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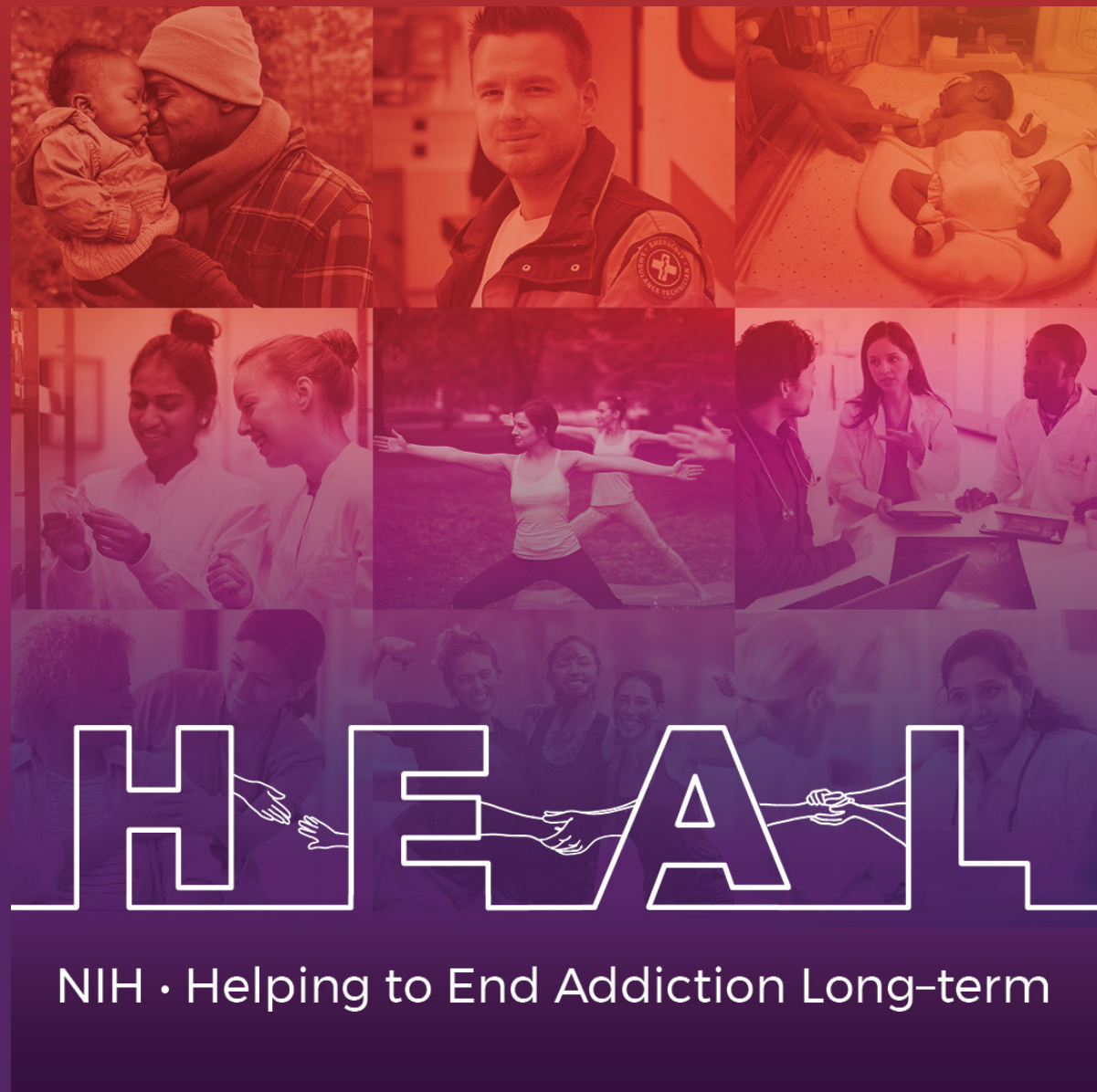
HEAL Research: Scientific Advances to Stem the Opioid Crisis

Rebecca G. Baker, Ph.D.,
Director, NIH HEAL Initiative



National Institutes of Health
HEAL Initiative

2018: Science-based response to the opioid crisis

Wednesday, April 4, 2018

NIH launches HEAL Initiative, doubles funding to accelerate scientific solutions to stem national opioid epidemic

"NIH is committed to bringing the full power of the biomedical research enterprise to bear on this crisis."

- NIH Director Dr. Francis Collins

Two-pronged approach:

- Prevent addiction through enhanced pain management
- Improve treatments for opioid misuse disorder and addiction

NIH HEAL Initiative in 2023

Supporting science-based solutions to the opioid crisis

- Over **$2.5 billion** in research, more than **1,000** research projects
- **42** research programs, projects in all **50** states
- **314** clinical trials under way
- More than **100** projects addressing back pain
- More than **200** projects addressing medications for opioid use disorder
- **41** FDA approvals for investigational new drugs or devices
- Active, ongoing partnerships with federal agencies, private sector, academia, and communities

Rebecca G. Baker, Ph.D. *Director,*
NIH HEAL Initiative

What is HEAL?

- Safe and non-addictive pain treatments
- Reduced risk for addiction, chronic pain, and suicide
- Effective and sustainable prevention and treatment strategies
- Community-chosen evidence-based interventions
- Healthy developmental paths for babies exposed to opioids
- New therapeutic options across the opioid addiction cycle

Rebecca G. Baker, Ph.D. *Director,*
NIH HEAL Initiative

HEAL Research: Cross-Cutting Themes

Target the biology of pain and addiction

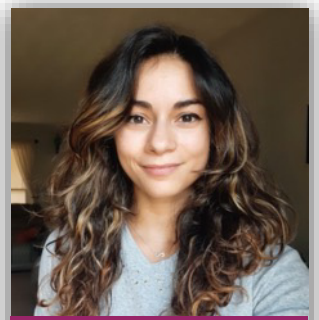
Focus research on needs of the whole person

Work with communities to bring research to life

Address health system challenges and inequities

Responsive to Key Issues Faced by Individuals Affected by Pain and Addiction


Philip Rutherford


Bianca Landaeta


Dawn Edwards

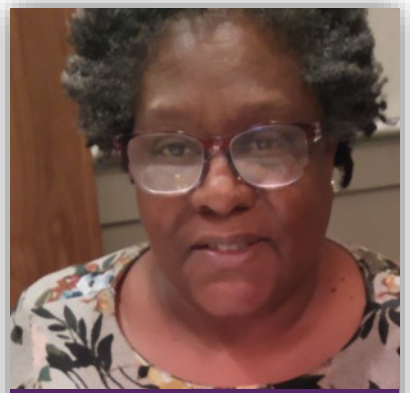

Kristen (Kri) Korte


Jonathon Valdez


Jessica Hulsey Nickel


Kevin Charles


Christin Veasley

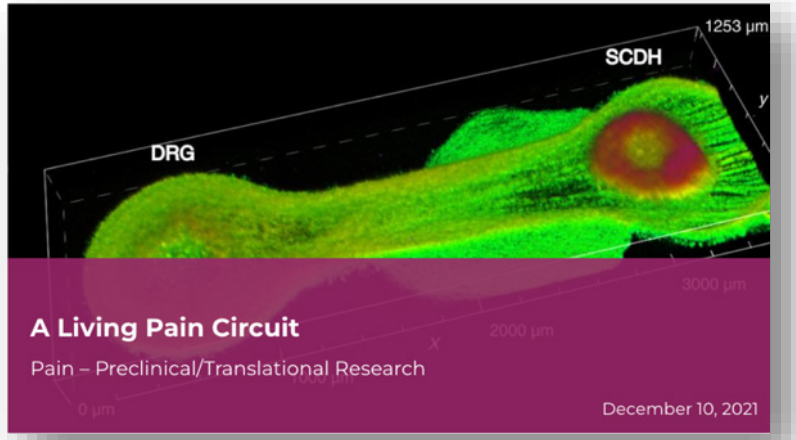

Stephanie G. Smith


Tom Norris

HEAL Community Partner Committee

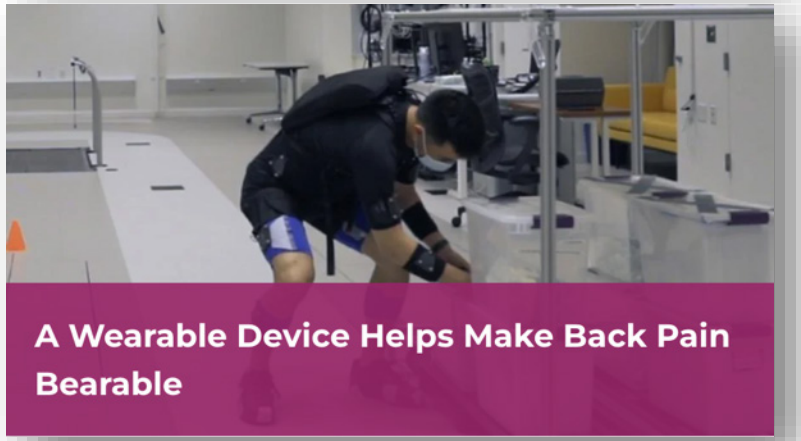
HEAL Research to Improve Pain Management

