The NIH Helping to End Addiction Long-term® Initiative, or NIH HEAL Initiative®, is an aggressive, trans-NIH effort to speed scientific solutions to stem the national opioid public health crisis. Launched in April 2018, the initiative focuses on improving prevention and treatment strategies for opioid misuse and addiction and enhancing pain management.

Overview

The Third Annual NIH HEAL Initiative Investigators Meeting was held April 11 to 12, 2022. The agenda, slides, and links to the videocasts of the event are available on the NIH HEAL Initiative website. The goals of the meeting were to:

- Share research breakthroughs and cutting-edge science.
- Explore commonalities and surface challenges and opportunities to build on the initiative’s successes.
- Strengthen collaboration in the NIH HEAL Initiative scientific community to advance pain and opioid use disorder research.
- Hear the diverse perspectives of individuals with lived experience, as well as patients and communities involved in HEAL studies.

April 11

Welcome and Introductory Remarks

Rebecca Baker, Ph.D., Director, NIH HEAL Initiative, welcomed the more than 400 attendees, including HEAL investigators, NIH staff, people with lived experience, and representatives of community organizations. She highlighted the unique focus of the NIH HEAL Initiative on simultaneously addressing both the need for improved pain management and the continuing challenges caused by opioid use disorder (OUD) and record numbers of overdose deaths. Although the NIH HEAL Initiative spans many research disciplines, they are united in their common goal of addressing the needs of people with pain and/or OUD.
Lawrence Tabak, D.D.S., M.D., Acting Director, NIH, emphasized the continuing critical need for the NIH HEAL Initiative as overdose deaths have risen to previously unimaginable numbers. This rise has been driven by the COVID-19 pandemic and its associated effects, such as extended social isolation, as well as by the increased availability of synthetic opioids such as fentanyl and the increase in polysubstance use. The HEAL investigator community has continued to meet this moment and all the challenges associated with the pandemic, adapting with novel ways to conduct research and implement new treatments. NIH and the HEAL Initiative are also grateful to the members of the HEAL Community Partner Committee, who represent the voices of the individuals, families, and communities affected by pain and OUD. The NIH HEAL Initiative Investigator Meeting provides participants with an opportunity to share their successes and challenges. It also serves as a touchpoint to understand the best ways of addressing the wide range of existing problems and confronting persistent disparities, such as inequities affecting ethnic minorities, increases in drug use among young people, and new patterns of drug use. To address these and many other issues, the NIH HEAL Initiative had announced about 40 new funding opportunities since October 2021, and dozens more were being prepared.

Keynote Address

Admiral Rachel Levine, M.D., Assistant Secretary of Health for the U.S. Department of Health and Human Services (HHS), delivered a keynote address on the Administration’s response to the opioid crisis and the new HHS Overdose Prevention Strategy. Since 1999, more than 840,000 people have died from opioid overdoses. The drugs driving the pandemic are constantly evolving, with increasing contributions of fentanyl and other synthetic opioids as well as stimulants in recent years. Additionally, in 2019, more than 50% of overdose deaths involved more than one drug. The COVID-19 pandemic has accelerated death rates, likely through increased stress and social isolation. This makes it even more important to increase access to behavioral health care for all Americans, particularly for groups often faced with systemic barriers and health disparities, such as ethnic minorities. The Administration’s new Overdose Prevention Strategy encompasses the full spectrum of measures to prevent opioid misuse, treat OUD, and address inequities. To achieve this, the Administration works with agencies like the Centers for Disease Control and Prevention (CDC) and the Substance Abuse and Mental Health Services Administration (SAMHSA) as well as supports research into all aspects of the opioid crisis. Cornerstones of the new strategy are prevention, such as interventions in the communities, in schools, and with the medical community; harm reduction approaches such as fentanyl test strips, increased naloxone availability, and syringe service centers; treatment with expanded access to medications as well as other treatments; and recovery support involving agencies across the spectrum. All Americans deserve access to timely and effective services.
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**Plenary Session — Helping to End Addiction Long-term® Initiative: Progress and Priorities**

Dr. Baker noted that NIH HEAL Initiative researchers faced numerous new challenges over the past year, such as increases in overdose deaths among teens and young adults and increased harm in traditionally underserved populations such as Blacks and American Indians/Alaska Natives. The HEAL community has met these challenges with creativity and dedication and achieved substantial progress. They have launched the [Integrative Management of chronic Pain and OUD for Whole Recovery (IMPOWR)](link) study that assesses integrated treatment for individuals with OUD and chronic pain. The [Advanced Clinical Trials in Neonatal Opioid Withdrawal (ACT NOW)](link) study has completed enrollment. The [Early Phase Pain Investigation Clinical Network (EPPIC-Net)](link) consortium started the first clinical trials of alternatives to opioid medications for pain associated with different health conditions. HEAL-funded researchers submitted more than 20 initial new drug applications for pain and OUD to the U.S. Food and Drug Administration (FDA). Enrollment has continued or finished for some comparative effectiveness trials of pain management for different conditions, and implementation studies such as the [Justice Community Opioid Innovation Network (JCOIN)](link) have made progress in implementing evidence-based treatments. For the coming year, new directions for HEAL research will focus on care coordination and collaboration; promotion of health equity; strengthening of data-driven research; new funding opportunities for harm-reduction approaches; identification of evidence-based interventions, especially for polydrug use and recovery support; and innovative approaches for overdose prevention. It is important to incorporate input from individuals with lived experience in these endeavors and to pursue a holistic approach for treatment of pain and OUD.

