. The appendix below provides more detailed project-by-project information.

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Table of HEAL Programs and Accomplishments

Focus Area	Program	Accomplishments
Novel Therapeutic Options for Opioid Addiction and Overdose	Focused Therapeutic Development for Opioid Use Disorder and Overdose	• 61 projects, $241 million to date, NIDA, NHLBI • 16 INDs have been filed with the FDA • HEAL goal to file 15 INDs in 5 years, which has been exceeded in 2 years • Biologics: First study in humans of an opioid vaccine was launched • Devices: One IDE to study Deep Brain Stimulation for Opioid Use Disorder • Novel medications and formulations • 32 New Molecular Entities (NME) and 23 repurposed medications • 50+ compounds being developed from early preclinical to late clinical phases • Anti-opioid immunotherapies (vaccines and monoclonal antibodies)
	Novel Immunotherapies to Opioids	• 10 projects, $30 million to date; led by NIAID in collaboration with NIDA
Enhanced Outcomes for Infants and Children	Advancing Clinical Trials in Neonatal Opioid Withdrawal (ACT NOW)	• Launched two clinical trials (“Trial to Shorten Pharmacologic Treatment of Newborns with NOWS”, and the “Eat, Sleep, Console” trial for soothing without medication) and one longitudinal study (“Outcomes of Babies with Opioid Exposure”); $41 million to date; led by NICHD and OD/ECHO • ACT NOW trials are enrolling for all three studies at more than 50 sites nationwide • Results from the completed 30-site observation study found significant site-to-site practice variation
	HEALthy Brain and Child Development Study (HBCD)	• $7.8 million to date , co-funded together with NIDA with NIMH, NIAAA, NINDS, NIEHS, NIBIB, NICHD, OBSSR, ORWH, and NIMHD

Focus Area	Program	Accomplishments
		• Fiscal Year 2021 Funding Opportunity Announcements to develop neuroimaging measures in infants and young children • HBCD researchers designed an MRI-compatible crib to increase success rate of imaging sleeping newborns and infants
	Small Business Innovation Research (SBIR)	• 2 small business research projects on nonpharmacological, noninvasive treatments for NOWS received Breakthrough Devices Designation by the FDA
New Prevention & Treatment Strategies for Opioid Use Disorder	Preventing Opioid Use Disorder in At Risk Populations	• 9 projects, $48.5 million to date; NIDA, NIAAA, NIGMS • Research addressing substance use among vulnerable adolescents and young adults, including research developing and testing 10 interventions to prevent opioid misuse and disorder among homeless young people, those involved in justice, welfare, or healthcare systems, and American Indian/Alaskan Native (AI/AN) young people.
	Optimizing Care for People with Opioid Use Disorder and Mental Health Conditions	• 13 projects, $56 million to date; NIMH led; NIDA, NIAAA • Testing collaborative care model for OUD treatment; improving treatment, management, and services for people with co-occurring conditions and suicide risk
	Sleep Dysfunction	• 10 projects, $25.6 million to date; NIDA, NHLBI • Basic mechanistic studies, clinical trials, and supplements for objective assessments of sleep during OUD treatment and recovery
	Enhancing the National Drug Abuse Treatment Clinical	• HEAL funding has added five “nodes” to the NIDA CTN, to better represent

Focus Area	Program	Accomplishments
	Trials Network to Address Opioids	new and understudied geographic areas • Launched a multisite clinical trial (STOP) to test a strategy for preventing progression from subthreshold OUD to more severe OUD • Launched a multisite clinical trial (RDD) to test strategies to improve retention in medication-based treatment for OUD as well as strategies to improve outcomes among patients who have been stabilized on OUD medications and want to stop taking medication
Translation of Research into Practice for Effective Treatments for OUD	Behavioral Research to Address Medications for the Treatment of OUD (BRIM)	• 8 grants, $26.5 million to date; NCCIH led • Test if behavioral/social interventions, mHealth, peer delivery help improve long-term outcomes for medication-based OUD treatment
	HEALing Communities Study	• 5 grants, $209 million to date; NIDA led • "Communities That Heal" menu of evidence-based interventions, including naloxone distributions, tested in 67 communities in four states hit hard by the opioid crisis • Communications campaign for community uptake of medications for OUD and naloxone • Data tools to monitor overdose spikes, geospatial analyses of opioid misuse risk environment, and service availability • National opinion surveys tracking perceptions of OUD and stigma
	Expanding the NIDA Clinical Trials Network to address Opioids	• 26 studies, $145 million to date; NIDA led • Launched several multisite clinical trials to test approaches for

