Improving Prevention and Treatment Strategies for Opioid Misuse and Addiction Through HEAL

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## Improving Prevention and Treatment for Opioid Misuse, Addiction and Overdose

### Priority Research Areas:

- **Expand Therapeutic Options**
- **Optimize Effective Treatment Strategies**
- **Develop New/Improved Prevention & Treatment Strategies**
- **Enhance Treatments for Infants with NAS/NOWS**

### Research Opportunities:

- **New formulations**
- **Longer duration**
- **Respiratory depression**
- **Immunotherapy**
- **New targets and approaches**

- **Clinical trials expansion**
- **Criminal justice innovation**
- **Collaborative care**
- **Behavioral interventions**
- **Multi-site implementation**

- **Treatment of early/moderate OUD**
- **Optimal length of medication treatment**
- **Prevention in transition to adulthood**

- **Brain development of opioid-exposed infants**
- **ACT NOW**
Expand Therapeutic Options: OUD and Overdose Reversal

• New Targets for OUD
• Drug combinations to improve retention (lofexidine + buprenorphine)
• Stronger, longer acting formulations and new targets for OD from synthetic opioids (e.g. fentanyl) and drug combinations (bdz + opioids)
• Stimulation devices to prevent respiratory depression
• OD, alert technologies, and naloxone autoinjectors
• Post-overdose interventions to ensure engagement in treatment
• New Medication Outcomes: Craving, Insomnia, Depression
  • RFA DA-19-002: Rolling acceptance of applications
Research Priority:
Develop New/Improved Prevention and Treatment Strategies

• Transition to Adulthood
  • Studies to prevent OUD in older adolescents and young adults

• Sleep Dysfunction
  • Sleep and circadian factors relevant to addiction

• Management of Subsyndromal and Low-severity OUD
  • Identify and treat patients in general medical settings with co-occurring pain/mental health disorders

• Optimal Length of Medication Treatment
  • Randomized clinical trial of buprenorphine and methadone

• Collaborative Care Model
  • Adapted to patients with OUD and mental health conditions
Addiction Prevention and Treatment: Preventing OUD in Older Adolescents and Young Adults (ages 16 -30)

• Goal: Develop the evidence base for interventions and strategies to prevent initiation of opioid misuse and development of OUD in at-risk older adolescents and young adults

• Focus: Healthcare, justice and other systems and settings opportune for accessing and engaging at risk adolescents and young adults

• Components: HEAL Prevention Cooperative - up to 10 research projects and 1 coordinating center.
  • Two FOAs published:
    • UG3/UH3 Research Projects (RFA-DA-19-035)
    • U24 Coordinating Center (RFA-DA-19-034)
  • Applications due - 3/2019; Award Date - Fall 2019
Optimize Effective Treatment Strategies: Justice and Community Opioid Network (JCOIN)

• Opioid Innovation in the Criminal Justice System
  • Justice Community Opioid Innovation Network (JCOIN)
  • Generate real-world evidence to address needs of individuals with OUD in justice-settings

• Progress to Date:
  • 11 supplement awards made in September 2018
  • Solicitations released December, 2018 for Research Centers, Coordination and Translation Center, and Methodology and Analytics Center
  • Expected awards total $30M, Awards expected Early Fall 2019
Optimize Effective Treatment Strategies:
Clinical Trials Network Expansion Project

• Focused studies on opioid addiction
  • Optimizing Retention, Duration and Discontinuation Strategies for OUD medications (MOUD) in healthcare
  • Strategies for inducting OUD medications in hospitalized patients and enhancing post-discharge care
  • Extended-release medications
  • Implement ED-initiated and compare formulations of buprenorphine
• Rural expansion of OUD medication treatment using telemedicine and mHealth approaches
• More effective models for linkage to care
• Opioid registry in diverse health care delivery systems
• RFA-DA-19-008
  • Awards for 4 new nodes in Summer 2019
Optimize Effective Treatment Strategies: The HEALing Communities Study

- Develop and test strategies to help communities respond to opioid crisis with a focus on achieving a 40% reduction in 3 years for OD fatalities
- Measure impact of integrating evidence-based prevention and treatment for opioid misuse, OUD, OD, and OD fatalities across multiple settings (healthcare, behavioral health, justice, communities.)
- Determine factors (structural, organizational, policy, etc.) that contribute to successful implementation and sustainability of the integrated interventions
- Determine cost-effectiveness of integrated intervention compared to standard of care
- Awards Expected: April 2019
Enhance Treatments for Infants with Neonatal Abstinence Syndrome/Opioid Withdrawal Syndrome

• Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome (ACT NOW)
  • Innovative ways to identify and treat newborns exposed to opioids

• HEALthy Brain and Child Development Study:
  • Large multi-site longitudinal study to examine brain, cognitive, behavioral, social, and emotional development beginning prenatally and extending through childhood.
  • Oversample for prenatal opioid exposure

• Progress to Date:
  • R34 Planning Grant Funding Opportunity Announcements RFA-DA-19-029; RFA-DA-19-036
    • Applications due: March 25, 2019;
    • Awards expected: September 2019
HEAL Research to Enhance Pain Management

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Director
National Institute of Neurological Disorders and Stroke
Priorities in Research to Enhance Pain Management

• Understand the biological underpinnings of chronic pain
• Accelerate the discovery and pre-clinical development of non-addictive pain treatments
• Advance new non-addictive pain treatments through the clinical pipeline
• Establish the best pain management strategies for acute pain and numerous chronic pain conditions

Read about the 2019 research plan:

www.nih.gov/heal-initiative
In 2017, NIH invested $516 million on pain research.