**Plenary Panel Discussion — The HEAL Community Partner Committee (HCPC)**

**Facilitators:** Walter Koroshetz, M.D., Director, National Institute of Neurological Disorders and Stroke (NINDS); Diana Bianchi, M.D., Director, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

**Speakers:** Kevin Charles, Family and Medical Counseling Inc.; Jessica Hulsey Nickel, Addiction Policy Forum; Bianca Prieto, Georgia Council on Substance Abuse; Philip Rutherford, Faces & Voices of Recovery; Stephanie Smith, person with lived experience; Christin Veasley, Chronic Pain Research Alliance

According to Dr. Koroshetz, the HCPC represents the individuals who the NIH HEAL Initiative is all about—the people who need help for their pain or opioid use disorder and addiction. Dr. Bianchi noted that the NIH HEAL Initiative recognizes the validity of the adage that “there is no research about me without me.” The HCPC works to include the voices of various stakeholders,
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reduce barriers, enhance outreach, and facilitate communication between investigators and the patient community. To this end, they have created a survey that has been mailed to all HEAL investigators regarding patient engagement in their studies.

Several HCPC members emphasized the importance of involving peer specialists and peer educators in all stages of research as well as the implementation of interventions. Peers with lived experience can enhance engagement, alleviate trust issues among affected populations, bridge cultural or language gaps, and help address the needs of specific communities. Generalizing findings and treatments to all populations is not possible.

Ms. Hulsey Nickel highlighted the connection between pain/trauma and OUD, including both physical and emotional pain. She noted that many people with OUD report multiple adverse childhood experiences that compound other influences.

Ms. Veasley noted that researchers often do not have any training in how to engage patients in their research projects; therefore, the HCPC aims to build bridges between the research and patient communities by learning how they can support researchers via the previously mentioned survey.

Ms. Smith emphasized the importance of addressing the opioid crisis by preventing unnecessary opioid use and developing new standards of care that do not see opioids as the default treatment for pain but offer other treatments or combinations of treatments.

Plenary Session — At the Intersection of Pain and Opioid Use Disorder

Facilitators: Walter Koroshetz, M.D., Director, NINDS; Nora Volkow, M.D., Director, National Institute on Drug Abuse (NIDA); Declan Barry, Ph.D., Yale School of Medicine

Speakers: Manisha Jhamb, M.D., M.P.H., University of Pittsburgh; Katie Witkiewitz, Ph.D., University of New Mexico

Dr. Volkow noted that the prevalence of pain in people with substance use disorder (SUD) is twice as high as in people without SUD. Neurobiological pathways for both conditions overlap. Comorbidity of OUD and pain is of clinical significance, especially if patients do not trust that their pain is adequately treated without opioids and clinicians do not trust patients to use opioid medications responsibly.

Dr. Koroshetz added that the science of pain has been revolutionized in recent years and that researchers are delineating pain circuits and brain nodes that are separate from those for
opioids and reward. Disconnecting the sensation of pain from the negative experience of pain could help therapy development.

Dr. Barry emphasized that there are multiple targets to intervene in patients with both chronic pain and OUD, and both patients and health care providers are interested in receiving or offering integrated treatment. In clinical trials of people with chronic pain and OUD, integrated treatment has shown promising outcomes in various parameters.

Dr. Jhamb described the HEAL-funded Helping People on Dialysis Manage Pain (HOPE) trial to reduce opioid use in patients with end-stage kidney disease undergoing regular dialysis. Pain in patients with end-stage kidney disease is often underdiagnosed and undertreated, and its management is challenging due to provider factors, patient factors, and systemic factors. The HOPE trial is evaluating the effect of a telehealth approach (12 weekly coping skills training sessions, followed by 12 weeks of daily assessment calls and Interactive Voice Response booster sessions) that can be delivered during dialysis on pain levels and opioid use in these patients. The study design includes a multidisciplinary team and diverse racial and geographic participant representation and was strongly influenced by patient advisors. As of March 2022, about 50% of targeted patients have been randomized to the study. A supplemental study aims to assess an intervention to reduce stigma associated with buprenorphine use in these patients.

Dr. Witkiewitz introduced the IMPOWR study that aims to generate patient-centered solutions and focuses on implementation and dissemination. It includes nine implementation and effectiveness studies assessing three behavioral pain treatments, two different buprenorphine dosing regimens, and four models of care delivery; six of these trials are aimed at underserved populations. Selected common data elements will be included in all studies across the IMPOWR centers, based also on input from people with lived experience. Three cross-cutting themes, such as stigma and involvement of public and private partners and people with lived experience, have been identified.

**Discussion:** The structure of the HOPE intervention can also be applied to other comorbid conditions associated with a lot of pain and may alleviate the lack of skilled therapists in a given region. For the IMPOWR trial, referrals and recruitment are coming from across the health care system, from primary care providers to opioid treatment programs. Both the HOPE and IMPOWR studies are inclusive for males, females, and other genders.

**Fireside Chat — Addressing Addiction and the Overdose Epidemic From Many Angles**

Rahul Gupta, M.D., Director, White House Office of National Drug Control Policy, joined Dr. Tabak for a Q&A session to discuss the Administration’s diverse approaches to addressing
the opioid crisis. The opioid crisis is complex, and there is no simple solution. The overdose crisis can be seen as a pyramid, with overdose deaths at the top, but below that is a larger number of nonfatal overdoses and an even greater number of people with SUD. There is a need for data particularly on nonfatal overdoses, to identify where and when they occur and link people to treatment before they have a fatal overdose. To address some of the issues, it is also important to evaluate existing data from a variety of sources.

