Helping to End Addiction Long-Term:
NIH HEAL Initiative

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Crisis of Addiction and Pain in America

- >2M Americans are addicted to opioids
  - Most started with prescription medicines
- 100M American adults are burdened by chronic pain
  - >25M report daily pain
- Research has revolutionized our understanding of addiction and pain
  - Rapid translation of new knowledge into non-addictive approaches to pain management is urgently needed
NIH Seeks to Respond to the Crisis…
With Research

Pain Management
Safe, more effective strategies

Opioid Addiction Treatment
New and innovative medications and technologies

Overdose Reversal Interventions to reduce mortality and link to treatment
Some Successful NIH-Supported Innovations

An SCN9A channelopathy causes congenital inability to experience pain


Nasal spray device
New NIH Initiative to Address the Crisis: HEAL: *Helping to End Addiction Long-term*

- Collaborative, cross-cutting research
  - From basic to behavioral – and everything between
  - Innovative partnerships – across agencies, sectors, organizations – will ensure rapid progress
- $500M/year provided by Congress in FY18 Omnibus
- Advances national priorities for pain, addiction research…
NIH HEAL Initiative: Selected Priorities for 2018

**Opioid Use Disorder**
- Improve therapeutic approaches to addiction and overdose
- Carry out real world implementation research to optimize interventions
- Evaluate treatments, consequences of Neonatal Opioid Withdrawal Syndrome (NOWS)

**Pain Management**
- Understand neurobiology of chronic pain
- Develop new non-addictive treatments for pain
- Build Clinical Trial Network for chronic pain
Helping to End Addiction Over the Long-term
The Research Plan for the NIH HEAL Initiative

Extraordinary focus by all segments of society is required to respond to the nation’s opioid crisis. Now is the time to channel the efforts of the scientific community to deliver effective—and sustainable—solutions to this formidable public health challenge. Recognizing this opportunity, Congress added $500 million to the base appropriation of the National Institutes of Health (NIH), starting in fiscal year 2018. The NIH will invest these much-needed resources to support science that advances national priorities for addiction and pain research with a bold new trans-NIH initiative called Helping to End Addiction Long-term (HEAL). In this Viewpoint, we outline the initial components of this cross-cutting, interdisciplinary program.

More than 25 million US adults are affected by daily pain. More than 2 million individuals in the United States have an opioid use disorder (OUD), most starting with opioid analgesics prescribed to them or procured from diverted medications, but once addicted, often shift-

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Additional Research Priorities

- Prevention (beyond improving prescriptions practices for pain)
- Precision treatments for addiction
- Non-pharmacological treatments
- Integrated models of pain management
- Linkages between pain, addiction, mental health
- Education
Follow HEAL on our Website...

www.nih.gov/heal-initiative
Nora Volkow, M.D.
Director, National Institute on Drug Abuse

IMPROVING TREATMENTS FOR OPIOID MISUSE AND ADDICTION
The Crisis: National Overdose Death Rates

1999 vs 2016

Legend for estimated age-adjusted death rate (per 100,000 population):
- <2
- 2-3.9
- 4-5.9
- 6-7.9
- 8-9.9
- 10-11.9
- 12-13.9
- 14-15.9
- 16-17.9
- 18-19.9
- 20-21.9
- 22-23.9
- 24-25.9
- 26-27.9
- 28-29.9
- 30+

Exciting Recent Developments on NIH-Supported Treatments

- XR-Naltrexone and Buprenorphine-Nx
  - Shown to be equally safe, effective in preventing relapse
- Sublocade™ (Buprenorphine ER), once-a-month injectable
  - FDA Approval, November 2017
- Lofexidine: treats opioid withdrawal symptoms
  - FDA approved May 16, 2018
HEAL – Opioid Misuse and Addiction

New Treatments for Addiction, Overdose Prevention and Reversal

- New ER formulations of existing medications to treat OUD
- Stronger, longer-acting formulations to counteract overdose
- Interventions against respiratory depression induced by opioids, other than MOR antagonists
- Novel medications (new targets) to treat withdrawal, craving, progression, and prevent relapse and overdose
- Immunotherapies

Projected Impact:
- 15 Investigational New Drug (IND) applications
- 5 New Drug Applications (NDAs)
HEAL – Opioid Misuse and Addiction

Novel Immunotherapies for OUD

- Decrease challenges associated with relapse in OUD treatment:
  - Provide a needed safety net for patients at “high risk” of OD
  - Complement existing therapies for OUD
  - Reduce long-term opioid use and overdose, with minimal risk of side effects

