

**Second Annual National Institutes of Health (NIH)  
Helping to End Addiction Long-term<sup>SM</sup> Initiative  
Investigator Meeting  
May 17-19, 2021  
Meeting Summary**

The Helping to End Addiction Long-term<sup>SM</sup> Initiative, or NIH HEAL Initiative<sup>SM</sup>, 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 Second Annual NIH HEAL Initiative Investigator Meeting was held May 17-19, 2021. 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:

- Highlight cutting-edge findings from NIH HEAL Initiative-funded projects.
- Build connections among HEAL Initiative investigators to strengthen research efforts.
- Identify shared opportunities to advance the goals of the initiative.

**May 17**

**Welcome and Introductory Remarks**

Rebecca Baker, Ph.D., Director, NIH HEAL Initiative, welcomed HEAL investigators and attendees. While HEAL studies are spread across the country and multiple scientific disciplines, all are united by their dedication to a future with access to safe, effective, and non-addictive methods to manage pain and the treatment and long-lasting recovery from opioid use disorder (OUD) and addiction. The 3-day meeting focused on adversities brought on by the COVID-19 pandemic, especially social isolation and the difficulties posed to research deployed in health care settings, and discussed methods to cultivate resilience and emotional wellbeing.

Francis Collins, M.D., Ph.D., Director, NIH, highlighted the need for the full weight of investigators' collective efforts to address the national pain and opioid public health crises, amid research challenges and pauses in data collection brought on by the pandemic. While many research endeavors were paused or altered, the need for opioid and pain-related research has increased. Resourceful and agile adjustments made by investigators have demonstrated the resilience and ingenuity of the HEAL community, while still making impressive research progress. For example, by leveraging telehealth services, investigators have expanded access to care, adapted pain treatment interventions, and developed innovative methods for engaging, recruiting, and retaining patients. Over the past 16 months, HEAL investigators have defined new targets and therapeutics for different types of pain, including neuropathic, post-surgical osteoarthritis, and pain induced by chemotherapy. Additionally, the first-in-human vaccine trials to protect against the harmful effects of opioids have been launched, with further progress toward the development of other vaccines and monoclonal antibodies against fentanyl and other opioids. HEAL is also designing culturally tailored interventions, particularly for traditionally underserved populations, such as American Indian and Alaska Native populations. Investigations will continue to address social inequities, such as housing insecurity or a lack of preventative health care services and their impact on addiction and opioid use.

### **Emotional Wellbeing and the Power of Connections to Fight the Opioid Epidemic**

Dr. Collins joined U.S. Surgeon General Vivek Murthy, M.D., to speak about the impact of loneliness, chronic stress, and isolation on health, productivity, and happiness. This [discussion](#) spoke to the need to appreciate the role of social connections within the context of research and care. Chronic stress, isolation, and loneliness are factors that can compound addiction and profoundly affect health, productivity, and happiness. Loneliness, a public health issue, increases an individual's risk of anxiety, depression, dementia, premature death, cardiac disease, and several other conditions. The pandemic has brought on additional stress, and mitigation efforts have increased isolation for many individuals. Apart from this additional stress, the pandemic has also provided new opportunities to investigate how loneliness and isolation affect resilience. Building a society centered around human connection and relationships can be a means toward resilience. The conversation also visited social supports as a broader cultural need that includes eliminating the stigma associated with addiction and substance use disorder (SUD). A shift toward positive recognition and sufficient reimbursement for physicians who show compassion and spend the necessary time to help patients will likely help to dismantle stigma.

### **The NIH HEAL Initiative and Meeting Overview**

Dr. Baker reminded attendees of the importance of the NIH HEAL Initiative in the face of a rapidly evolving public health emergency of opioid misuse, addiction, and overdoses. The COVID-19 pandemic led to increases in opioid misuse and overdose deaths and intensified contributors to pain and addiction. During the 12-month period between October 2019 and October 2020, nearly 89,000 Americans died from drug overdoses, the majority of which were associated with opioids. Solutions should focus not only on individuals with SUD but also on the millions of Americans in pain. HEAL has funded more than 500 research projects that intentionally build teams, form scientific partnerships with communities, and emphasize care settings with the greatest potential to help others.

The NIH HEAL Initiative has two overarching goals—enhancing pain management and improving prevention and treatment strategies for opioid misuse and addiction spread across [six research focus areas](#). Significant progress is apparent. For example, there are now two patents for small molecule modulators of pain receptors; 16 investigational new drug applications have been filed with the U.S. Food and Drug Administration (FDA); improvements have been implemented in the prescription opioid registry, communications campaigns have been launched to reduce the stigma of OUD, and enrollment in the Advanced Clinical Trials in Neonatal Opioid Withdrawal (ACT NOW) has begun. The [2021 NIH HEAL Initiative Annual Report: Research in Action](#), details this progress.