The prevalence of synthetic drugs fuels the overdose crisis, and the Administration is working with various agencies to disrupt drug supplies from outside the country. Equally important is developing methods to quickly detect synthetic drugs such as fentanyl, xylazine, and methamphetamine.

The Administration is supporting harm reduction approaches, such as wider availability of naloxone, fentanyl test strips, and syringe services. In addition, programs to support recovery—for example, in terms of housing or employment—are being worked on.

Establishing health equity is another important issue. More information is needed on why people do not access treatment, in some cases even when treatment is available, possibly because of cultural bias. Other approaches needed to reduce inequities include treatment expansion in the criminal justice system and better insurance coverage of nonpharmacological treatment approaches.

The research community can contribute by providing data to inform policies. Better data on nonfatal overdoses can help improve targeted allocation of naloxone and linkage to treatment. Research on the evolving drug landscape is needed to be able to proactively address emerging threats of new drugs. Research into nonaddictive pain management approaches needs to be expanded. With more data-driven approaches as well as expanded access to diversion prevention programs and other strategies to ensure that people are not just arrested but get the care they need, we can start to bend the curve.

Discussion Group — Lessons from HEAL Stigma Research

Facilitators: Wendy Weber, N.D., Ph.D., M.P.H., National Center for Complementary and Integrative Health (NCCIH); Gavin Bart, M.D., Ph.D., University of Minnesota

Discussants: Karen Derefinko, Ph.D., University of Tennessee; Samantha Meints, Ph.D., Brigham and Women’s Hospital; Stephanie Smith, person with lived experience
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About **38% of patients with chronic pain experience internalized stigma**. Stigma is also common in the addiction field. However, research has addressed stigma only over the last 10 years or so, rarely focusing on interventions to combat it.

- Dr. Derefinko introduced the concept of intersecting stigma, defined as the presence of more than one type of stigma (e.g., substance use and racial/ethnic minority). A behavioral economics-based intervention in Memphis, Tennessee, sought to intervene at multiple levels aimed at the individual, their family or support network, and the community to reduce intersecting stigma. However, stigma runs deep; improved access to treatment did not increase treatment uptake, and community interventions did not lower stigma but avoided increases in stigma.

- Dr. Meints described the effect of intersectional stigma related to pain, mental health problems, and opioid use on treatment of negative affect in chronic low back pain. A new study compares the effectiveness of enhanced fear avoidance rehabilitation and antidepressant therapy alone or together in people with chronic low back pain and negative affect. The study will also examine how intersectional stigma differs between patients treated with and without opioids.

- Ms. Smith emphasized the need to offer alternatives for opioid-based pain management and for patients to advocate for themselves against physicians’ default treatment strategies.

**Discussion**: Racial, generational, and gender differences, as well as differences in the underlying causes of pain need to be considered at multiple levels of stigmatization and with intersecting stigma. As there are different levels of stigma, a single measure likely will not work, but gold standards in the three realms of stigma would be helpful. Addressing stigma at the provider level is incredibly important.

**Discussion Group — Expanding Patient and Community Engagement in HEAL Studies**

**Facilitators**: Linda Porter, Ph.D., NIDA; Megan Irby, Ph.D., Wake Forest University

**Discussants**: Christin Veasley, Chronic Pain Alliance; Afton Hassett, Psy.D., University of Michigan; Cynthia Rogers, M.D., Washington University School of Medicine

Community engagement in research is a process of inclusive participation among people affiliated by geographic location, shared interests, or similar circumstances. It serves to address issues affecting well-being within patient and community systems.

- Dr. Hassett reported on efforts to improve community engagement in the Chronic Pain & Fatigue Research Center as part of the [Back Pain Consortium (BACPAC)](https://www.backpainconsortium.org) Research
Program. They developed a tailored recruitment model with various approaches to improve willingness of people to participate and developed novel community partnerships. Also important was a community advisory board that provided input. The challenge is to balance competing needs and ensure long-term productivity and sustainability.

- Dr. Rogers described community engagement efforts in the HEALthy Brain and Child Development (HBCD) study. They established a Diversity, Equity, and Inclusion Coordinating Committee to support patient/community engagement during study preparation, implementation, and ongoing phases. Locally, they are employing community advisory boards, peer recovery navigators, community health workers, and social workers.

Discussion: Community engagement efforts are often funded through supplements to the main grant; these are generous but not always sufficient in the longer term. How do we shift the paradigm of research so that this is a part of every clinical study going forward? Include these activities in requests for proposals and before grant submission. It would be helpful if NIH provided some resources for training and guidance on community engagement.

**Discussion Group — Addressing the Unique Needs of Pediatric Populations**

**Facilitators:** Janani Prabhakar, Ph.D., NIDA; Alice Graham, Ph.D., Oregon Health and Science University

**Discussants:** Deena Chisolm, Ph.D., Nationwide Children's Hospital; Kathryn Humphreys, Ph.D., Ed.M., Vanderbilt University

- Dr. Chisholm reported on analyses of opioid prescribing in children with pain. Analyses of medical records found that disparities in opioid prescribing existed for children undergoing the same type of surgery based on race, treatment facility (children’s hospital vs. other), and location (urban vs. rural). Prescribing patterns of opioids for chronic sickle cell disease pain were influenced by policy changes, but reductions in opioids were not compensated with other pain medications. Health literacy of parents is important so they understand what treatment their children receive.