- Opioid vaccines will not interfere with use of:
  - Non-opioid pain relievers
  - Structurally distinct opioids for emergency situations
HEAL – Opioid Misuse and Addiction
Novel Immunotherapies for OUD

- Opioid Vaccine Consortium
  - Vaccine development
  - Immunogen design and optimization
  - Adjuvants to improve antibody affinity, titers, and duration
  - Formulation, dosing, and delivery
  - cGMP manufacturing

- Vaccine pre-clinical testing in animal models
  - Vaccine efficacy, Pharmacology and toxicology

- Phase I-II clinical trials
HEAL – Opioid Misuse and Addiction

Improve Therapeutic Approaches to Addiction

Using antibodies to help block drug from entering the brain

Opioid  Blood  Brain Cells
HEAL – Opioid Misuse and Addiction

Improve Therapeutic Approaches to Addiction

Using antibodies to help block drug from entering the brain
HEAL – Opioid Misuse and Addiction
Advancing Clinical Trials in NOWs: Pilot Study

- 1 year pilot funding from Director’s Discretionary Fund 2017
- 20 clinical sites participating
- Assess prevalence of NOWs at different sites, current approaches to treatment, and develop common protocols for future studies
HEAL – Opioid Misuse and Addiction
Expanded ACT NOW

- Clinical trials for care of infants with NOWs
  - Determine effectiveness of currently used medications to treat withdrawal
  - Compare pharmacologic approaches to drug-free strategies
    - Eat, sleep, console
  - Assess impact of prenatal exposure to opioids
    - Effects on developing brain structure and function
    - Higher risk for school performance problems
    - Long-term risk for addiction
- Determine best practices to improve short- and long-term outcomes
HEAL – Opioid Misuse and Addiction
Enhanced Clinical Trials Network

- NIDA collaboration with academics and community providers
  - Develop, validate, refine, and translate into practice new treatment options

- Expand the size and scope of the CTN
  - Expand clinical research capabilities of CTN with ED and primary health care providers
  - Facilitate implementation science
  - Develop and validate new models of OUD care and new metrics for evaluation

- Contribute to improved quality of and access to treatment for OUD
  - Introduce sustainable interventions in highly impacted areas
  - Implement OUD treatment practices in general medical and specialty settings
  - Expand clinical research workforce in OUD screening and treatment
HEAL – Opioid Misuse and Addiction
Justice Community Opioid Innovation Network

- Increase collaborations between justice systems and community-based treatment providers to improve continuity of care
  - Enhance access and retention in OUD treatment
- Justice community-related research through network of investigators
  - National survey of addiction treatments in jails, prisons and communities
  - Effectiveness and implementation studies of new and existing medications, interventions, and technologies in justice settings
  - Leveraging existing data sources
  - Developing innovative research methods
HEAL – Opioid Misuse and Addiction
Optimize Effective Treatments

An Immediate Challenge

- OUD crisis is escalating
- Most Americans with an OUD (~80%) don’t get effective treatment

Can we draw on all we know now… and develop integrated intervention strategies to stem the crisis quickly?

- Study ways to integrate evidence-based interventions comprehensively
  - In select areas highly affected by the crisis…
HEAL – Opioid Misuse and Addiction
Optimize Effective Treatments

- *Pilot Demonstration Project* – a competitive process involving wide-ranging federal, state, local partnerships, integrating ALL of the stakeholders
  - Health care (ED and primary care), criminal justice, treatment programs, government agencies, emergency rooms, first responders

- Test and evaluate evidence-based prevention and treatment interventions in select communities to
  - Prevent OUD and OD
  - Screen and diagnose
  - Engage and retain in medication-assisted treatment
  - Help sustain long-term recovery

- *Goal: Decrease OD deaths and OUD*
Pilot Demonstration Project – a competitive process involving wide-ranging federal, state, local partnerships, integrating all of the stakeholders

- Health care, criminal justice, treatment programs, government agencies
- Care providers including ER, primary care, mental health, first responders

Williams AR, Nunes E, Olfson M. Health Affairs Blog, 2017
Walter Koroshetz, M.D.
Director, National Institute of Neurological Disorders and Stroke

ENHANCING PAIN MANAGEMENT
Overview of FY18 HEAL Programs for Pain

Discovery
- Acute to Chronic Pain Signatures
- Target Identification and Validation

Preclinical Development
- Preclinical Screening Platform
- Therapeutics Development
- Biomarker Discovery, Development, and Testing

Clinical Trials
- Data and Asset Sharing Partnership
- Clinical Trial Network
HEAL – Pain Management

Acute to Chronic Pain Signatures

- Identify a *mechanistic objective signature* to identify those at risk for transition to chronic pain
  - Phenotyping, genotyping, imaging, -omics