### **Plenary: Helping to End Addiction Long-term—NIH Trends and Perspectives**

Nora Volkow, M.D., Director, National Institute on Drug Abuse (NIDA); Walter Koroshetz, M.D., Director, National Institute of Neurological Disorders and Stroke (NINDS)

### **Emerging Issues in the Opioid Crisis: Collisions of COVID-19 on Overdose and Treatment**

Dr. Volkow described a shift over the last 6 years in the main drivers, geographic locations, and racial distribution of overdose deaths, which now more frequently involve stimulants, focused in urban and suburban centers, and show the highest increases among American Indians. In addition, individuals with SUD are more vulnerable to severe COVID-19 infection, and social factors also decrease the likelihood that those with SUDs will seek medical treatment, leading to worse outcomes. Data from 2019 and 2020 show an increase in substance use and overdose deaths in both years, with a dramatic rise in fentanyl use immediately after emergency pandemic-related mitigation strategies were imposed in early 2020.

Dr. Volkow described a need for researchers to design randomized clinical trials that treat multiple facets of pain, particularly for individuals with exposure to polysubstance use.

## The Intersection of Pain and Addiction

Dr. Koroshetz focused on the intersection of pain management and opioid misuse. He noted research challenges, including (1) how to best prescribe opioids to patients at a higher risk of misusing them (e.g., use of other substances, previous or familial history with a SUD), and (2) how to best treat patients with both pain and OUD. Chronic pain is frequently part of a web of disorders contributing to complex treatment. Future work should investigate targets associated with the intertwined connection between reward and pain signals in the brain. Researchers should also address the patient burdens that stem from the many affective dimensions of pain.

## Discussion

Patient populations are complex. Polysubstance use and comorbidities that lead to high relapse rates are common. Dr. Volkow suggested that treatment retention could be improved by treating comorbid conditions. HEAL investigators should aim for models of care that are sustainable, accessible, and designed for patients with comorbidities. Dr. Koroshetz added that increasing knowledge among primary care providers about patients experiencing pain can help reduce the risk of OUD. Some patients may be both at a higher risk for OUD and reluctant to take opioids for their pain and will thus need alternative treatments. Physicians should also be ready to perform additional follow-up and provide support to patients at higher risk, and explain that it is possible to be quickly weaned off a medication. In the wake of COVID-19, the scientific community has the potential to make great progress on resolving the opioid epidemic through bold and collective efforts.

## Plenary Panel Discussion: Empowering Discovery and Collaboration: The HEAL Data Ecosystem

**Facilitator:** Jessica Mazerick, Ph.D., NIH HEAL Initiative

**Panelists:** Robert Grossman, Ph.D., University of Chicago; Phil Schumm, University of Chicago; Stanley Ahalt, Ph.D., Renaissance Computing Institute at the University of North Carolina at Chapel Hill (RENCI); Kira Bradford, Ph.D., RENC I

The [HEAL Data Ecosystem](#) encompasses the HEAL Data Platform and HEAL Data Stewards for data-management support. Through this ecosystem, HEAL intends to integrate its data into the broader NIH data ecosystem by ensuring all HEAL data is modernized and FAIR (Findable, Accessible, Interoperable, Reusable) to ensure access to HEAL data by multiple stakeholders and to maintain digital assets beyond single program awards. Scientists at the University of Chicago are currently building the HEAL Data Platform. Launching in July 2021, the platform will enable access to FAIR data with intuitive search features and the ability to analyze study data within a secure workspace. Investigators can begin registering their data in the HEAL Data Platform immediately. Metadata and data are first uploaded to an NIH-approved repository and then become searchable and requestable through a user-friendly interface and ready to analyze with tools like RStudio and Jupyter. Investigators are invited to join the [HEAL Ecosystem Slack workspace](#) to stay up to date with developments. The HEAL Data Stewards (RENCI and Research Triangle Institute) will enable data harmonization, data collection, and data sharing within a federated data ecosystem. With the expansion of FAIR data, databases will become publishable and thus provide researchers publication credit and an additional incentive to share data. Attendees may express any data needs via [HEAL Stewards Connect](#).

## Discussion

Sharing FAIR data supports broader community access to HEAL datasets, increases opportunities to reproduce studies, and creates more opportunities for students to learn and conduct their own research. Further, sharing analysis-ready datasets that do not need cleaning or harmonization can help

to reduce the misinterpretation of data and provide a bridge to increase reproducibility efforts. Though many researchers are already comfortable with modern data-sharing practices, those who may be reluctant to share proprietary data, such as intellectual property-protected data, are encouraged to work with the HEAL Data Stewards.

### **Scientific Symposia: Advancing Research in Opioid Misuse and Pain**

**Moderators:** Helene Langevin, M.D., Director, National Center for Complementary and Integrative Health (NCCIH); Donald Penzien, Ph.D., Wake Forest University

**Panelists:** Anna C. Wilson, Ph.D., Oregon Health & Science University; Jeffrey Samet, M.D., M.P.H., Boston Medical Center; Gail D'Onofrio, M.D., Yale University; Ajay Wasan, M.D., University of Pittsburgh; Sindhu Srinivas, M.D., University of Pennsylvania

### **ROAM: Risk for Opioid Abuse and Misuse in Adolescents**

Dr. Wilson described a study investigating young adults who are prescribed opioids for acute pain management that seeks to identify psychological risk factors for chronic pain, risk factors for opioid use, and potential intervention targets for high-risk patients. Dr. Wilson found a persistent over-prescription of opioids and associations between cannabis and opioid use, which was associated with higher levels of depression, anxiety, anger, and pain catastrophizing.