- Dr. Humphreys discussed challenges of research with infants based on her experiences in the HBCD study. These include the rapid pace of infant development, greater time demands, lower quality of data, and resource intensity. These challenges can be met using diverse teams, partnering with community organizations to recruit during pregnancy, extensive staff training, patience and comfort provision, and specific strategies to maintain participant retention.
Discussion: Increasing health literacy in parents but also in affected children is important, especially for chronic conditions like sickle cell disease, where children eventually need to be in charge of their own care. You need to help them develop the skill set to make decisions about their health care, including pain treatment. Measures to improve recruitment success for pediatric/infant populations can include having consistent coordinators to strengthen personal associations, keeping in contact (regular follow-up or marking birthdays), empowering families to make their own decisions, and involving peer navigators/people with lived experience.

Discussion Group — Advances in Digital Therapeutics and Other Technologies

Facilitators: Will Aklin, Ph.D., NIDA; Suzette Glasner, Ph.D., University of California, Los Angeles

Discussants: Bin He, Ph.D., Carnegie-Mellon University; Hilary Luderer, Ph.D., Pear Therapeutics

Developing safe and effective treatments for chronic pain, including non-pharmacological approaches, is essential to mitigate the need for opioids and prevent opioid misuse. Innovations in mobile health applications show promise for tackling OUD by removing barriers and enhancing treatment adherence.

- Dr. He described transcranial focused ultrasound (tFUS) neuromodulation as a non-surgical, low-energy, precise, and portable technique to mitigate pain. His lab has shown that tFUS can reduce pain sensitivity up to 60% in humanized sickle cell disease mice. The technique has promise for more generalized applications for treating pain, but more research is needed.

- Dr. Luderer discussed FDA’s regulatory process for prescription digital therapeutics (PDTs), such as ReSET-O+. Scientists used formative research to develop ReSET-O+, which will be evaluated in a 10-patient feasibility study as part of the approval process. PDTs can help overcome stigma and barriers and enhance treatment access by engaging people where they are.

Discussion: Given the growing number of digital health solutions in the marketplace, clinical validation is vitally important so patients can make informed decisions about their use. Other important considerations for non-pharmacological treatments include regulatory approval, safety, good manufacturing processes, and data. Pharmacists can be involved in implementing digital therapeutics. NIDA funding priorities for digital and other technology-based therapeutics include prevention of substance use initiation, enhanced medication adherence for OUD and pain conditions, and treatment of withdrawal while ensuring patients are engaged in the interventions.
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Discussion Group — Improving Access to Medication Treatment

Facilitators: Kristin Huntley, Ph.D., NIDA; Edward Nunes, M.D., Columbia University

Discussants: Jessica Hulsey, Addiction Policy Forum; Gail D’Onofrio, M.D., M.S., Yale School of Medicine; Benjamin Linas, M.D., M.P.H, Boston University

Medications for treatment of OUD (MOUD) are effective if used as recommended, but dropout rates are high, and many people don’t access treatment.

- Ms. Hulsey summarized findings from 60 patient journey interviews regarding treatment access. The patients identified numerous barriers, including wait time, high cost, insurance issues, various types of stigma, and lack of treatment for co-occurring conditions. Medication treatment in particular was associated with stigma from patients, friends, and health care providers, and lack of recovery literacy among health care providers was noted.

- Dr. D’Onofrio described the implementation-effectiveness Emergency Department-INItiated bupreNOorphine and VAlidaTIOn Network Trial (ED-INNOVATION) study offering treatment initiation with buprenorphine to patients with OUD or overdose in the emergency department (ED). Although ED-initiated buprenorphine is effective, logistical barriers to uptake, adoption, and patient success exist. The ED-INNOVATION trial evaluates the use of extended-release buprenorphine formulations (injectable CAM2038) for patients with OUD and a Clinical Opiate Withdrawal Scale (COWS) score ≥4.

- Dr. Linas explained how simulation modeling can be used to determine which changes in MOUD uptake could help reach the NIH HEAL Initiative-defined goal of reducing opioid overdoses by 40%. The models analyzed the effects of initiating more people on MOUD, improving retention on MOUD, and distributing more naloxone. All three measures are necessary to make reaching the goal achievable, as well as expansion of MOUD offers to syringe service programs.

Discussion: Support from leadership is essential to making sure MOUD is offered in health care settings. Implementation efforts should include pharmacists and nursing staff, and education of all stakeholders is necessary to reduce stigma associated with MOUD.
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Scientific Symposium — Advancing Research to Practice

Facilitators: Helene Langevin, M.D., NCCIH; Donald Penzien, Ph.D., Wake Forest School of Medicine

Presenters: Elizabeth Evans, Ph.D., University of Massachusetts Amherst; Craig Lefebvre, Ph.D., RTI International; Andrea Cheville, M.D., Mayo Clinic Rochester; Lauren Brinkley-Rubinstein, Ph.D., University of North Carolina at Chapel Hill

Dr. Evans presented findings from the Massachusetts JCOIN assessing mortality and recidivism after buprenorphine treatment during incarceration in county jails in rural western Massachusetts. MOUD during incarceration was associated with fewer subsequent arraignments and re-incarceration, prolonged time to recidivism, and overall reduction of recidivism by 32%. Buprenorphine treatment had no effect on mortality during the study period.

Dr. Lefebvre described findings from studies assessing the impact of community health campaigns in the framework of the HEALing Communities Study; these campaigns aimed to promote naloxone, reduce stigma, promote MOUD, and promote treatment retention. Analyses found that such campaigns can reduce stigma and promote uptake of interventions. For increased effectiveness, communication planning should be incorporated in community interventions from the beginning; include customized, localized materials; and understand local cultural stigma and barriers.