Novel tools to screen new pain medications



Trials testing new pain medications

Person-centric treatments for pain



Personalized pain management after surgery

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NIH HEAL Initiative

HEAL Research: Across the Addiction Lifecycle

Evidence-based interventions selected by communities

Starting buprenorphine in the emergency department

Opioid treatment in jails reduces re-arrest and re-incarceration

Evidence-based care for infants with NOWS

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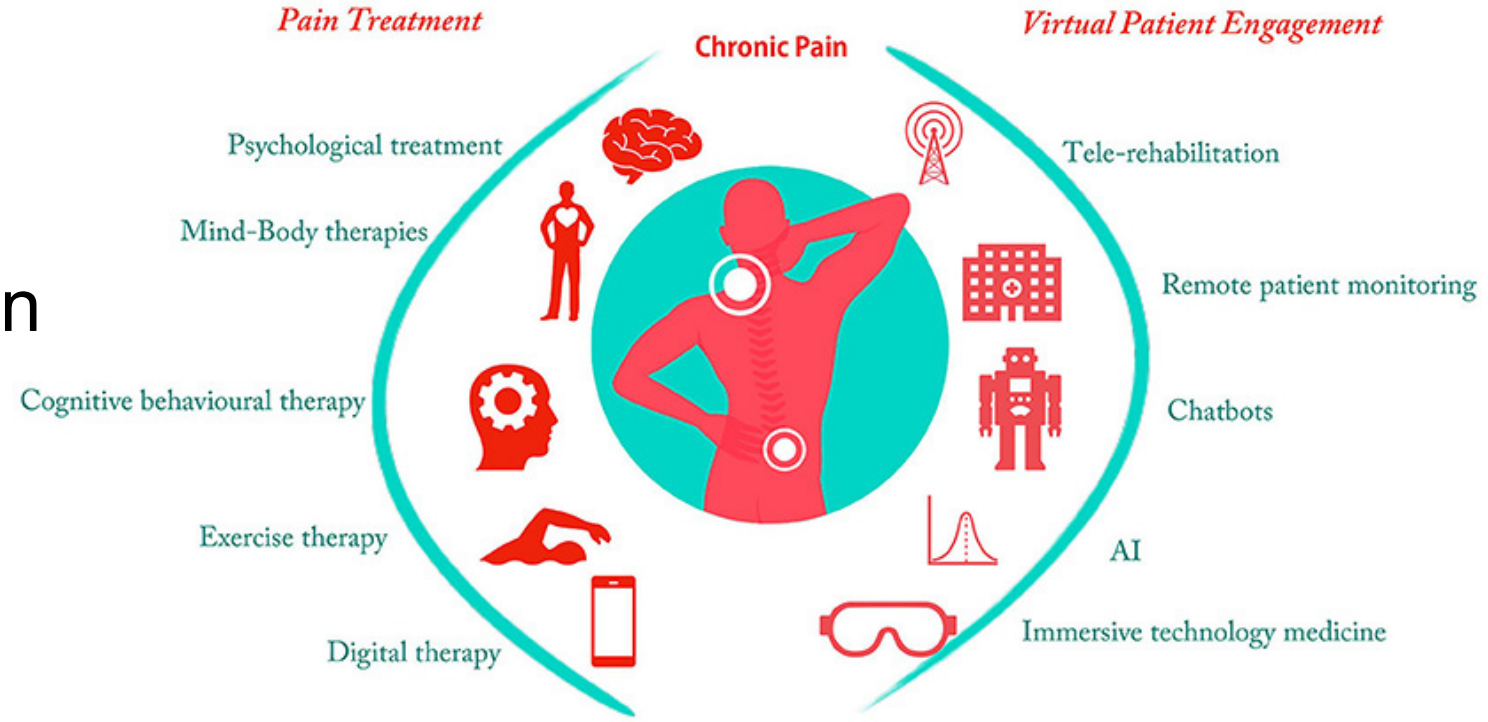
NIH HEAL Initiative

@NIHendaddiction

New Research: Coordinate Pain Management

- Healthcare systems
- Rural populations
- Quality of life for patients on long-term opioid therapy
- Sickle cell pain



New Research: Optimize Addiction Care and Prevention

- Improved addiction care quality
- Social determinants (e.g., housing, employment, trauma)
- Harm reduction
- Recovery support
- Opioid use in adolescents

Future Needs for HEAL Research

- Pain management research
  - Children with pain
  - Variation in pain among patients
  - Mental health and sleep factors
- Opioid treatment research
  - New treatment opportunities:
    - EMS drivers, syringe services programs
  - Mothers and post-partum persons
- Data re-analysis on clinical outcomes
- Training the next generation of scientists

Thank you!

heal.nih.gov/impact

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HEAL Digest
HEAL Director's Message
Subscribe at heal.nih.gov

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HEALquestion@od.nih.gov

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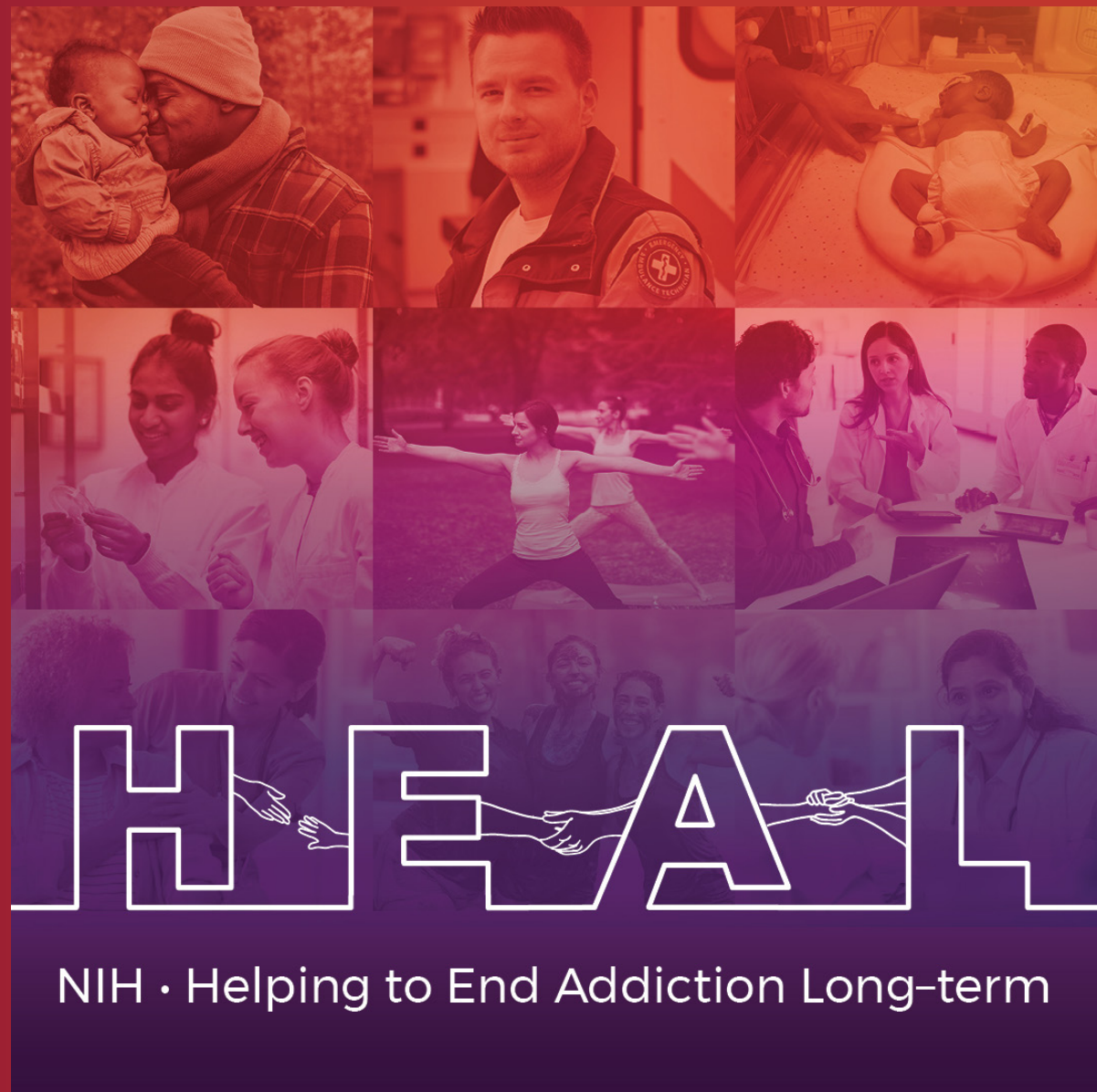
How HEAL is Addressing the Opioid and Overdose Crisis