### **Improving Opioid Addiction Treatment in Real-World Settings**

The HEALing Communities Study (HCS) intends to reduce overdose deaths across 67 communities in four states by 40 percent in 3 years. This integrated approach to addressing opioid misuse, addiction, and overdoses relies on close partnerships between HEAL investigators, community coalitions, and state officials. Although COVID-19 has posed many challenges, it has broadened the acceptance and use of telemedicine, which can also be used to treat OUD. Throughout the different communities, communications campaigns were disseminated to increase community knowledge of treatment options. A special issue of [Drug and Alcohol Dependence](#) outlines the HCS, goals, and progress to date.

### **Emergency Department-Initiated Buprenorphine Validation Network Trial (ED-INNOVATION)**

Dr. D'Onofrio noted several logistical barriers inhibiting the progress of this research, including a decrease in emergency department (ED) visits during the height of the pandemic that significantly reduced the number of patients who could participate in this research. The hybrid effectiveness-implementation design study on ED patients with untreated OUD will assess the utility of an extended-release version of buprenorphine (XR-BUP), including on patients with minimal or no withdrawal symptoms. This research seeks to develop and validate emergency health record opioid-related phenotypes, which can be used to automatically characterize opioid-related illnesses.

### **Phase II Proof of Concept Study to Treat Negative Affect in Chronic Low Back Pain**

Dr. Wasan described how negative affect (i.e., negative thoughts, emotions, and behaviors) can lead to pain catastrophizing, which may exacerbate pain perception, depression, and physical disability. Dr. Wasan's study investigates the effectiveness of a combination therapy including antidepressant medication and enhanced fear-avoidance physical therapy, as well as each component on its own, toward improving pain, self-assessed physical function, depression, and anxiety.

### **Prescription After Cesarean Trial (PACT)**

A cesarean is the most commonly performed major surgical procedure in the United States, and most new mothers are prescribed opioids following the procedure. Using a patient-centered approach, HEAL research aims to evaluate whether an individualized opioid prescription protocol that includes shared

decision-making is better (non-inferior) to a fixed opioid prescription of oxycodone. The protocol was delayed for 6 months and modified to account for early discharge for mothers during COVID-19, transitions from in-person to telehealth postpartum visits, and the inclusion of COVID-19 test results but still reached 50 percent enrollment.

### Discussion

Dr. Wasan clarified that generic antidepressants—most frequently a serotonin-norepinephrine reuptake inhibitor—are used within research on negative affect. He added that the combination of antidepressants and fear avoidance physical therapy should be highly applicable across multiple pain conditions. Dr. Srinivas' research could be improved by reductions in reporting lag time to the prescription drug monitoring programs (PDMPs). Improved PDMP accuracy would allow more accurate monitoring of patient prescription use. Standardized education for patients being discharged from the hospital, including opioid epidemic education, could help hospitals that discharge a high volume of new mothers. Dr. Samet clarified that HCS had an explicit understanding with participating sites that addiction has been greatly impacted by structural racism and high incarceration rates. Individuals released from incarceration are connected to care to help avoid release-related overdoses.

Dr. D'Onofrio noted that the broad geographic range of ED-INNOVATION was designed to include sites from diverse areas and was supported by a network of researchers linked by common interests.

### May 18

#### Plenary Panel Discussion: Engaging Communities for Action

**Moderator:** Walter Koroshetz, M.D., Director, NINDS

**Speakers:** Jennifer Reynolds, M.P.H., Oak Ridge Associated Universities; Philip Rutherford, Faces and Voices of Recovery

Dr. Koroshetz explained that including individuals with lived experiences will increase the effectiveness of research outcomes. NIH has published a [Notice of Special Interest](#) through the HEAL Initiative to help researchers enhance the diversity and inclusion of their clinical trials.

- As part of the HCS, Ms. Reynolds is working with multiple institutions to engage individuals and communities in reducing the stigma of OUD and to develop communications campaigns to increase demand for evidence-based strategies. Successful communications campaigns will be informed by data and local community knowledge, avoid any stigmatizing language, and focus on the positive impacts that accompany evidence-based intervention uptake.
- Mr. Rutherford described community engagement, paths to and definitions of recovery, and how each varies across communities. Recovery Community Centers (RCCs) and Recovery Community Organizations (RCOs) now take full advantage of data collection to help promote recovery services. Many communities consider survival just a first step in successful addiction treatment.

### Discussion

Sustainability planning facilitated by community partnerships (especially for small organizations like RCOs) will help ensure that research progress and communications campaigns can continue over the long term. Many communities lack the financial support and large-scale infrastructure to continue to support the community engagement dimension of clinical research.