Dr. Cheville summarized the design of the Non-pharmacological Options in post-operative Hospital-based And Rehabilitation pain Management (NOHARM) pragmatic trial. NOHARM interventions include a portal-based guide and individualized messages for patients that support nonpharmacological pain care (NPPC) education, decision-making, and use; self-management educational materials and Zoom support calls for patients; and clinician-directed clinical decision support tools. The trial will assess various pain- and opioid use-related outcomes. Patients can choose their preferred NPPC approaches that are supported by care staff throughout the post-surgery period. To date, about 44,000 patients have been recruited.

Dr. Brinkley-Rubinstein shared information on the JCOIN Providing Interventions for Enhancing Recovery during Supervision (PIERS) program, which seeks to improve linkage to evidence-based care for people on parole or probation. The project involves baseline observations of existing procedures for linking individuals under supervision to MOUD; organizational assessments from stakeholders, focus groups, and staff; development and implementation of
local change teams led by JCOIN PIERS-provided facilitators; and ultimately a randomized controlled trial.

**Discussion:** Tailoring of community campaigns can be achieved through selection of specific messages about naloxone, MOUD, or stigma. Certain images and messages resonate across communities, but then can be tailored (e.g., through local images) and distributed at sites specific to the community.


Science hasn’t been effective at changing public perception of addiction and reducing stigma; however, personal stories can contribute to enhancing understanding by focusing on the humanity of people with addiction. Addiction is still misunderstood by the public, especially as they are getting conflicting messages. On the one hand, addiction is described as a disease, while on the other hand it is criminalized and often labeled as a “moral failing.”

Radical empathy is necessary when discussing addiction. It can be promoted through listening to people, meeting people where they are, and finding common ground. Fear and inequality work against empathy. The challenge is getting people to accept the complex contexts of drug use and to move from fear to understanding.

Harm reduction approaches are also important, such as safe supplies and recognizing that people sometimes need to continue using drugs in a safe way until they are ready for more significant change. In addition, it is essential to make treatment inviting and to help people with addiction look at the role of drugs in their life without judgment.
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**Plenary Session — The Opioid Crisis: Scientific Challenges and Opportunities**

Dr. Volkow summarized the main challenges associated with the opioid crisis, particularly the rapid changes in the drugs driving it. Additionally, polysubstance use has been increasing in recent years. The number of people who are vulnerable also has risen and diversified, with particularly high vulnerability in underserved populations, such as American Indians/Alaska Natives and Blacks. Also, in recent years, an extreme increase has occurred in overdose deaths among adolescents, which seems to be driven mainly by fentanyl contamination of other prescription medications obtained over the internet.

The most urgent needs are for non-addictive pain treatments as well as treatments for OUD and other SUDs. Although these new treatments are crucial, they are not sufficient. Also needed are new treatments for overdose, particularly overdoses of stimulants and drug combinations; prevention interventions that also screen for mild to severe SUD; and more timely data on fatal and nonfatal overdoses as well as on emerging new drugs such as xylazine. Another important focus must be on the social determinants of health, as they are one of the main factors driving the overdose crisis.

**Scientific Symposium — Advancing the Pain and Addiction Therapeutic Research Pipeline**

**Facilitators:** Joni Rutter, Ph.D., National Center for Advancing Translational Science; Sandra Comer, Ph.D., Columbia University

**Presenters:** Stephanie Seidlits, Ph.D., University of Texas Austin; Richard Scranton, M.D., M.P.H., Lyndra Therapeutics; Sarah Linnstaedt, Ph.D., University of North Carolina Chapel Hill; Amol Patwardhan, M.D., Ph.D., University of Arizona

Dr. Seidlits described a new organ-on-a-chip system that is hoped to be useful for modeling opioid reinforcement and withdrawal as well as the negative affective components of pain. The model is based on induced pluripotent stem cells cultivated to form cell networks with dopaminergic and GABAergic neurons. In initial tests, the networks respond as expected to treatment with morphine, naloxone, GABA antagonists, and other compounds and can also be used to test the effects of chronic morphine exposure. The goal is to ultimately integrate the cell networks into a larger model of the blood brain barrier that can serve as a high-throughput system for drug development.

Dr. Scranton reported on his company’s efforts to develop a long-acting form of methadone to allow for once-weekly oral treatment. The technology is based on a dosage form that expands
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in the stomach and cannot pass directly into the intestine. It slowly releases the medication and only breaks apart after the desired dosing period. The technology is being investigated for various disease states in addition to OUD. Preclinical analyses demonstrated the feasibility of weekly levomethadone dosing. Phase 1 and Phase 2 studies are being planned. Together with digital monitoring technologies, such a weekly levomethadone formulation could enhance treatment access and adherence and reduce the risk of diversion and stigma.

Dr. Linnstaedt presented findings on the evaluation of stress protein FKBP51 as a promising therapeutic target for the prevention of chronic posttraumatic pain. Individuals experiencing traumatic stress events often develop chronic pain. Data from both animals and humans indicate that FKBP51, which is part of the HPA axis stress response, plays a role in chronic pain development. In a single prolonged stress (SPS) animal model that causes enduring hyperalgesia, treatment with a FKBP51 inhibitor could prevent hyperalgesia. Treatment effect and duration depended on the timing of FKBP51 inhibition after SPS.

Dr. Patwardhan described research on spinal neurotensin receptor 2 as a non-opioid, clinically relevant target for pain management of chronic high-impact pain using intrathecal drug delivery. Current drugs are not suitable for intrathecal delivery but agents that target spinal neurotensin receptor 2, such as the cone snail venom peptide contulakin-G, may provide a solution. In preclinical models, contulakin-G specifically interacted with neurotensin receptor 2 and achieved analgesia without causing a motor block. Further analyses found that contulakin-G acted presynaptically and resulted in downstream inhibition of voltage-gated calcium channels. Clinical trials will start soon, but data to date show no side effects when applied at the spinal level and no rapid development of tolerance.