Pain cuts across all 27 NIH Institutes and Centers.

The NIH Pain Consortium was established with the goal of enhancing pain research and promoting collaboration across NIH.
Understand the biological underpinnings of chronic pain
Acute to Chronic Pain Signatures

• Objective biosignatures to identify susceptibility or resilience to chronic pain
  • Phenotyping
  • Genotyping
  • Sensory tests
  • Imaging
  • -omics

• Outcomes
  • Mechanisms
  • Novel therapeutic targets
  • Cohort stratification
  • Prevention

Structure:
- Clinical Coordination Center
- Clinical Centers
- Omics Data Generation Centers
- Data Integration and Resource Center

Awards expected in Spring 2019
https://comm/onfund.nih.gov/pain
Accelerate the discovery and pre-clinical development of non-addictive pain treatments

Discovery
- Acute to Chronic Pain Signatures
- Discover and Validate Novel Targets for Safe and Effective Pain Treatment
- Preclinical Screening Platforms + Novel Drug Development

Preclinical Development
- Translating Discoveries Into Effective Devices For Pain Treatment

Clinical Trials
- Discovery and Validation of Biomarkers, Biomarker Signatures, and Endpoints for Pain Indications

Implementation/Dissemination

NIH
National Institutes of Health
Turning Discovery Into Health
Discover and Validate Novel Targets for Safe and Effective Pain Treatment

To promote the basic science discovery and validation of targets for the treatment of pain that can be used to develop treatments that have minimal side effects and little to no abuse/addiction liability.

- Encourage collaboration from other fields
- Designed to reveal novel targets for small molecules, natural products, biologics, devices
- Devices: discovery of new sites for stimulation or electrophysiological signatures
- Open to all pain systems in CNS or periphery

Previously identified targets

Basic biology target discovery projects

- Novel in vitro/ex vivo assays
- Animal model systems development
- Multidisciplinary tools
- Multisite validation; robustness; reproducibility
- Validation of pharmacodynamic and predictive biomarkers

RFA-NS-18-043 – R01
RFA-NS-18-042 – R21
NOT-NS-18-073 – Administrative Supplements

More info coming later today!
Develop Human Cell-based Screening Platforms and Novel Drugs to Treat Pain, Addiction, and Overdose

- Support preclinical optimization and development of safe, effective, and non-addictive small molecule and biologic therapies to treat pain.

- Develop human cell/tissue models
  - Peripheral and central nervous system
  - Normal and disease states
  - iPSC-derived neurons, 3D printed organoids, tissue chips

- Advance investigational drugs for new targets
  - Human tissue constructs to identify new probes/drug leads
  - Automated chemical synthesis
  - Artificial Intelligence to identify new chemical structures
  - IND-enabling studies: Optimization of Non-addictive Therapies [Small Molecules and Biologics] to Treat Pain

RFA-NS-19-010, RFA-NS-19-020 (SBIR)

More info coming later today!
Preclinical Screening Platform for Pain (PSPP)

- Will establish a one-stop preclinical testing platform that promotes the testing and characterization of non-addictive modalities for the treatment of pain
- Incentivize academia & industry to accelerate discovery of non-addictive, effective therapies
- Develop or refine animal models of pain conditions-available to research community
- Generate high quality data to support partnerships, translational programs
- Provide access to research community

![Diagram of Preclinical Screening Platform]

- Small molecules
- Biologics
- Devices
- Natural products

Preclinical Screening Platform
- In vitro µ-opioid receptor screening
- Acute pain models
- Chronic pain/disease models
- In vivo addiction screening

Successful compounds/devices move to clinical trials

More info coming later today!

https://www.ninds.nih.gov/Current-Research/Trans-Agency-Activities/NINDS-Role-HEAL-Initiative-PSPP
Translating Discoveries into Effective Devices for Pain Treatment

• Reduce reliance on opioids through the enhanced targeting and reduced invasiveness of diagnostic and therapeutic devices to manage pain
• Leverage ongoing mapping / target discovery activities in BRAIN, SPARC, and other HEAL Initiatives
• Late stage device development
• Verification and validation to accelerate regulatory approval
• Early clinical studies to de-risk new and improved pain treatments
Discovery and Validation of Biomarkers, Endpoints and Signatures for Pain Conditions

Analytical and/or Clinical Validation of a Candidate Biomarker for Pain: Facilitate the discovery and development of high-quality biomarkers to accelerate the development of non-addictive therapeutics for the treatment of pain conditions

RFA-NS-18-046 - R61/R33

Discovery of Biomarkers, Biomarker Signatures, and Endpoints for Pain: Goal is to support the analytical and clinical validation of candidate biomarkers for use in the discovery and development of non-opiate alternatives to the treatment of pain conditions using retrospective and/or prospective methods