Nora D. Volkow, M.D.
Director, NIDA



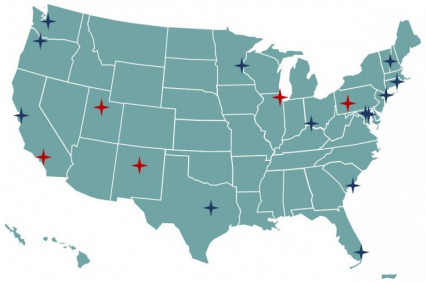
National Institutes of Health
HEAL Initiative

Provisional* Drug Overdose Deaths 12-months Ending In Select Months

	ALL DRUGS	HEROIN	NAT & SEMI SYNTHETIC	METHADONE	SYNTHETIC OPIOIDS (mainly illicit fentanyl)	COCAINE	OTHER PSYCHO-STIMULANTS (mainly meth)
8/2021*	104,038	10,488	13,970	3,708	67,624	22,571	30,876
12/2021*	109,179	9,411	13,906	3,765	72,484	25,174	33,637
8/2022*	107,477	6,863	12,272	3,357	73,102	26,786	33,534
Percent Change 8/21-8/22	**3.3%**	**-34.5%**	**-12.2%**	**-9.5%**	**8.1%**	**18.7%**	**8.6%**

*NCHS Provisional drug-involved overdose death counts are PREDICTED VALUES, 12 months ending in select months.
https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

NIDA Clinical Trials Network

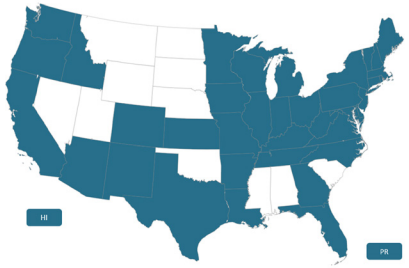


Conduct rigorous, multisite clinical trials to determine effectiveness of treatment strategies in diverse clinical settings and populations

- Optimizing Retention in MOUD
- Subthreshold OUD Trial
- ED-INNOVATION
- ER Buprenorphine for MOUD
- Polysubstance Use Disorder
- Rural Initiative
- Telehealth for SUD

HEAL INITIATIVE JCOIN

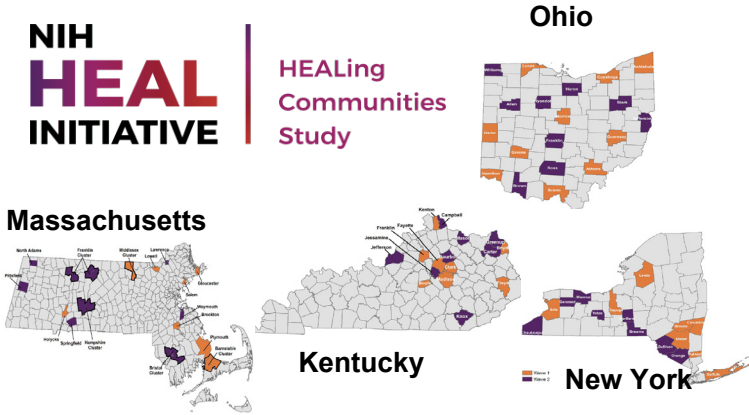
JUSTICE COMMUNITY OPIOID INNOVATION NETWORK



Build evidence for OUD treatment in justice populations

- 66 approved research protocols
- 12 multisite clinical trials: including MOUD trials
- National surveys: stigma, SUD services, state/local policies
- Simulation, predictive & geospatial modeling
- Pilot studies on emerging service delivery
- Diversity supplements

NIH HEAL INITIATIVE | HEALing Communities Study



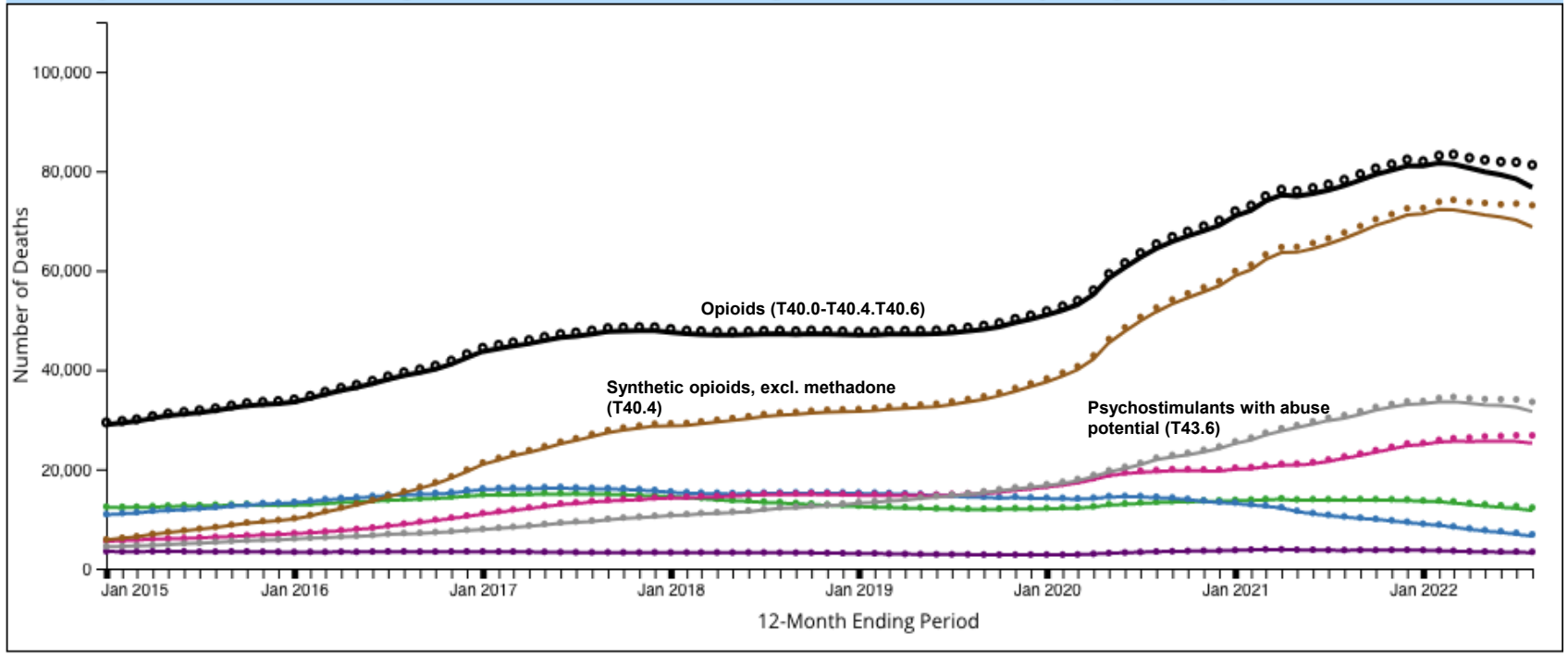
Test integration of EB prevention and treatment interventions in 67 communities in 4 states

- Goal: Reduce opioid-related OD deaths
- OD education and naloxone distribution
- Increase access/utilization MOUD
- Decrease high-risk prescribing

Synthetics Are Now Linked to Almost 90% of Opioid Overdose Deaths

HEALthy Brain and Child Development
Babies · Brains · Bright Futures

Figure 2. 12 Month-ending Provisional Number of Drug Overdose Deaths by Drug or Drug Class: United States



←81,231
←73,102

Legend for Drug or Drug Class

- Cocaine (T40.5)
- Heroin (T40.1)
- Methadone (T40.3)
- Natural & semi-synthetic opioids (T40.2)
- Opioids (T40.0-T40.4,T40.6)
- Psychostimulants with abuse potential (T43.6)
- Synthetic opioids, excl. methadone (T40.4)