Plenary Session — Better Together—Collective HEALing Through Data Sharing

Facilitator: Jessica Mazerik, Ph.D., NIH HEAL Initiative; Kira Bradford, Ph.D., Renaissance Computing Institute (RENCI)

Presenters: Terry Jernigan, Ph.D., University of California San Diego; Ty Ridenour, Ph.D., Research Triangle Institute; Laura Wandner, Ph.D., NINDS; Andrea Tentner, Ph.D., M.P.H., University of Chicago; Robert Grossman, Ph.D., University of Chicago; Phil Schumm, M.A., University of Chicago

Dr. Jernigan shared experiences on data sharing from the Adolescent Brain Cognitive Development (ABCD) study, that follows 11,880 children ages 9 to 11 (and their caregivers) into young adulthood. The study aims to develop national standards for normal brain development and measure individual developmental trajectories, including the onset and progression of
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Mental disorders and the influence of substance use on outcomes. The study follows an open science model; it offers data access to qualified researchers who have to sign data use agreements. To date, 3,700 users from 32 countries have received ABCD data. In 2021, more than 140 publications were based on ABCD data, including more than half from outside investigators, and many of these studies analyzed scientific questions not directly included in the ABCD study, demonstrating the utility of data sharing.

Dr. Ridenour presented information on data harmonization of HEAL prevention outcome studies. The HEAL Prevention Initiative includes 10 research projects conducted in a variety of settings along the continuum from promotion through prevention and treatment to recovery, as well as a coordinating center. Data harmonization using prospective standardizing of measures, logical harmonization of items, and statistical harmonization through moderated non-linear factor analysis facilitates integrative data analysis across all studies. Additionally, substance use is determined using “anchor items” that are consistent across studies.

Dr. Wandner introduced the HEAL Pain Common Data Elements (CDE) program, which allows cross-study comparisons and access to meaningful data across pain conditions. A multi-step approach to identify and evaluate pain domains and pain questionnaires identified a set of core CDEs for each pain domain that all HEAL pain clinical trials must collect. CDEs were defined for adult and pediatric acute and chronic pain. Supplemental CDEs may be unique to specific studies or pain conditions. All core and supplement measures can be found on the NIH HEAL CDE Box account.

Dr. Tentner demonstrated the HEAL Initiative Study-level Metadata Model, which can help researchers identify studies of interest through the HEAL Platform. Metadata are available in 12 categories. They are provided by the investigators, but where available are imported from existing metadata sources (e.g., NIH RePORT) so that investigators only have to add supplemental metadata.

Dr. Grossman and Mr. Schumm described the evolution of data platforms up to the HEAL Data Ecosystem, in which the data strategy is to leverage various existing data repositories and leverage metadata to “connect” the data and allow central search, data access, and tools for compute and analysis through the HEAL Platform. They walked through a demonstration of the HEAL Platform functions, including searching for and identifying studies, launching workspaces, and creating data visualizations using notebooks and analytical tools.
**Discussion Group — Better Together: Collaborations in AI and HEAL Data**

**Facilitators:** Kira Bradford, Ph.D., RENCI; and Stan Ahalt, Ph.D., RENCI

**Discussants:** Chris Bizon, Ph.D., RENCI; Matthew Might, Ph.D., Harvard Medical School

The session provided an overview of the National Center for Advancing Translational Science Data Translator project and conducted a collaborative activity so that the attendees could learn about the Translator and its capabilities. The presenters mentioned that the Translator has tremendous potential to benefit translational science and, by extension, humanity. Many opportunities exist for groups like Translator and HEAL to work together. The Translator tool has a sensing mind map, actively mining the literature of many different biomedical datasets to build an enormous graph of biomedical knowledge. It also combines with powerful automated reasoning systems so that disparate parts of this biomedical graph can work together. The presenters demonstrated how it can be applied for science and the service of individual patients as part of precision medicine. The attendees participated in a data exercise by suggesting interesting and unsolved scientific research questions, voting on the questions, which led to a discussion on identifying data sets that could help answer questions. HEAL would also like to reach out to this group to spin off a future codeathon, with an anticipated kick-off in the summer.

**Discussion Group — Building the Translational Research Pipeline: Pain Pathways and Biology**

**Facilitators:** Michael Oshinsky, Ph.D., NINDS; Miriam Goodman, Ph.D., Stanford University

**Discussants:** Kip Ludwig, Ph.D, University of Wisconsin-Madison; Fan Wang, Ph.D., Massachusetts Institute of Technology

Dr. Ludwig discussed the development of implantable devices for pain treatment. Implantable devices (e.g., spinal cord stimulators) are complex and often associated with pain. They developed an injectable device that is injected on a deep nerve but can be pulled to the surface to be stimulated noninvasively and can be removed easily. It has been tested in dorsal root ganglia of pigs as well as in 10 patients.

Dr. Wang reported on efforts to develop pain medications to be used during operations but without loss of consciousness as occurs with general analgesia. They identified certain cell groups in the central amygdala that are activated during general anesthesia. Experimental activation of these cells in animal models stopped pain behaviors. They are investigating whether conditioning (pairing activation of these cells with a certain context) can lead to placebo analgesia by exposure to the context/stimulus alone, without requiring experimental activation of the cells.
Discussion: Attendees inquired about more specific details for both models that had been presented. Particular interest was expressed in the types of cells found in the central amygdala that mediate pain responses and how they can be activated; there seem to be different cell types that work together.