**Plenary Panel Discussion: Advancing Health Equity and Inclusion Through HEAL Research**

**Moderator:** Monica Webb Hooper, Ph.D., Deputy Director, National Institute on Minority Health and Health Disparities

**Speakers:** Nabila El-Bassel, Ph.D., Columbia University; Emily Wang, M.D., Yale University

ODD research and interventions that emphasize health equity are critical because opioid-related death patterns mirror other racial and socioeconomic disparities, including graduation rates, infant mortality, poverty, incarceration, unemployment, homeownership, and suicide.

- Dr. El-Bassel shared implementation strategies within the HCS to help achieve health equity and inclusion. Achieving health equity requires addressing stigma, discrimination, racism, and their collective consequences. To guide its health equity mission, HCS relies on the principles of community-based participatory research.
- Dr. Wang described the linkages between health and incarceration along with the inequities that occur within the criminal justice system. He described barriers to ODD treatment after release from correctional facilities, adding that including and hiring individuals with lived experiences of incarceration in governance and health research is a successful method to overcome these barriers.

**Discussion**

Dr. Wang shared methods to recruit formerly incarcerated individuals through institutionalized pathways (e.g., established pipelines like “Prison to Ph.D.”). Dr. El-Bassel noted the significant challenge of a lack of data on race and ethnicity. Integrating voices of individuals of color and making all individuals participating in HEAL-centered coalitions feel safe while sharing their experiences will advance health equity.

**Plenary Panel: Perspectives on Community Engaged Research**

**Moderators;** Rena D’Souza, D.D.S., Ph.D., Director, National Institute of Dental and Craniofacial Research; Jessica Robinson-Papp, M.D., Icahn School of Medicine at Mount Sinai

**Speakers:** Richard Schottenfeld, M.D., Howard University; Jessica Hulseley Nickel, Addiction Policy Forum; Megan Irby, Ph.D., Wake Forest University; Dawn Edwards, Patient Advocate; Ardith Doorenbos, Ph.D., R.N., University of Illinois at Chicago

Dr. D’Souza opened the panel by articulating challenges related to COVID-19 and noting that dental pain remains one of the most complicated and difficult types of pain to resolve.

- Dr. Schottenfeld addressed the local problem of overdose deaths within the District of Columbia, with the highest rates among Black males, particularly within racially segregated and medically underserved communities where medications for opioid use disorder (MOUD) remain underused. Input from Community Advisory Boards highlights a need for solutions to focus on strengthening communities (e.g., by addressing social determinants of health) rather than only increasing medication uptake.
- Ms. Hulseley described strategies for successfully engaging patients and families/caregivers in research by engaging with them from the outset, clearly describing desired outcomes and timelines, translating and simplifying engagement discussions, and disseminating findings through common media, ensuring there are guardrails to keep participants safe and stable, and ensuring participants have resources and supports available.



- Dr. Irby described ongoing research within the Internet-Delivered Management of Pain Among Cancer Treatment Survivors (IMPACTS), which relies heavily on qualitative interviews to determine whether pain coping skills training can yield a significant improvement in pain severity and interference in cancer patients with persistent pain. She noted the importance of community engagement in research.
- Patient advocate Ms. Edwards described her personal involvement in HEAL research through the patient-centered Hemodialysis Opioid Prescription Effort (HOPE) study. She highlighted that patient engagement allows non-scientists to contribute to the future of research.
- Dr. Doorenbos described the human-centered Guided Relaxation and Acupuncture for Chronic Sickle Cell Disease Pain (GRACE) trial and shared its practices surrounding implementation, recruitment, retention, and dissemination of results.

## Discussion

Dr. Robinson-Papp opened the floor for audience questions about continuing community engagement beyond study completion. Ms. Edwards noted that she would like to continue to help with other research studies beyond the HOPE study and pointed to the need to share study results in layman's terms as well as through traditional journals so that both the general public and other researchers can see the benefits of patient-centered research and increase its prevalence.

## Hot Science Lunch Q&A

### Health Disparities

**Moderators:** Nick Zaller, Ph.D., University of Arkansas for Medical Services; Jane Atkinson, M.D., National Center for Advancing Translational Science (NCATS)

**Speakers:** John Schneider, M.D., M.P.H., University of Chicago; Ryan McCormack, M.D., New York University; Leslie Boone, M.P.H., Vanderbilt University

Moderators presented a set of questions about engaging with underrepresented communities, recruiting participants, training a diverse set of research study members, and achieving health equity for patients with SUD and chronic pain. The majority of health disparities are structurally based, and telehealth can be used to help overcome some of these barriers, particularly for rural communities and those at high risk for COVID-19. Panelists noted the importance of building trust with individual researchers and building bridges to communities.

### Emerging Trends: Polysubstance Abuse

**Moderators:** Geetha Subramaniam, M.D., NIDA; Christian Heidbreder, Ph.D., Indivior Inc.

**Speakers:** Madhukar Trivedi, M.D., University of Texas Southwestern Medical Center; Stephen Higgins, Ph.D., University of Vermont; Lisa Marsch, Ph.D., Dartmouth College

This session addressed the complex nature of polysubstance use and its prevalence among fatal opioid overdoses. There are now several opportunities to broaden clinical endpoints to help address the challenges of new synthetic opioids that have increased in prevalence during the COVID-19 pandemic. Research opportunities include medication combinations, psychosocial interventions (e.g., contingency management), digital therapeutics, and digital data capture (e.g., wearables that complement clinical understanding by collecting non-physical health status metrics, such as mood and cravings).