---- Reported Value

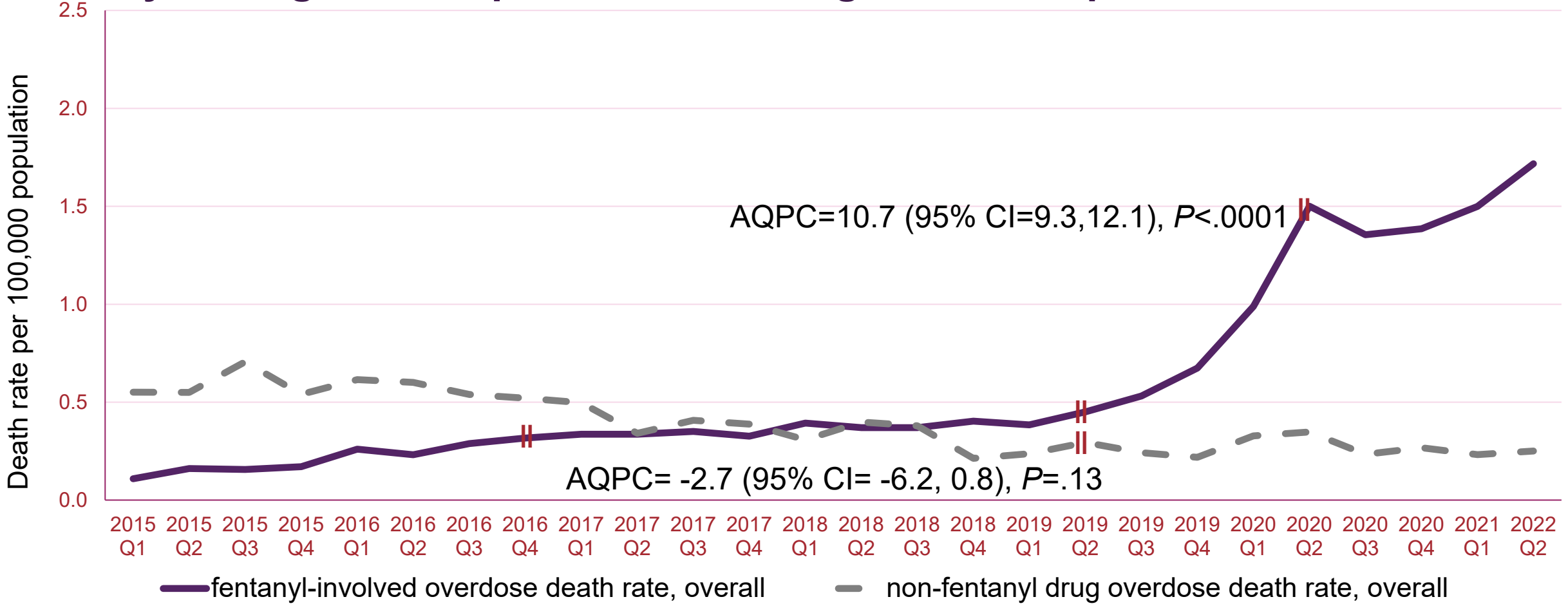
O Predicted Value

Ahmad FB, Rossen LM, Sutton P. Provisional drug overdose death counts. National Center for Health Statistics. 2022

Why are fentanyl and its analogues so dangerous?

- Potency: fentanyl is ~50x more potent (mg/kg basis) than heroin; 2mg can be lethal
- Lack of pharmaceutical standards; fentanyl doses used to lace other drugs vary (ie for counterfeit pills DEA reports that doses can range from .02 to 5.1 mg)
- Fentanyls are more lipophilic than heroin; rapid brain penetration→ faster onset [reduced time for naloxone rescue]
- **Overdose reversals from fentanyl require higher and multiple naloxone doses**
- **Physical dependence from fentanyl is stronger than for heroin making treatment initiation with medications for OUD more challenging**.

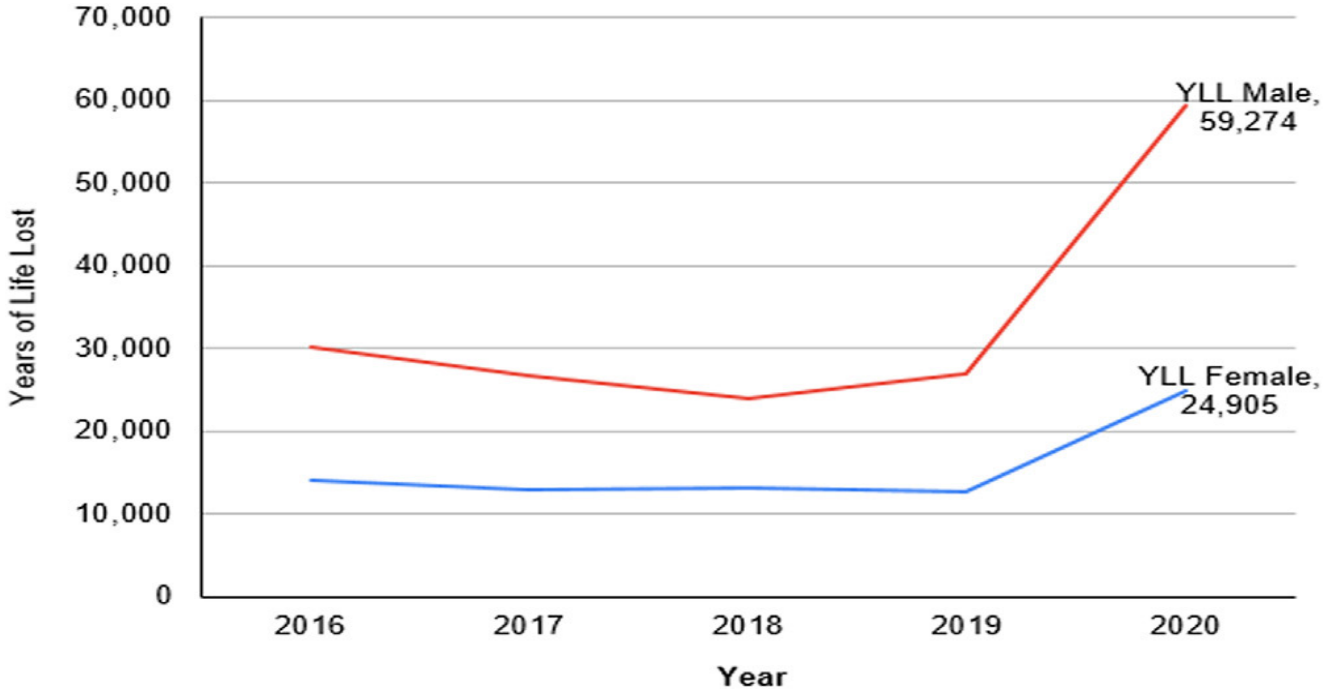
Fentanyl-involved and non-fentanyl overdose death rates in US youth aged 15-19 prior to and during the COVID pandemic



National Vital Statistics System multiple-cause-of-death 2015-2020 final and 2021 provisional data U.S. census monthly data. ‖: Joinpoints indicate significant changes in nonlinear trends using Bayesian Information Criterion. AQPC=average quarter percentage change during 2015 Q1-2022 Q2. ICD-10 cause of death code: synthetic opioids other than methadone (T40.4, primarily fentanyl and analogs).

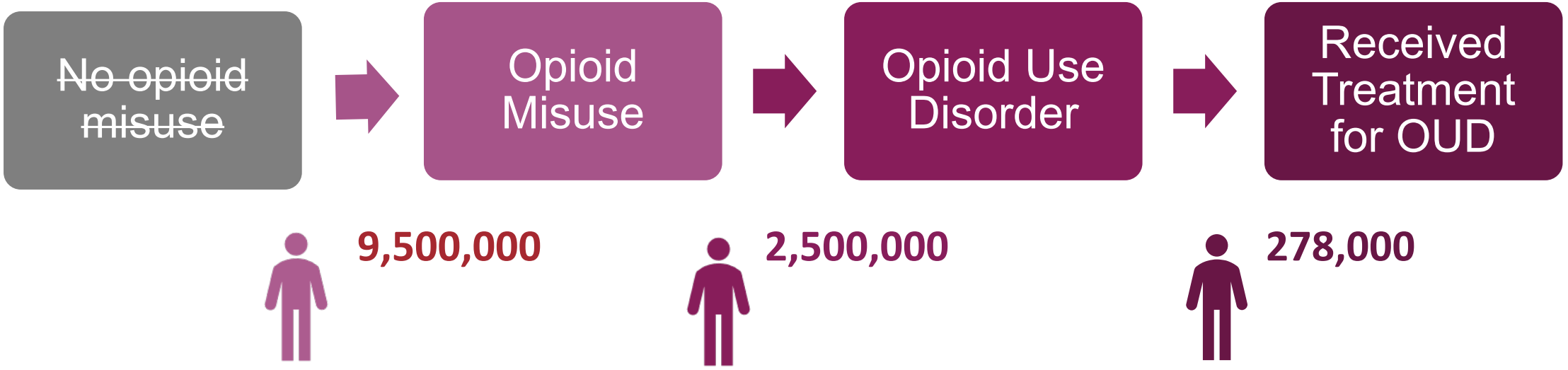
Years of Life Lost (YLL) to Unintentional Drug Overdose Rapidly Rising in the Adolescent Population, 2016-2020

YLL to unintentional overdose in adolescents by gender from 2016 to 2020



The number of adolescent YLL to unintentional drug overdose in the US more than doubled from 2019 to 2020 after remaining relatively stable between 2016 and 2019

Hermans, SP et al., J Adolescent Health 2022.