Discussion Group — Making Treatments More Specific and Effective Through Phenotyping and Biomarkers

Facilitators: Aron Marquitz, Ph.D., National Institute of Arthritis and Musculoskeletal and Skin Diseases; William Marras, Ph.D., Ohio State University

Discussants: Alan Prossin, M.D., McGovern Medical School at UT Health; Laura Simons, Ph.D., Stanford University; Christin Veasley, Chronic Pain Research Alliance

One of the goals of the HEAL BACPAC research program is to use patient-specific phenotyping to better understand and personalize treatment for patients with chronic low back pain. BACPAC will start the national Biomarkers for the Evaluation of Spine Treatments (BEST) trial that assesses treatment efficacy as well as many potential biomarkers and traits to determine which may best predict treatment success. Also, phenotyping using standard assessments of certain movements are hoped to greatly increase pain prediction in the future.

Dr. Prossin introduced a study to assess the levels of various proteins and cytokines (e.g., IL-1) in the blood to predict pain in patients scheduled for surgery. Before the surgery, they are measuring inflammatory protein levels as well as response to a pain challenge with and without pretreatment with the IL-1 receptor antagonist anakinra. They are then evaluating the patient’s pain experience at two time points after surgery. Initial results indicate that anakinra pretreatment can reduce pain experience during the pain challenge.

Dr. Simons reported on a study of biological signatures as predictors of recovery or persistence in pediatric pain, where the complexity of factors influencing pain experiences is exacerbated by the ongoing brain development. A significant portion of youth with chronic pain did not respond to intensive treatment, particularly among teens. They are now phenotyping youth based on neuroimaging, self-report, sensory profiles, and immune profiles to develop a predictive model and be able to tailor treatment.

Ms. Veasley noted that for patients with chronic pain, the most frustrating part is that despite all the research, data are still lacking to make informed clinical decisions on what therapies should be used in which combination or which order for a given patient.
**Discussion:** What are next steps of these projects to translate them into meaningful clinical information? Only some parts of the assessments being used in studies are suitable for translating into the clinic; it is important to find the markers that are cost-effective and can be used as proxies to guide interventions. The studies may also identify new targets for non-opioid interventions as well as guide preventive interventions to minimize pain during and after surgeries to reduce the need for opioids. When developing predictive models, it is important to include a variety of indicators, but not too many factors to overload the system. There are opportunities to use phenotyping data across different diseases, conditions, and age groups, but also challenges for data integration. From a patient perspective, it is also important to consider how chronic pain conditions interact with other chronic conditions; a systems biology approach is needed.

**Discussion Group — Disparities and Social Determinants of Health**

**Facilitators:** Aria Crump, Sc.D., NIDA; Cheryse Sankar, Ph.D., NINDS; Daniel Dickerson, D.O., M.P.H., University of California Los Angeles

**Discussants:** Uchenna Umeh, M.D., NYU Langone Health; Natasha Slesnick, Ph.D., Ohio State University; Philip Rutherford, Faces & Voices of Recovery; Stephanie Smith, person with lived experience

The focus on social determinants is extremely timely and urgent given the ongoing opioid crisis, growing awareness of racial injustices in the United States, and the ongoing COVID national emergency. Social determinants of health (SDOH) lead to health disparities through systematic, direct, and indirect effects on the development and progression of disease as well as access to health promotion, prevention, and treatment resources. More research is needed to understand the roles of various SDOH, but community trust, buy-in, and engagement are needed for these studies.

Dr. Umeh presented the Postsurgical Pain After Mastectomy study, that will study racial and socioeconomic barriers to understanding and treating postmastectomy pain syndrome. Studies have suggested that socio-demographic factors such as race (especially African American), ethnicity, and neighborhood disadvantage are risk factors for this syndrome. The study, expected to start in May 2022, will conduct questionnaires at baseline and 3 months after mastectomy to eligible patients.

Dr. Slesnick reported on a supplement to the Housing, Opportunities, Motivation, and Engagement prevention study, which will assess disparities and SDOH among youth experiencing homelessness. This population, which includes a high proportion of Black youth
and sexual/gender minorities, has significantly higher rates of substance use, physical and mental health problems, and mortality but rarely access available services. The study will assess service utilization and discriminatory experiences.

**Discussion:** Building relationships is needed to overcome the challenges of mistrust, recruitment, and retention. Such measures include representation, peer engagement, and people with lived experience on the study team; advisory boards that includes community members; cultural adaptation; lack of judgement; boots on the ground to meet patients where they are; and sharing research findings back with the community.

**Discussion Group — Helping Individuals with Polysubstance Use and Fentanyl Use: Challenges and Promising Approaches**

**Facilitators:** Geetha Subramaniam, M.D., NIDA; David Fiellin, M.D., Yale University

**Discussants:** Jennifer McKeely, M.D., M.S., NYU Grossman School of Medicine; Kathryn Hawk, M.D., M.H.S., Yale School of Medicine; Kayla Zawislak, M.S.W., Addiction Policy Forum

Among people entering OUD treatment, almost all have also used at least one non-opioid drug. Many drugs target the same brain pathways, and people often use more than one drug for their additive, synergistic, and sometimes complementary effects. However, many questions remain regarding polysubstance use, its causes, consequences, and treatment, as well as the challenges associated with rising prevalence of fentanyl and other new drugs.

Dr. McKeely presented steps toward identifying and addressing polysubstance use in medical settings such as primary care and hospitals. The U.S. Preventive Services Task Force recommends screening adults for alcohol and drugs. Several simple universal screening tools are available, including the new Tobacco, Alcohol, Prescription medication, and other Substance use tool. Identification and treatment of polysubstance use, particularly subthreshold SUD, is difficult but can be achieved with collaborative care models.