### **Psychosocial and Behavioral Interventions in HEAL Studies**

**Moderator:** Dave Clark, Dr.P.H., NCCIH

**Speakers:** Suzette Glasner, Ph.D., University of California, Los Angeles; Jennifer Rabbitts, M.D., Seattle Children's Hospital; Julie Fritz, Ph.D., University of Utah

Panelists described the importance and limitations of adapting interventions to remote delivery to address the impact of COVID-19 and to leverage the significantly increased uptake of digital health apps on the market, which could enable implementation research.

### **Innovative Approaches to Engage Diverse Patient Populations**

**Moderators:** Michele Staton, Ph.D., University of Kentucky; Petra Jacobs, M.D., NIDA

**Speakers:** Yulin Hswen, Sc.D., University of California, San Francisco; Ludmila Bakhireva, M.D., Ph.D., University of New Mexico

Engaging diverse communities can improve public health, promote innovative thinking, and bring the desires of more diverse communities to the forefront. Panelists described strategies to successfully recruit Black, Indigenous, and other people of color. Investigators must understand the history of medical racism, identify reasons for lack of trust, learn about the community prior to a study, and create an advisory board of active community members.

### **Therapeutics Development in Pain and Addiction Research**

**Moderators:** Jessica Robinson-Papp, M.D., Icahn School of Medicine at Mount Sinai; Ivan Montoya, M.D., M.P.H., NIDA

**Speakers:** Adam Bisaga, M.D., Columbia University Medical Center; Yasmin Hurd, Ph.D., Icahn School of Medicine at Mount Sinai; Richard Traub, Ph.D., University of Maryland, Baltimore

Finding treatments for polysubstance misuse is critical, and early-phase drug development is now beginning in animal models, but it is complicated by FDA requirements for specific and pointed clinical endpoints. Patient input is also key, and additional efforts (including surveys) are underway to better understand what areas patients find most critical for pain research.

### **Public Health Policy Considerations**

**Moderators:** Karen Derefinko, Ph.D., University of Tennessee Health Science Center; Emily Einstein, Ph.D., NIDA

**Speakers:** Pilar Ossorio, J.D., Ph.D., University of Wisconsin; Kara Zivin, Ph.D., University of Michigan

Dr. Derefinko invited participants to explore issues and concerns related to the dissemination of HEAL-funded research findings into communities. Dr. Ossorio noted that while policies and laws related to prenatal exposure to substance use (which are increasing in number) intend to protect infant outcomes, those that require SUD reporting decrease treatment seeking among birthing parents.

### **Early Investigator Data Blitz**

Dr. Baker introduced eight exceptional early-career scientists who gave brief presentations on their HEAL research.

- Bridget Mueller, Ph.D., Icahn School of Medicine at Mount Sinai, found that Medicaid-insured pain patients were less likely to engage in video visits and that Black and Hispanic patients



were more likely to access care over the phone during shutdowns and more likely to take advantage of in-person care once it became available.

- Ellen Goldstein, Ph.D., University of Wisconsin, has found that among pregnant women with SUD, barriers to research recruitment and retention include invasive sampling, inconvenience, pregnancy loss, and multiple shifts in caregivers. Building relationships that foster trust and confidence, and understanding cultural norms and values, can improve outcomes for these women.
- Carla Freire, Ph.D., Johns Hopkins University, found that intranasal leptin can be used to prevent opioid-related respiratory depression and deaths in acute and chronic opioid users, and identified leptin resistance in some obese individuals.
- Michael Raleigh, Ph.D., University of Minnesota, described his work on heroin and oxycodone vaccines, as well as a multivalent vaccine against the two opioids.
- Juliana Navia Pelaez, Ph.D., University of California, San Diego, described her research on how the normalization of cholesterol metabolism in spinal microglia can alleviate chemotherapy-induced peripheral neuropathy via apoA-I binding protein targets.
- Mary Kleinman, M.P.H., is examining the effects of stigma related to SUD and methadone maintenance treatments on OUD treatment outcomes via a mixed-methods study design.
- Augustine Kang, Ph.D., Brown University, explained that racial disparities in MOUD treatment for incarcerated individuals in Rhode Island were significantly higher prior to the expansion of access to MOUD.
- Laura Brandt, Ph.D., Columbia University Irving Medical Center, shared a protocol for software tool development and validation to produce clinically meaningful outcomes in OUD clinical trials.

## Cross-Cutting Discussion Sessions

### Early Investigator Discussion Room

**Moderator:** Christine Colvis, Ph.D., NCATS

The acceptance and use of pandemic-driven virtual platforms enabled more researchers to attend conferences and virtually network and connect with researchers in a variety of disciplines. As the NIH HEAL Initiative moves forward, participants emphasized the importance of providing additional funding for international researchers and opportunities for junior investigators to build connections with senior investigators through a mentoring program.