HEAL Preventing OUD Research Program

A portfolio of research aiming to prevent opioid misuse and use disorder by advancing science in 4 strategic areas:

1) risk identification,
2) social determinants, health equity, and policy,
3) intervention development, and
4) dissemination, implementation, scale-up and sustainment of prevention services.

Data Source: National Survey on Drug Use and Health

Challenges in Implementing Evidence- Based Prevention Programs

- No home for prevention – programs try to fit into settings where they are not the priority (e.g., school, justice, social services).
- Strengthening workforce is needed; prevention workforce is not well-defined.
- Need to support wide-scale implementation of prevention programs.
- Those delivering prevention programs may not know where to find information on what is evidence based.

Novel Therapeutic Options for Opioid/Stimulant Use Disorder and Overdose

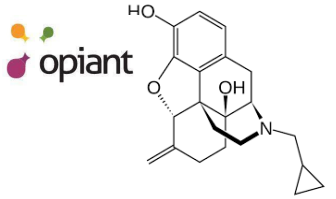
Program Scope:

- Development of new medications opioid and stimulant use disorders and overdose
- New formulations of existing medications to treat OUD
- Longer-duration opioid antagonists to counteract fentanyl overdose
- New interventions for opioid-induced respiratory depression
- Novel digital and neuromodulatory therapeutics for OUD
- Biologics, including vaccine and antibody development
- Oral consequences of MOUD

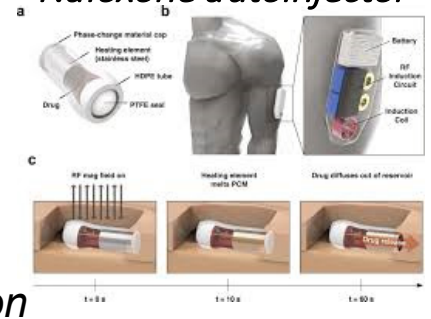
Progress so far:

- **70 compounds and 9 new targets being evaluated**
- **34 Investigational New Drug applications filed with the FDA**

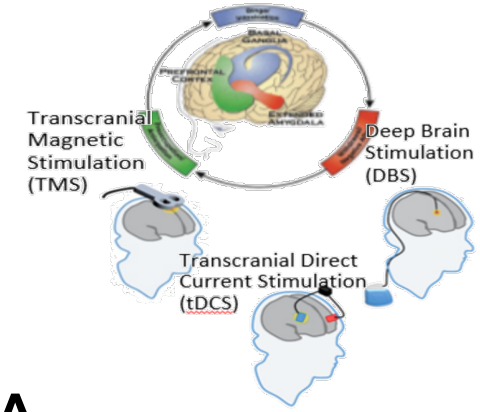
Nalmefene



Naloxone autoinjector



Neuromodulation



Thank you

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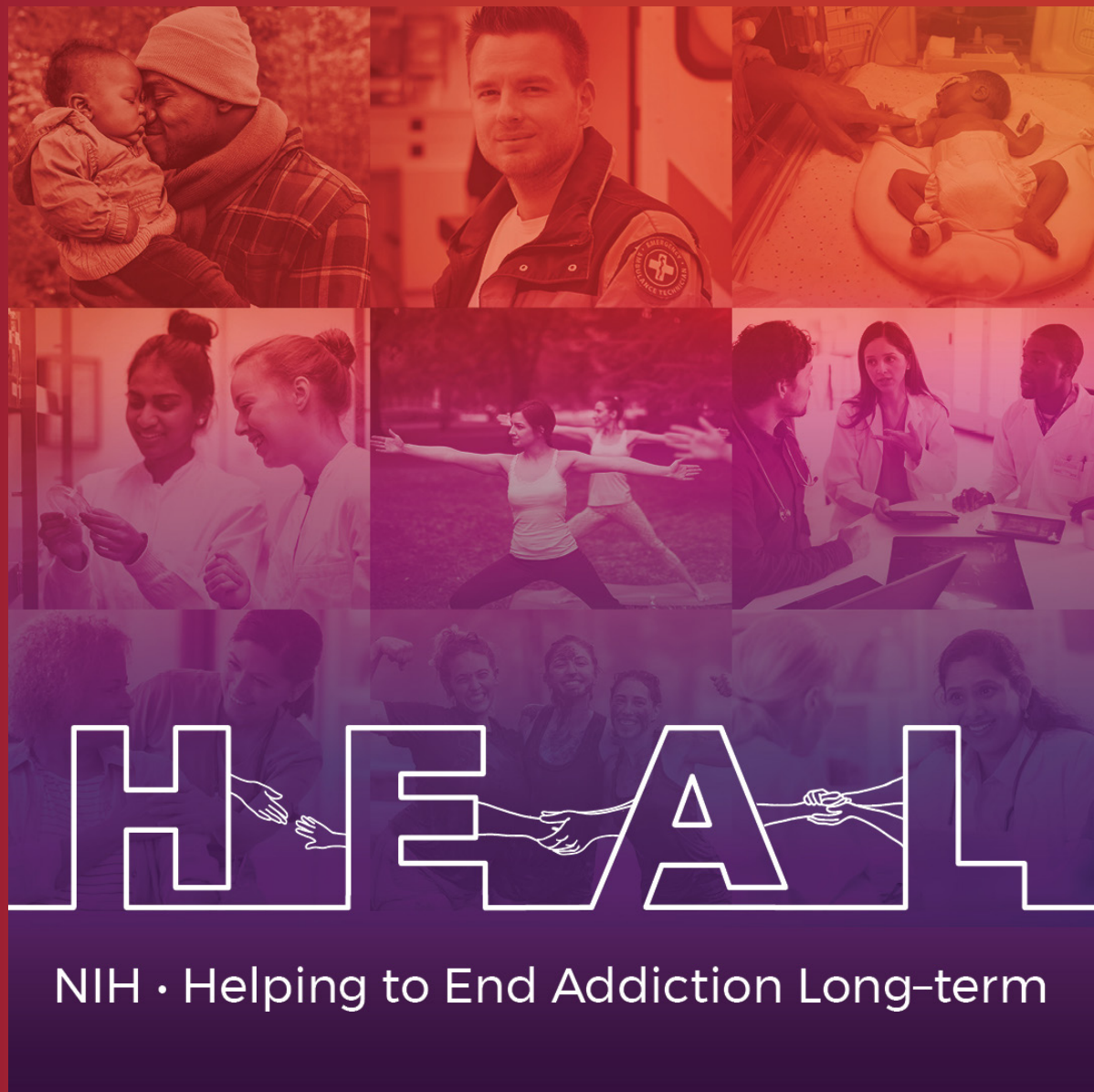
How HEAL is Targeting Pain Underlying the Opioid Crisis

Walter J. Koroshetz, M.D.
Director, NINDS



National Institutes of Health
HEAL Initiative

Pain – Public Health Crisis and Individual Burden

Nationwide prevalence of pain is high

50 million adults with chronic pain

25 million report severe pain daily

20 million with high impact chronic pain*

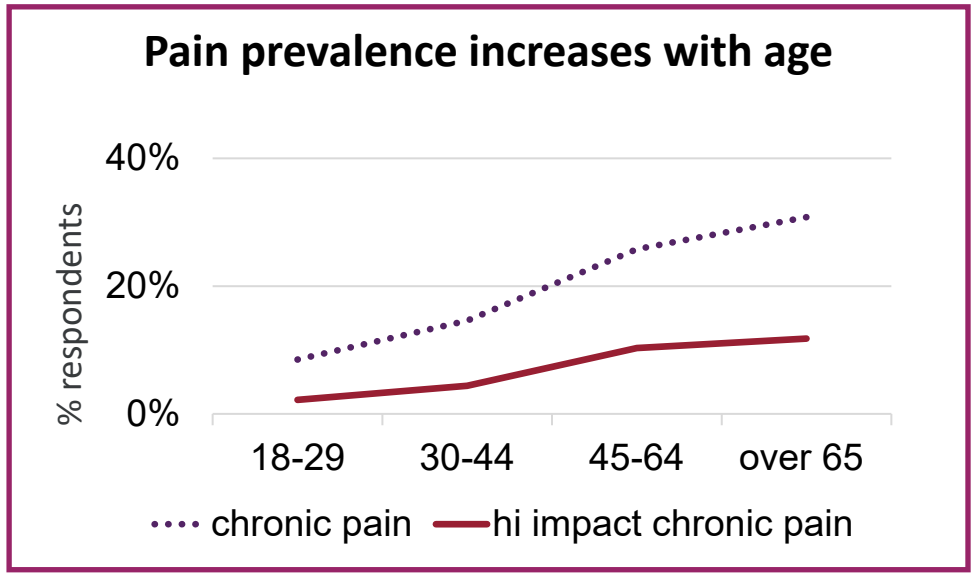
More rural than urban dwellers report pain