Dr. Hawk reported on the prevalence of polysubstance and fentanyl use in patients visiting EDs across the United States. The ED-INNOVATION study analyzed urine samples from patients with OUD for presence of other drugs and categorized findings by region (East vs. West). Variability between sites existed in the prevalence of polydrug use, and East-West differences existed in the prevalence of specific drug combinations. Also, ED visits for OUD and overdose increased during the early stages of the COVID-19 pandemic.

Ms. Zawislak presented patient perspectives on polysubstance use based on the Addiction Policy Forum’s patient journey map. One-third of interviewed individuals reported
polysubstance use disorder, and 98% reported using multiple substances during active addiction. Patients faced numerous barriers to accessing treatment and on average utilized four different services for treatment and recovery.

**Discussion:** Given fentanyl’s long reported half-life after chronic use, how does that affect induction of treatment with buprenorphine? In the ED-INNOVATION study, there have only been a few cases of precipitated withdrawal; for patients with COWS ≤12, and 8 mg dose of buprenorphine was used (4 mg + 4 mg), and if withdrawal did occur, it resolved with observation and required no hospitalization.

**Federal Roundtable: How can Science Inform the Federal Response to the Opioid Crisis?**

**Facilitator:** Dr. Tabak

**Discussants:** Robert Califf, M.D., Commissioner of Food and Drugs, FDA; Miriam Delphin-Rittmon, Ph.D., Assistant Secretary for Mental Health and Substance Use, SAMHSA; Debra Houry, M.D., M.P.H., Acting Principal Deputy Director, CDC

Researchers have generated a lot of data on the causes, prevention, and treatment of SUD and chronic pain, but it is the federal partners that transform these findings into policies and guidelines for treatment. Therefore, the NIH HEAL Initiative is committed to working together with those federal agencies, including CDC, FDA, and SAMHSA.

Dr. Houry described how CDC works with other agencies to prevent overdoses and link people with OUD to treatment. Specific activities included allowing federal funding to be used for fentanyl test strips, participation in the development of the HHS Overdose Prevention Strategy, development of a harm reduction guide, measures to combat stigma, and education campaigns for young adults. Houry noted that improved collection of real-time data is needed. CDC is currently in the process of updating the 2016 opioid prescribing guidelines for treating chronic pain, with the new guidelines expected to be released in late 2022. Finally, CDC is promoting prevention efforts such as the Drug-Free Communities program with more than 700 community coalitions. A holistic approach is needed to address the escalating overdose crisis.

Dr. Califf noted that for bridging the gap between research and clinical practice, there is still a great need for reliable evidence obtained with quality measures that certain interventions lead to better outcomes. In terms of pain management, it is also important to distinguish between acute and chronic pain. Also, the best solution to addressing the opioid crisis is to prevent opioid use. This requires development of non-addictive pain medications; prescriber education about appropriate opioid prescribing for those patients who need these medications; and development of processes to deal with unused prescription opioids to prevent diversion. Also
needed is research into the workings of the illicit drug trade, how teenagers can order medications over the internet that are often contaminated with fentanyl, and the economics of the drug trade. Harm reduction approaches need to be evaluated and roadblocks removed, as well as practical clinical trials conducted for evaluating recovery support measures.

According to Dr. Delphin-Rittmon, SAMHSA’s priority is to prevent overdoses through the new Overdose Prevention Strategy that focuses on prevention, harm reduction, treatment, and recovery support as well as ensuring health equity. Policy changes have been implemented to that end (fentanyl test strips and exemptions for buprenorphine X-waivers to allow more physicians to prescribe buprenorphine). SAHMSA is also offering new harm reduction grant opportunities over the next 3 years to support efforts at the community level. Their evidence-based practices resource center provides accessible, reliable, and valid information to states, communities, nonprofit organizations, and other entities. They have also announced an “Office of Recovery” to ensure that recovery is a guiding principle in their efforts.

Discussion: There is a substantial increase in overdose deaths in teenagers—more studies are needed to assess drug use in adolescents. This also includes studies of the role of adverse childhood experiences and their role in drug use risk. Particularly important are interventions in schools, which includes training and education of teachers and other staff to recognize students who are struggling, as well as attention to the intersection between drug use and mental health problems.

Update of the CDC 2016 opioid prescribing guidelines includes broadening the focus beyond chronic pain, looking at different settings, and including information on opioid tapering and discontinuation.

Given the problem of stigmatization of OUD treatment, should alternative measures to provide these prescriptions be taken? This is a difficult issue, and more quality evidence is needed to determine which alternatives are most likely to work and to overcome objections. Stigma is generally an issue, including stigma associated with MOUD, and more research is needed in that field as well.

Closing Remarks

Dr. Tabak and Dr. Baker

At the end of the meeting, Dr. Tabak noted that the meeting had shown that even with the ongoing pandemic, the HEAL research community continued to meet the moment and show remarkable resourcefulness. Other important achievements over the past year that were
highlighted throughout the meeting included meaningful participation of individuals with lived experience; a focus on a more integrative and collaborative approach to HEAL research, and patient engagement.

Dr. Baker summarized the key themes that had emerged during the meeting. She also referred to new funding opportunities that will be published soon and will be available via the NIH HEAL Initiative website. In addition, there will be a few new research directions in 2023, such as a focus on rural communities, medications in diverse groups, social determinants of health, and a focus on data-driven research. The opioid epidemic keeps evolving with new drugs emerging and new populations being more strongly affected, bringing with it new challenges and needs.