### HEAL Data Ecosystem

**Moderators:** Robert Grossman, Ph.D., University of Chicago; Stanley Ahalt, Ph.D., University of North Carolina-Chapel Hill

The HEAL Data Ecosystem presents an opportunity for investigators (particularly early-career investigators) to generate hypotheses and acquire access to larger datasets to conduct secondary analyses. The platform may be used to enable precision medicine approaches, discover specific clinical characteristics that best predict treatment outcomes, and find potential collaborators. Potential improvements include a messaging system within the platform to facilitate discussions between investigators and a data dictionary that links metadata provided by all participating HEAL investigators.

### **Artificial Intelligence and Machine Learning**

**Moderator:** Laura Biven, Ph.D., NIH Office of Data Science Strategy

Both artificial intelligence (AI) and machine learning (ML) methods can contribute to OUD treatment via mobile apps and primary care provider portals. For example, AI technologies can analyze patient communications and help to identify whether interventions are needed. AI/ML methods could also be employed to (1) help understand complex patients with comorbidities, (2) phenotype pain in SUD patients, (3) discover factors that lead to poor outcomes, (4) increase diversity and inclusion, and (5) close gaps between advancements in human and animal models.

### **Translational Research Pipeline**

**Moderators:** Ivan Montoya, M.D., NIDA; DP Mohapatra, Ph.D., NINDS

To translate biomarkers and therapeutics from discovery into clinical practice, participants agreed to focus HEAL's pipeline on product development and reduce the focus on publications. Participants noted that the NIDA Division of Therapeutics and Medical Consequences provides several resources for HEAL investigators. In addition, investigators who have completed the UH3 phase of their award can apply for a second HEAL award to help prepare for a new drug application filing with the FDA.

### **Harnessing Digital Health to Advance Research**

**Moderator:** Will Aklin, Ph.D., NIDA

Research developing digital therapeutics has outpaced the validation of therapeutic technologies, and disparities in its availability (due to high-speed internet and technological access and abilities) have hindered use. Digital therapeutics are further challenged by the need to comply with the Health Insurance Portability and Accountability Act (HIPAA) and 42 CFR Part 2 regulation requirements. To enhance the availability of digital therapeutics to underserved communities, expanded access is needed, as is infrastructure for data harmonization and increased social networking to facilitate connectedness.

### **Advancing Research in a Virtual World**

**Moderator:** Amy Goldstein, Ph.D., NIDA

Major technological improvements have occurred over the past year, and acceptance of telehealth technologies has spread across platforms. These enhanced technologies have increased participant engagement but have also uncovered complications (e.g., internet access, disparities in participation, adjustments to research design). Flexible, hybrid approaches may allow both virtual and in-person engagement.

### **Disseminating HEAL Research**

**Moderator:** Jack Stein, Ph.D., NIDA

Participants emphasized the importance of communicating research to intended communities, which can be achieved through local news outlets and community-based publications. Participants recommended that HEAL engage with institutional communications offices to build relationships. Highlighting individual and personal stories makes research more accessible and can correct negative or stigmatizing language.

**May 19****Plenary: The Collision of National Public Health Crises****NIH Facilitator:** Shannon Zenk, Ph.D., M.P.H., Director, National Institute of Nursing Research (NINR)**Speakers:** Lynn DeBar, Ph.D., Kaiser Permanente Washington Health Research Institute; Edward Nunes, M.D., Columbia University

The overdose and pain crises have overlapped with the COVID-19 pandemic to magnify economic stressors, social isolation, and caregiving responsibilities. Researchers have adjusted their approaches to assess the multitude of factors that affect individuals' experiences of these crises, such as financial insecurity, stress, and poor mental health.

- The COVID-19 pandemic has led to a significant increase in reports of anxiety, suicidal ideation, and substance use. Though virtual delivery of nonpharmacological treatments increased, reliance on virtual delivery methods increases the digital divide, placing those with less access at a further disadvantage. However, online pain-related interventions have the potential to ease restrictions that inhibit access to opioid treatment.
- Dr. Nunes noted that as research adapted to the COVID-19 pandemic, patient recruitment became more difficult, although the full effect has been difficult to evaluate. However, in March 2020, the Drug Enforcement Agency, Substance Abuse and Mental Health Services Administration (SAMHSA), and state agencies relaxed guidelines for SUD treatments (e.g., permitting telehealth, expanding methadone take-homes), which have made them more accessible.

**Panel: Adapting in a Time of Change: Responding to the Collision of Public Health Crises****NIH Facilitator:** Shannon Zenk, Ph.D., M.P.H., NINR; Francis Keefe, Ph.D., Duke University**Speakers:** Sharon Walsh, Ph.D., University of Kentucky; Faye Taxman, Ph.D., George Mason University; Kevin Vowles, Ph.D., Queen's University Belfast; Elizabeth D'Amico, Ph.D., RAND Corporation

- Evidence-based practices for the HCS are implemented in conjunction with public health communications campaigns aimed at reducing stigma.
- The Justice Community Opioid Innovation Network (JCOIN) vision is to provide all individuals with SUD within the justice system access to effective treatment—expanding access to telehealth during the COVID-19 pandemic.
- The Pain and Opioids: Integrated Treatment In Veterans (POSITIVE) trial aims to offer an integrated intervention from the interference of chronic pain and OUD; it transitioned to a telehealth pilot study.
- The Traditions and Connections for Urban Native Americans (TACUNA) project serves young adults (age 18-25) and assesses the effectiveness of culturally centered information about opioid misuse and the influence of social networks on individuals. Throughout the pandemic, participants participated in culturally relevant virtual cooking sessions to retain engagement.