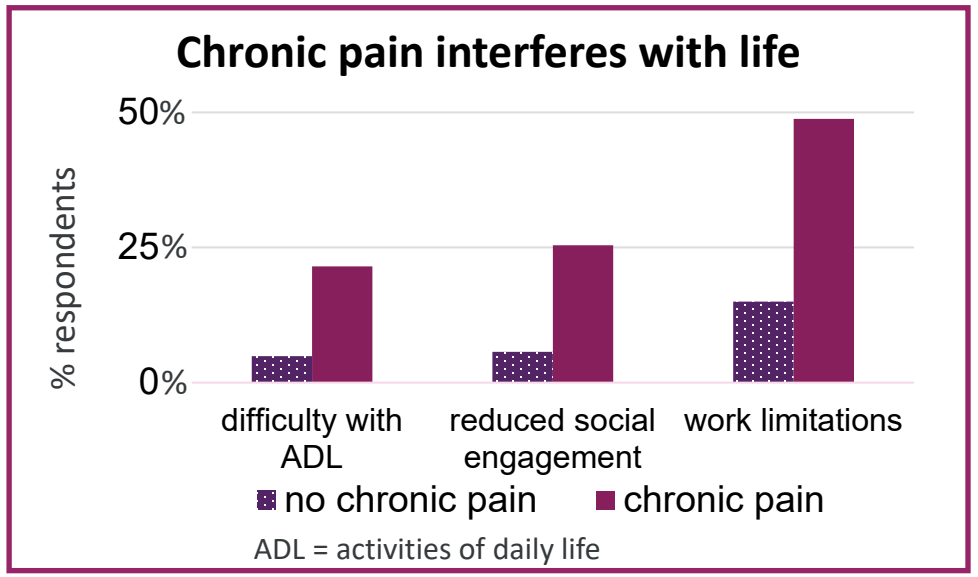
28% of rural & 16% of urban residents with chronic pain

11% of rural & 6% of urban residents with hi impact chronic pain

*high impact chronic pain = pain lasting more than 3 months that interferes with life (school, work, social life, etc.)

https://www.cdc.gov/nchs/products/databriefs/db390.htm





HEAL Initiative: How we got here

National Opioids Settlement

New national opioid settlements have been reached with Teva, Allergan, CVS, Walgreens, and Walmart. This revised and updated website provides copies of these agreements and earlier national opioid settlements with Janssen and distributors Cardinal, McKesson, and AmerisourceBergen, as well as additional documents and information concerning these proposed settlements. The agreements themselves control the terms of the settlements, and entities eligible to participate in the settlements should consult with counsel about participation. The site was created and is maintained by the Plaintiffs' Executive Committee.

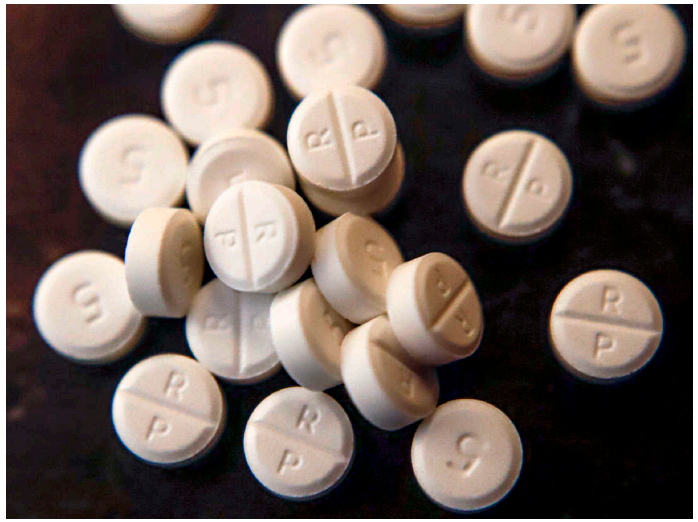
Teva & Allergan Settlements

Walmart, Walgreens, & CVS Settlements

Distributor & Janssen Settlements

FAQs, Explanatory Charts, & Frequently Referenced Documents

State Participation Chart & Documents



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$26 Billion Agreement with Opioid Distributors/Manufacturer

On July 21, 2021, a bipartisan coalition of attorneys general announced final agreements with Johnson & Johnson, a manufacturer of prescription opioids, and the three major pharmaceutical distributors — Amerisource Bergen, Cardinal Health, and McKesson. These agreements resolve legal claims against those companies stemming from actions that fueled the opioid addiction epidemic in return for their payment of $26 billion and commitment to make major changes in how they do business to improve safety and oversight over the distribution of prescription opioid.

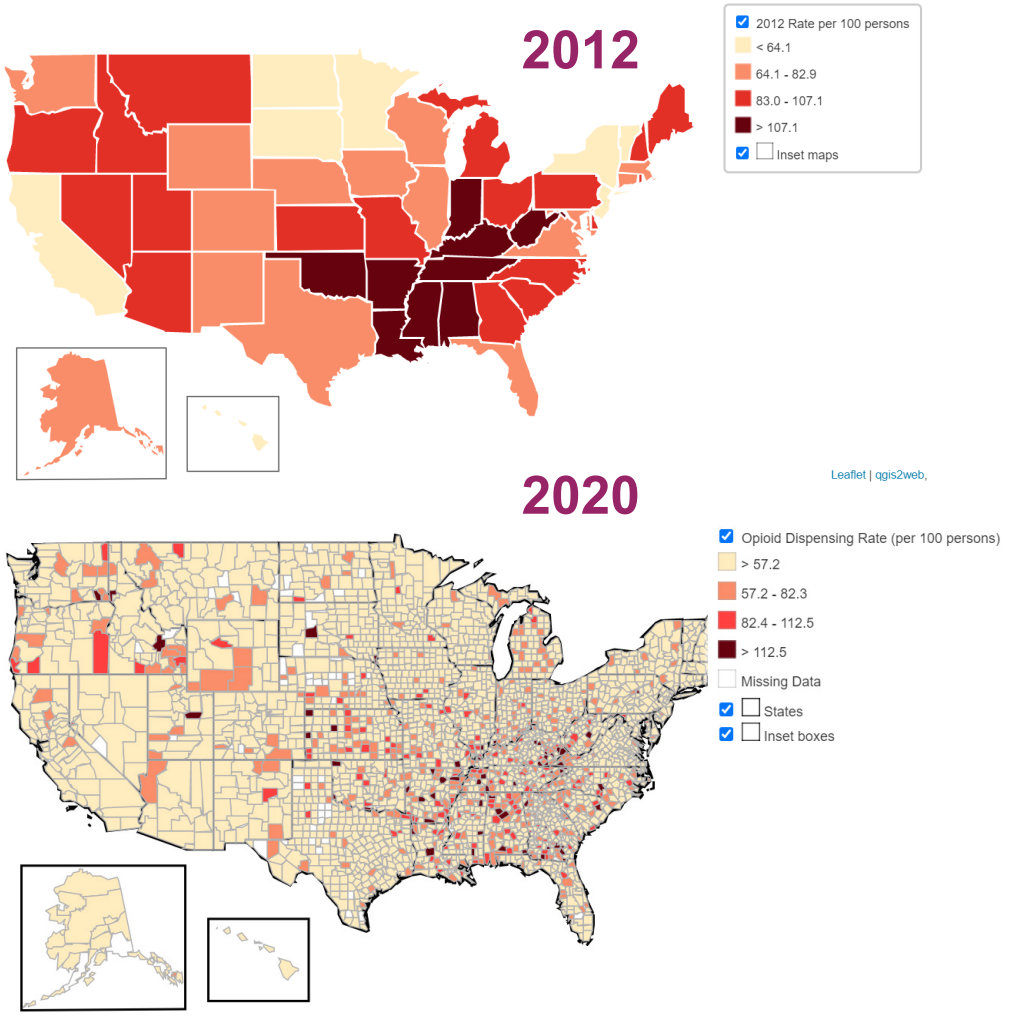
Most of the funds from the settlement… will go to health care and drug treatment programs designed to ease the opioid crisis

HEAL Initiative: Where we are now

- Opioid prescriptions have dropped from 81.3/100 persons in 2012 to 43.3/100 persons in 2020.

- Dispensing rates for opioids vary widely across different states and counties with some 9x's the national average. Emerging hotspot areas are identified by the darker colors on the maps.