Focus Area	Program	Accomplishments
		optimizing treatment with medications for OUD
	Justice Community Opioid Innovation Network (JCOIN)	• 15 projects, $83.6 million to date; NIDA led • Collaborative with justice systems in 27 states studying the quality care for opioid misuse and OUD in justice populations • 13 multisite clinical trials, nine modeling projects, 11 surveys • Compilation of emerging best practices for criminal justice agencies on addressing OUD in the context of COVID-19
Preclinical and Translational Research in Pain Management	Discovery and Validation of Novel Targets for Safe and Effective Pain Treatment	• 34 projects, $69 million to date; NINDS led; NIDCR, NIAMS, NCCIH, NIA, NCI, NIDDK, NIDA • Multiple diverse target types and pain conditions, e.g. neuropathic, post-surgical, osteoarthritis, and chemotherapy induced pain • Two separate patents for small molecule modulators of pain receptors; includes chronic pain and migraine therapies • Validated the ability of a portable thermoelectric device to inhibit pain signals in two different peripheral nerves
	Optimizing Non-Addictive Therapies to Treat Pain	• Six contracts focused on four small molecules and two biologics; $7.5 million to date; NINDS led
	Translating Discoveries into Effective Devices for Pain Treatment	• 11 projects, $23 million to date; NINDS and NIBIB • Testing implanted devices, such as electrodes, and noninvasive targeted stimulation of nerve cells and regions of the brain associated with pain perception
	Human Based Models and Candidate Testing for	• Five awards, $7 million to date; Intramural-extramural collaborative

Focus Area	Program	Accomplishments
	Nociception, Addiction, and Overdose	projects and prizes $63 million to date; NCATS • hiPSC-based DRG tissue chip model of acute and chronic nociception and multi-organ human-on-a-chip
	Biomarkers, Signatures, and Endpoints for Pain	• Nine projects, $31.7 million to date; NINDS led • Pain associated with sickle cell disease, eye pain, musculoskeletal disease, nerve pain and spinal cord injury, persistent headache after concussion
	Small Business Innovation Research (SBIR)	• IND for a first-in-class nonaddictive drug candidate for the treatment of chronic pain
Clinical Research in Pain Management	Early Phase Preclinical Investigation Network (EPPIC-Net)	• 14 grants for infrastructure; $32 million to date; NINDS led • Trial for CCR2 antagonist for knee osteoarthritis pain in the start-up phase
	Back Pain Consortium	• 14 research projects totaling $117 million to date; NIAMS led • Three mechanistic research centers, seven technology sites, two phase II trials, data center, and one supplement to study back pain in the context of OUD • Iterative model to inform precision medicine for chronic low back pain • Multiple contributions to chronic low back pain and treatment interventions – from anxiety to tissue damage and from psychotherapy to surgery
	Hemodialysis Opioid Prescription Effort (HOPE)	• Eight clinical sites and data center; $28 million to date; NIDDK led • Test nonpharmacological interventions and buprenorphine for pain in patients in kidney dialysis • FDA IND for use of buprenorphine for pain management as part of multidisciplinary pain management

Focus Area	Program	Accomplishments
		for patients on dialysis for end stage renal disease
	Pain Effectiveness Research Network (Pain ERN)	• Eight projects, $60 million to date; NCATS infrastructure with NICHD, NIA, NIAMS, NIDA, NINR, NCI trials • Pain conditions studied: knee osteoarthritis, postsurgical pain in adolescents, post-mastectomy pain, acute pain post cesarean, chronic pain in cancer survivors, chronic pain in veterans with OUD • Data harmonization through a set of pain-unique Common Data Elements for HEAL clinical pain studies
	Pragmatic and Implementation Studies for Management of Pain to Reduce Opioid Prescribing (PRISM)	• Seven projects $23 million to date; NCCIH NIA, NIAMS, NINR • Nonpharmacological management of diffuse fibromyalgia pain, post-surgery, sickle cell, and chronic low back pain