**Discussion**

To address variations in access to high-speed internet and devices, some communities may only need a few critical resources (e.g., mobile phones and mobile devices) to increase patient access to care. In some situations, allowing individuals to use virtual media can also reduce stress. For example, judges noticed a significant reduction in stress when incarcerated individuals could attend court hearings virtually.

**Plenary Panel: Moving Research into Action****NIH Facilitator:** Lawrence Tabak, D.D.S., Ph.D., Principal Deputy Director, NIH**Speakers:** Tom Coderre, Acting Assistant Secretary for Mental Health and Substance Use, SAMHSA; Debra Houry, M.D., M.P.H., Director, National Center for Injury Prevention and Control, Centers for Disease Control and Prevention (CDC); Janet Woodcock, M.D., Acting Commissioner, FDA

Each of the respective federal agencies represented during this panel shared their plan for addressing the pain and opioid crises in the wake of COVID-19.

- Mr. Coderre shared his personal journey to recovery and encouraged investigators to highlight that long-term recovery is possible. He emphasized the need for research on addiction recovery and efforts to increase the number of individuals with SUD that receive treatment. SAMHSA aims to increase access to evidence-based practices and interventions through the Evidence-Based Practice Resource Center.
- Dr. Houry described CDC surveillance and prevention strategies, which include the State Unintentional Drug Overdose Reporting System (SUDORS), Drug Overdose Surveillance and Epidemiology System (DOSE), and the Opioid Rapid Response Program. The CDC is also conducting research to understand how the drug overdose epidemic is evolving and is working to communicate the risks of opioid use through communications campaigns.
- Dr. Woodcock highlighted the FDA's Digital Health Center of Excellence, which aims to help patients maintain their medication-based treatments and engagement with clinicians and therapists. External groups are consulted to help educate physicians on prescribing methods, specifically to reduce overprescribed opioids.

**Discussion**

Federal agency representatives emphasized their reliance on HEAL-funded research findings to transition research knowledge into practice. Solid evidence drives uptake and implementation. Primary prevention of opioid misuse requires more evidence than currently available (e.g., childhood exposures to opioids) for individuals and communities. Other areas that could benefit from additional research include recovery support, recovery sustainability, and guidance that describes the proper use of opioid pain medications in varied situations.

**Discussion Groups****Promising Practices for Research During a Pandemic****Moderator:** Constance Weisner, Dr.P.H., M.S.W., Kaiser Permanente Northern California; Wendy Weber, N.D., Ph.D., M.P.H., NCCIH**Speakers:** Greg Simon, M.D., M.P.H., Kaiser Permanente Washington; Jonathan Purtle, Dr.P.H., Drexel University; Rebecca Rossom, M.D., HealthPartners Institute; Elizabeth Turner, Ph.D., Duke University

The COVID-19 pandemic has led to multiple changes in processes, consent, analyses, and standards of care. While these changes required flexibility, they also created opportunities for many patients, particularly those with transportation difficulties.

- Dr. Simon noted that some changes in data coding strategies to account for telehealth services could be interpreted in multiple ways and that data from electronic health records have limitations.
- Dr. Purtle observed that during the pandemic, policymakers were concerned about the mental health impacts on socially disadvantaged youth but did not necessarily increase youth access to mental health services.
- Dr. Rossom described the Priority Wizard, a clinical decision support tool that enables screening, diagnosis, and treatment of OUD in primary care clinics. This research struggled as their model relied on in-person visits, but to partially compensate, patients were provided online access.
- Many embedded pragmatic clinical trials required adjustments due to COVID-19, and as many shifted to virtual data collection, internet connection issues impeded study adherence.

### **Technology Development to Stem the Opioid Crisis**

**Speakers:** Brennan Spiegel, M.D., Cedars-Sinai Medical Center; Gwendolyn Sowa, M.D., Ph.D., University of Pittsburgh; Ivana Cuberovic, Ph.D., Ripple LLC; Ausaf Bari, M.D., Ph.D., University of California Los Angeles

Technology is leveraged throughout all components of the NIH HEAL Initiative and can be used to improve diagnostics and treatments for both pain and OUD. Speakers highlighted ongoing research and evaluations of technological advancements.

- Dr. Spiegel described virtual reality-based therapies to recalibrate unhealthy perceptions about chronic low back pain via at-home training.
- Dr. Sowa described a network-phenotyping strategy that allows large datasets to be grouped into clinical clusters, then analyzed to identify common factors and potential predictors for clinical outcomes.
- Dr. Cuberovic noted that therapeutic devices need to have longevity and usability, and be able to support the patient-care lifecycle.