- **Treating pain continues to be a significant challenge.**



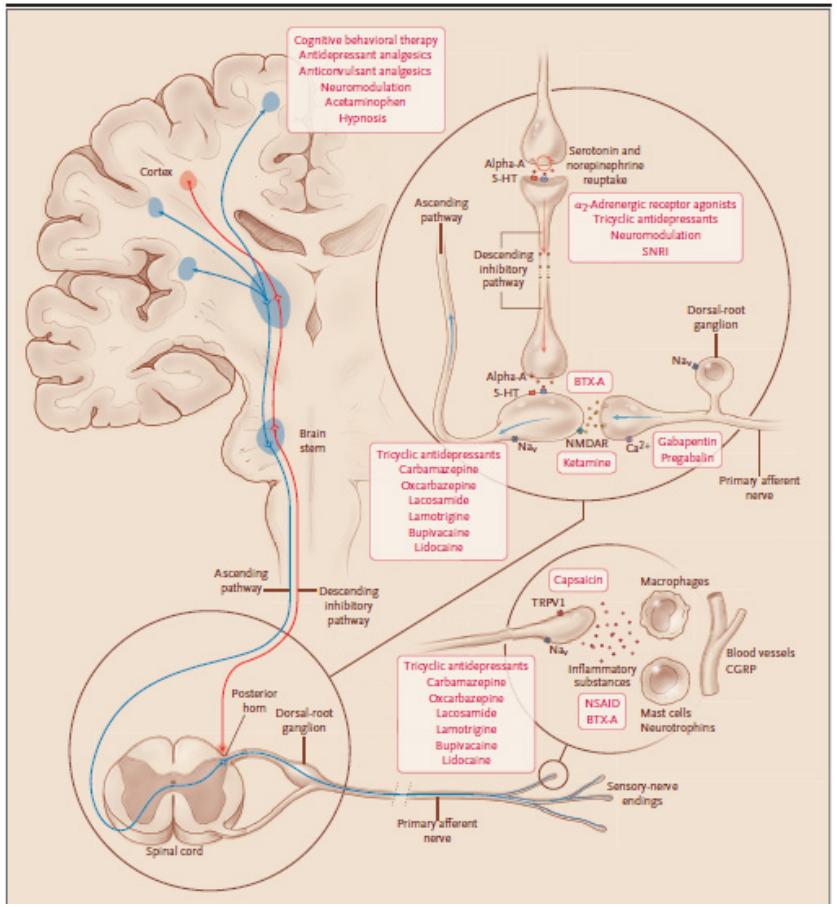
We have been here before

- 1817: Friedreich Sertuerner discovers active ingredient-morphine. Physicians believe opium has been tamed. Morphine called “God’s own medicine” for long-lasting effects and safety.
- 1827: Merck starts commercial manufacture of morphine.
- 1895: Bayer company purifies heroin and used to wean individuals with morphine dependence.
- 1898: 1/200 persons in the US have an opioid use disorder, 60% are women.
- 1905: US Congress bans opium.
- 1914: US requires doctors prescribing narcotics to register.

OPIUM—THE POOR CHILD'S NURSE.

Advances in Pain Science

- The last few decades have seen a revolution in our understanding of the pain system.
- Nobel Prize in 2021 for molecular discovery pain science.
- Human genetics identified causes of both insensitivity to pain and hypersensitivity.
- BRAIN Initiative produced tools to map, monitor and modulate pain circuits.



The Pain Therapeutics Landscape: Industry

- Industry-wide clinical pipeline for pain therapeutics has **declined 44%** in the past 5 years.
- Venture capital into U.S. companies with novel drug programs in pain totaled $0.86 billion over the last 10 years. By comparison, oncology venture investment raised during the same 10 years was $35.7 billion.
- There is a definitive need for small businesses to come into this space to de-risk projects that can be partnered for Phase II and commercialization.

Excluding drugs for migraine headaches, no drugs with novel targets have been approved in the last five years for pain.

HEAL Initiative: Pain Research Priorities

Enhance Pain Management

- Accelerate the discovery and pre-clinical development of non-addictive pain treatments.
- Advance new non-addictive pain treatments through the clinical pipeline.
- Inform best practices for effective pain management while minimizing risk of addiction.

HEAL and the Development of Effective, Non-Addictive Pain Treatments

A primary goal of the HEAL Initiative is to accelerate the development of non addictive pain treatments by de-risking key steps

1. Focus on what is really worth investing in for drug development.
   - Validate biologic **targets** for their robust ability to affect specific pain conditions.

2. Ensure that we can robustly measure whether a drug is working as intended
   - Identify and validate **biomarkers** in human pain conditions that can be useful in learning what will work when test in people with a specific pain condition.

3. De-risk investment in pain treatments
   - Seed the **initial development** of novel treatments in specific pain conditions of unmet need to the point that subsequent steps can be completed by commercial entities.

Analgesics Development:

- ✓ Focus on deliverables
- ✓ Focus on scientific challenges
- ✓ Reduce program complexity
- ✓ Incentivize industry to reinvest

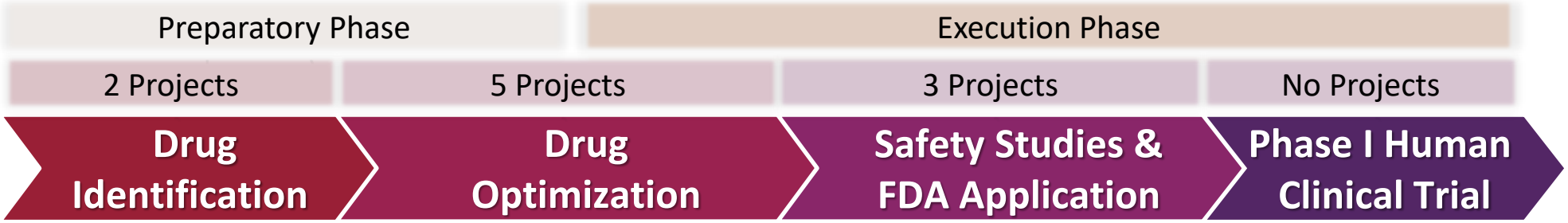
HEAL Pain Therapeutics Development Program (PTDP)

HEAL Funded Projects (pre-2019)

- ✓ **1 Completed Phase I Clinical Trial**
- ✓ **1 licensed to Vertex Pharmaceuticals**

Current Program At-A-Glance

- PTDP began in **2019**
- **15** awards made, **>100** applications received
  - **6** advanced to Execution Phase
    - ✓ **1 Licensed to Biohaven Pharmaceuticals**
  - **2** did not advance to Execution phase due to milestones not met
  - **7** in Preparatory Phase
  - **2** being awarded



Non-dilutive funding to support pain therapeutic development that maintains the IP of the grantee

Lead=Preclinical Candidate

Addressing Pain Through US Small Businesses

- **46 companies** funded for **49 projects**, spanning the pain interests of **9 NIH Institutes.**
- **$50M** allocated to HEAL small business programs targeting pain management.

→ **HEAL-funded businesses working in pain have raised over $160M in private investment since HEAL's inception.**

Example HEAL Pain Management Small Business Projects:

- Development of new non-addictive analgesics
- Drug discovery for novel pain targets
- Devices to treat pain
- Objective diagnostic tools
- Screening tools for pain therapy development
- Tools for basic pain research

Pain Circuit Science Advancing with New Tools

NEUROSCIENCE

An amygdalar neural ensemble that encodes the unpleasantness of pain

Gregory Corder[1,2,3,4*†], Biafra Ahanonu[5,6,7*], Benjamin F. Grewe[5,7‡], Dong Wang[1], Mark J. Schnitzer[5,6,7,8§], Grégory Scherrer[1,2]

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

PAIN

Neuromodulation using ultra low frequency current waveform reversibly blocks axonal conduction and chronic pain

Martyn G. Jones[1,2], Evan R. Rogers[3,4], James P. Harris[5], Andrew Sullivan[5], D. Michael Ackermann[5], Marc Russo[6], Scott F. Lempka[3,4,7], Stephen B. McMahon[2*]

nature neuroscience

ARTICLES

https://doi.org/10.1038/s41593-020-0632-8

Check for updates

General anesthetics activate a potent central pain-suppression circuit in the amygdala

Thuy Hua[1,3✉], Bin Chen[1,3], Dongye Lu[1], Katsuyasu Sakurai[1], Shengli Zhao[1], Bao-Xia Han[1], Jiwoo Kim[1], Luping Yin[1], Yong Chen[2], Jinghao Lu[1] and Fan Wang[1✉]