RFA-NS-18-041 - R61/R33

Goal is to facilitate the discovery of robust biomarkers, biomarker signatures and objective endpoints for pain conditions
Advance new non-addictive pain treatments through the clinical pipeline

- **Discovery**
  - Acute to Chronic Pain Signatures
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  - Preclinical Screening Platforms + Novel Drug Development
- **Preclinical Development**
  - Translating Discoveries Into Effective Devices For Pain Treatment
  - Discovery and Validation of Biomarkers, Biomarker Signatures, and Endpoints for Pain Indications
  - Data & Asset Sharing Partnership
- **Clinical Trials**
  - Early Phase Pain Investigation Clinical Network
- **Implementation/Dissemination**
  - Back Pain Research Consortium
Early Phase Pain Investigation Clinical Network + Data and Asset Sharing Partnership

Improve quality, consistency, efficiency of early phase pain clinical trials

- EPPIC-net will test compounds and devices judged highly meritorious in peer review that come from industry and academia
- Clinical Coordination Center, Data Coordination Center, 10 specialized clinical sites (hub and spoke design)
- Incentivize, accelerate Phase II trials
- Focus on well-defined pain conditions with high-unmet need
- Reduce the time to start, enroll, run, and complete trials
- Incorporate biomarker studies
- Accommodate platform trial designs

Data and Asset Sharing Partnership
- EPPIC-net Data Coordination Center will host data and biosample repositories from HEAL programs and industry partners
- FNIH and the HEAL Partnership Committee will encourage submission of assets for phase 2 clinical trials

More info coming later today!
Back Pain Research Consortium: BACPAC

Back Pain Consortium (BACPAC) Research Priorities
A patient-centric, translational research program

BASIC: Integrated model of Low Back Pain through improved understanding of mechanisms, leading to new therapies

TRANSLATIONAL: Clinical trails, integrating new therapies into multimodal interventions, combined with deep phenotyping and patient-reported symptoms and outcomes

CLINICAL: Algorithms to match patients to best treatments based on phenotype and psychosocial context

NIH National Institutes of Health
Turning Discovery Into Health
Establish the best pain management strategies for acute and chronic pain conditions

- **Discovery**
  - Acute to Chronic Pain Signatures
  - Discover and Validate Novel Targets for Safe and Effective Pain Treatment

- **Preclinical Development**
  - Preclinical Screening Platforms + Novel Drug Development

- **Clinical Trials**
  - Translating Discoveries Into Effective Devices For Pain Treatment
  - Discovery and Validation of Biomarkers, Biomarker Signatures, and Endpoints for Pain Indications

- **Implementation/Dissemination**
  - Data & Asset Sharing Partnership
  - Early Phase Pain Investigation Clinical Network

- **Back Pain Research Consortium**
  - Hemodialysis Pain Management
  - Pain Effectiveness Research Network
  - Pragmatic and Implementation Studies for the Management of Pain
Pain Management Effectiveness Research Networks and Trials

• To inform clinicians about the effectiveness of interventions or management strategies that will improve functional outcomes and reduce pain across the continuum of acute to chronic pain associated with many types of pain conditions

• Evaluate the effectiveness of pharmacologic and nonpharmacologic therapies for a broad array of pain conditions
  • Comparative Effectiveness Research Network: leverage NCATS Trial Innovation Network
  • Pain expertise in coordinating centers
  • NIH will solicit proposals for Phase 3 clinical trials to inform best practices in pain management and minimize risk of addiction
  • Coordinate data elements and storage with EPPIC-net and PRISM

More info coming later today!
Integrated Approach to Pain and Opioid Use in Hemodialysis Patients

• To develop tailored interventions for pain control and reduce reliance on opioids for hemodialysis patients

• Develop a multipronged and non-opioid approach to managing pain that uses precision treatment strategies based on individual needs
  • Evaluate non-addictive analgesics to reduce pain
  • Evaluate behavioral approaches for pain management
  • Identify risk factors for opioid dependence
  • Assess and treatment co-morbid conditions
  • Enhance electronic health records to capture study outcome data
Pragmatic and Implementation Studies for Management of Pain to Reduce Opioid Prescribing: PRISM

• Integrate interventions with demonstrated efficacy into health care systems, and implement health care system change toward evidence-based pain management

• Conduct efficient, large-scale pragmatic trial or implementation science studies to improve pain management
  • Embed the intervention under study into real world settings
  • Collect data through the electronic records of the health care system
  • Leverage the NIH Health Care Systems Collaboratory
  • Focus on non-pharmacological approaches
  • Collaboration with CMS for Medicare coverage consideration
HEAL Programs for Pain Cover the Research Spectrum

- **Discovery**
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  - Back Pain Research Consortium

- **Preclinical Development**
  - Data & Asset Sharing Partnership
  - Early Phase Pain Investigation Clinical Network

- **Clinical Trials**
  - Hemodialysis Pain Management
  - Pain Effectiveness Research Network

- **Implementation/Dissemination**
  - Pragmatic and Implementation Studies for the Management of Pain