### **HEAL Innovation Research**

**Moderator:** Emily Caporello, Ph.D., NINDS

**Speakers:** Rajesh Khanna, Ph.D., University of Arizona; Rajita Sinha, Ph.D., Yale University; Timothy Wagner, Ph.D., Highland Instruments, Inc.

- Dr. Khanna discussed non-opioid solutions for chronic pain and novel opportunities for therapeutics to address the diverse landscape of pain and its linkage to multiple conditions through validated and selective biological targets.
- Dr. Moreno described investigations designed to target genes in the dorsal root ganglia and provide long-lasting analgesia (44 weeks).
- Dr. Sinha emphasized that addressing chronic stress is a method to help reduce high relapse rates for patients experiencing pain.
- Dr. Wagner discussed the use of neuromodulation (combination of electrical and ultrasonic energy) in therapeutic settings to treat nerve pathologies and reduce various types of pain.

## Bringing Pain and Addiction Researchers Together

**Moderator:** Shelly Su, Ph.D., NIDA

**Speakers:** Dylan Lindholm, Person With Lived Experience; Eric Garland, Ph.D., University of Utah; Nora Nock, Ph.D., Case Western Reserve University; Katie Witkiewitz, Ph.D., University of New Mexico

Patients often experience multiple types of pain, but care is fragmented. Providers may have expertise in only a single area, forcing patients to seek multiple providers and thus lack a holistic care plan. Researchers spoke about the integration of co-occurring chronic pain and opioid use disorder.

- Mx. Lindholm shared a patient perspective and described their experience of being in pain. As a former paramedic, Mx. Lindholm had extensive knowledge of medical terminology; however, this knowledge did not lead to more supportive care but instead increased suspicions from medical providers regarding their intentions for needing medication. Without support and pain relief, Mx. Lindholm used illicit substances to alleviate pain. Working with a physician that actively listened to and involved Mx. Lindholm in the decision-making process improved their health care experience and enabled effective management of their chronic pain.
- Dr. Garland discussed his research on mindfulness, reappraisal, and savoring to address pain severity, emotional distress, opioid misuse, and OUD.
- Dr. Nock spoke about her research to investigate the value of assisted exercise and psychotherapy to modulate dopamine levels in the brain, toward alleviating pain and co-occurring conditions.
- Dr. Witkiewitz described common challenges in the cycle of chronic pain and drug use that include pain, emotional distress, cravings for drugs to relieve pain, and drug use that repeats in a cyclical fashion. Each stage in this cycle is a potential intervention point.

## Scientific Symposia: Harnessing Innovation in Pain and Addiction Research

**NIH Facilitator:** Michael Oshinsky, Ph.D., NINDS

**PI Facilitator:** Marco Pravetoni, Ph.D., University of Minnesota

**Speakers:** Sandra Comer, Ph.D., Columbia University; David Clark, M.D., Stanford University; Paul Kenny, Ph.D., Icahn School of Medicine at Mount Sinai; Yu-Qing Cao, Ph.D., Washington University Pain Center; Marco Pravetoni, Ph.D., University of Minnesota

Speakers within this session have developed innovative methods or therapeutics with novel targets to help treat pain and addiction.

- Dr. Comer described a new chemical entity that displays a unique combination of receptor interactions with the potential to treat multiple SUDs without developing dependence, withdrawal reactions, or negative effects on the gastrointestinal system or pulmonary function. A single ascending dose study funded by NIDA is ongoing.
- Dr. Clark described a novel target that could be useful for pain therapeutics, noting that contributions from autoimmune diseases may be significant for certain types of pain.
- Dr. Kenny is investigating novel therapeutics that modulate Gpr151, a receptor present in the medial habenula, the part of the brain most often associated with pain and addiction.
- Dr. Cao is attempting to modulate neuroimmune interactions that target regulatory T cells to reverse sensitivity for patients with chronic headache disorders. These cells are involved in multiple mechanisms that suppress the function of all other immune cells while maintaining homeostasis.



- Dr. Pravetoni described his efforts to develop vaccines and monoclonal antibodies that may lead to reduced drug effects for patients diagnosed with OUD or SUD and that may be administered alongside other approved therapies.

**Closing Remarks**

Francis Collins, M.D., Ph.D., Director, NIH, and Rebecca Baker, Ph.D., Director, NIH HEAL Initiative

Dr. Baker summarized the 3-day meeting's key themes, including adapting research to COVID-19; supporting patient engagement in research, advancing health equity, and strengthening researcher–community partnerships; and sharing HEAL-generated results broadly. She noted that throughout the meeting, attendees demonstrated resilience and adaptability, affirming Dr. Murthy's initial comments about the importance of emotional wellbeing, compassion, and kindness as sources of strength.

Dr. Collins acknowledged the collision of major, intersecting public health crises, including the epidemic of opioid misuse and overdose, untreated pain, and the COVID-19 pandemic, and increased recognition of the effects of structural racism and its effects on health equity. He thanked all NIH HEAL Initiative investigators for their flexibility, creativity, and resilience in working toward HEAL's important goals and applauded those efforts with a performance of an original song "Somewhere, past the pandemic."