- Desired outcomes
  - Mechanisms
  - Novel druggable targets
  - Cohort stratification
  - Prevention strategies
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Develop New Non-Addictive Treatments for Pain

- Opioids are often not effective for chronic pain and carry risks
- NIH and private sector partners to develop non-addictive pain management approaches
  - Predict and track treatment responses
  - Test new drugs
  - Define clinically meaningful outcomes
  - Establish a clinical pain research network to test new therapies
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Discover and Validate Novel Treatments for Pain

- Identify potential new therapeutics: small molecules, biologics, natural products; focused neuromodulation by device
- Coordinate best science across research network

Modulate pain circuits and their molecular pathways

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Preclinical Screening Platforms

- Develop human cell/tissue models
  - Peripheral, spinal, and brain
  - Normal and diseased physiologies
  - iPSC-derived neurons, 3D printed organoids, tissue chips

- Advance investigational drugs directed toward new targets
  - Human tissue constructs to identify new probes/drug leads
  - Automated chemical synthesis
  - Artificial Intelligence to identify new chemical structures
  - IND-enabling studies
**HEAL – Pain Management**

**Preclinical Screening Platforms**

- Incentivize academic, industry communities to accelerate discovery of non-addicting but potent therapies for pain
  - Develop or refine animal models of specific pain conditions
  - Provide access to research community
  - Generate high quality data to support business partnerships, translational programs

**Preclinical Screening Platform**

- *In vitro* μ-opioid receptor screening
- Acute pain models
- Chronic pain/disease models
- *In vivo* addiction screening

Small molecules  
Biologics  
Devices  
Natural products  

**Successful compounds/devices move to clinical trials**
HEAL – Pain Management
Discovery and Preclinical Development

Target identification

Pain target validation and preclinical screening

Previously identified targets

Other NIH therapeutic development programs
- Blueprint Neurotherapeutics Network
- IGNITE
- CREATE
**HEAL – Pain Management**

**Data Sharing and Asset Repurposing**

- *Ultimate goal:* enable companies to access data that will speed their development efforts
- *Data sharing:* relevant clinical, preclinical, pharmacokinetic data
- *Asset Repurposing:* accruing, analyzing pharmacological assets from academia, pharma, device companies

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<td>Report generation and analysis</td>
<td>Develop dossiers on submitted assets</td>
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<tr>
<td>Data sharing of prior pain efforts</td>
<td>Industry partners review data from successful and failed pain therapy programs to inform in house strategies</td>
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<td>Asset prioritization / scientific review</td>
<td>Prioritization and triaging to clinical trials network</td>
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HEAL – Pain Management
Discovery and Development of Biomarkers for Pain

- Better define patient populations and response to therapies being tested; accelerate non-addictive pain therapy development

- Discovery
  - Markers would include:
    - Quantitative sensory tests
    - Neuroimaging
    - Circulating markers (-omics)
    - Phenotypic characteristics
    - Genetic markers
  - Biomarker, Endpoint, Biomarker Signature Projects
    - In diverse pain conditions

- Validation
  - Response biomarkers
  - Predictive biomarkers
  - Study types
    - Retrospective
    - Pilot prospective
    - Prospective – in conjunction with the Clinical Trials Network....
HEAL – Pain Management

Clinical Trials Network for Pain

- Goal: improve quality, consistency, efficiency of clinical trials for pain
  - Focus on well-defined pain conditions with high unmet need
  - Incentivize, accelerate Phase II trials
  - Test compounds and devices from industry, academia
  - Incorporate biomarker studies
  - Accommodate other platform trial designs

- Build on existing NIH investments; hub and spoke design
- Reduce the time to start, enroll, run, and complete trials
HEAL – Pain Management
Clinical Trials Network for Pain

Biomarkers and assets from PPP, other sources

Data Coordination Center
- Statistical expertise
- Trial expertise

Clinical Coordination Center
- Clinical expertise
- Pain expertise
- Designs trials
- Organizes hubs

Centers of Excellence for Pain: Examples
- GI
- Orthopedics
- Cancer
- Diabetes
- Pediatric
- Pelvic
- Headache
- Orofacial
- Sickle cell

Biorepository
Collects biological samples and biomarker data

Data repository
Biomarkers, phenotype, clinical data storage
HEAL – Pain Management
Public Private Partnerships

Academia

Pharma and Device Industry

Foundation for NIH

NIH/FDA

Data and Asset Sharing

Pain Biomarker Discovery

Clinical Trial Network

Pain Biomarker Validation
QUESTIONS?
NIH... Turning Discovery Into Health

www.nih.gov/hope
## Research Plan for the NIH HEAL Initiative

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