NEUROSCIENCE

Layer-specific pain relief pathways originating from primary motor cortex

Zheng Gan[1], Vijayan Gangadharan[1†], Sheng Liu[1], Christoph Körber[2], Linette Liqi Tan[1], Han Li[1], Manfred Josef Oswald[1], Juhyun Kang[1], Jesus Martin-Cortecero[3], Deepitha Männich[1], Alexander Groh[3], Thomas Kuner[2], Sebastian Wieland[2,4], Rohini Kuner[1*]

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

PAIN

Closed-loop stimulation using a multiregion brain-machine interface has analgesic effects in rodents

Guanghao Sun[1,2,3], Fei Zeng[2], Michael McCartin[2], Qiaosheng Zhang[2,3], Helen Xu[2], Yaling Liu[2], Zhe Sage Chen[1,3,4,5*], Jing Wang[2,3,4,5*]

Translating Discoveries into Effective Pain Treatments: HEAL's programs to advance medical device technologies

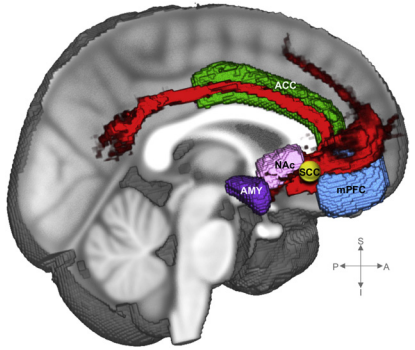
Concept Generation → Device Development → Device Optimization → Pre-IDE Studies → First in Human / EFS → Clinical Trials

HEAL Translational Development of Devices (U18)

HEAL Translational Devices (UG3 / UH3 / U44)

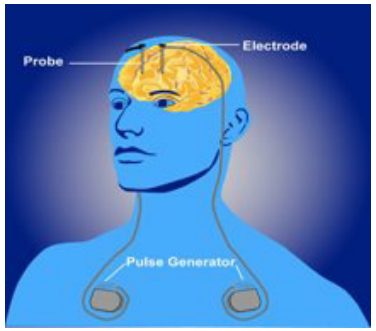
HEAL Clinical Devices (UH3)

HEAL EPPIC-Net



Novel Devices to Address Untreated Pain

Nader Pouratian, University of Texas Southwestern Medical Center



IDE = Investigational Device Exemption (submission to FDA)

Thank You!

Walter J. Koroshetz, M.D.
Director
National Institute of Neurological Disorders and Stroke
Email: koroshetzw@ninds.nih.gov
Website: http://www.ninds.nih.gov/

Follow me @NINDSdirector

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Novel Devices to Address Untreated Pain: A Brain Pacemaker for Chronic Low Back Pain

Nader Pouratian, M.D., Ph.D.
UT Southwestern Medical Center, Department of Neurological Surgery

Ausaf Bari, M.D., Ph.D.
David Geffen School of Medicine at UCLA, Department of Neurosurgery

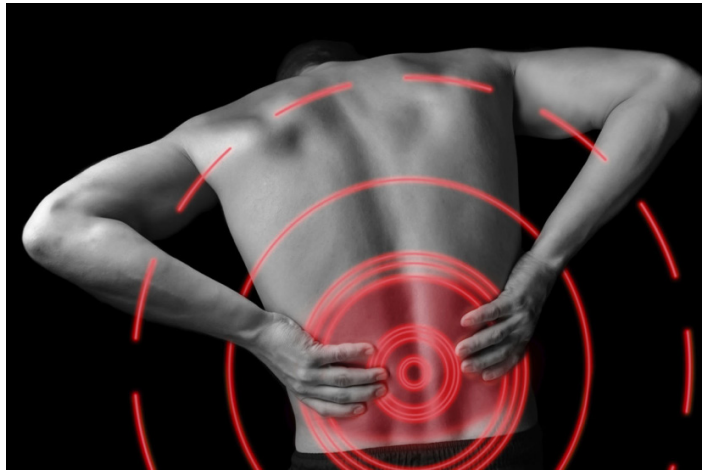
NIH National Institutes of Health
HEAL Initiative

Chronic Low Back Pain is the Leading Cause of Chronic Pain

The most common subtype of chronic pain: CHRONIC LOW BACK PAIN

***The* most common reason people will see a physician.**

Increase in long-term opioid use and a contributor to the opioid epidemic.



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Ausaf Bari, M.D., Ph.D.

Distinct Types, Mechanisms, and Targets for Treating Pain

(1) **Physical Pain**: Nociceptive

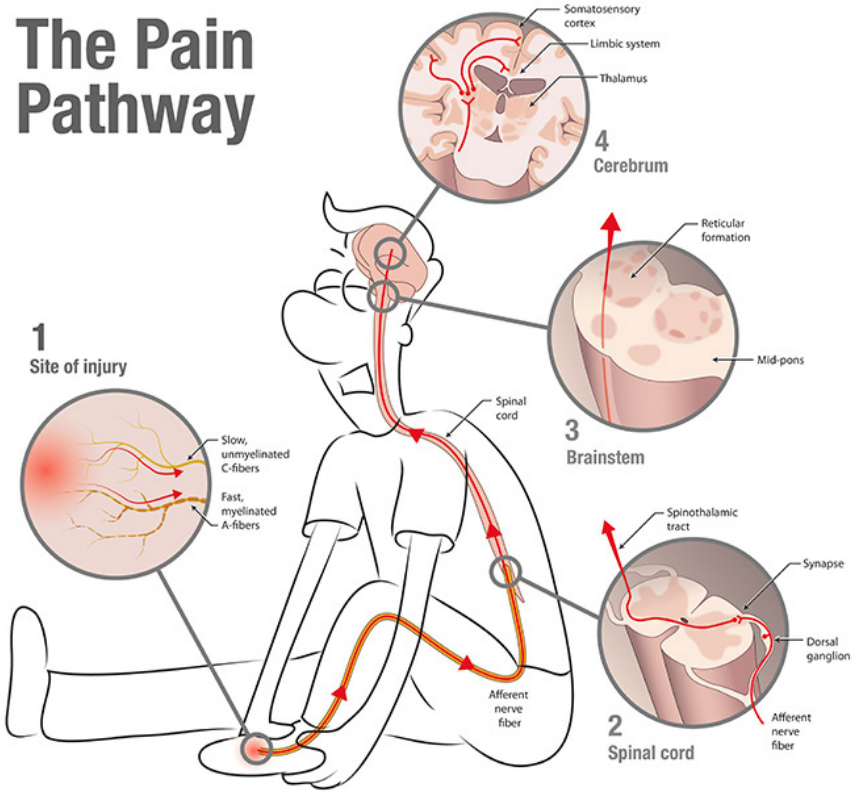
- Noxious stimuli continually irritating intact pain pathway
  - Cancer pain, inflammatory processes, myofascial pain

(2) **Nerve Injury**: Neuropathic

- Damaged neural structures abnormally transmitting signals in the absence of stimuli
  - Phantom limb pain, post-herpetic neuralgia, diabetic neuropathy, etc.

(3/4) **Pain in the Brain**: Emotional/Affective

- Psychological reinforcement of pain state



Our Approach: Target Pain Pathways in the Brain Using a Brain Pacemaker

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Ausaf Bari, M.D., Ph.D.

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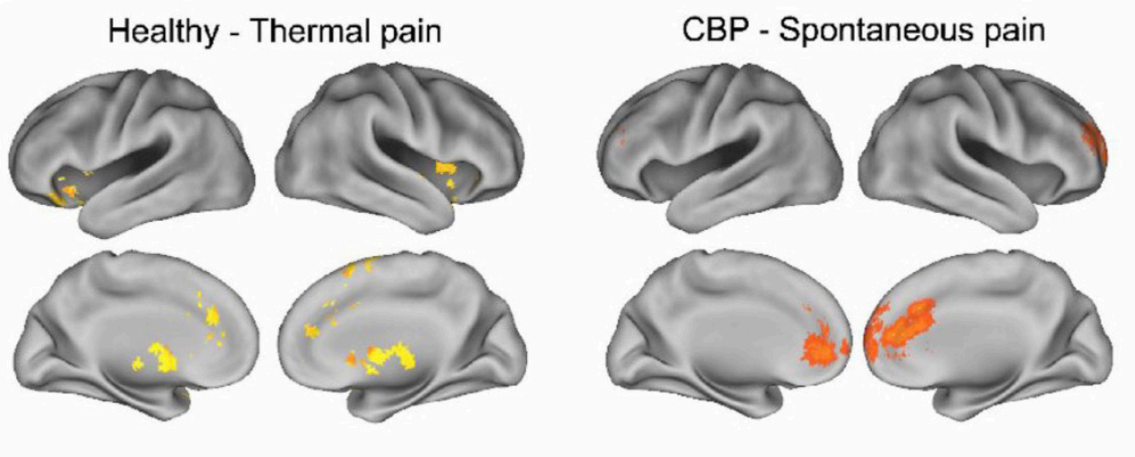
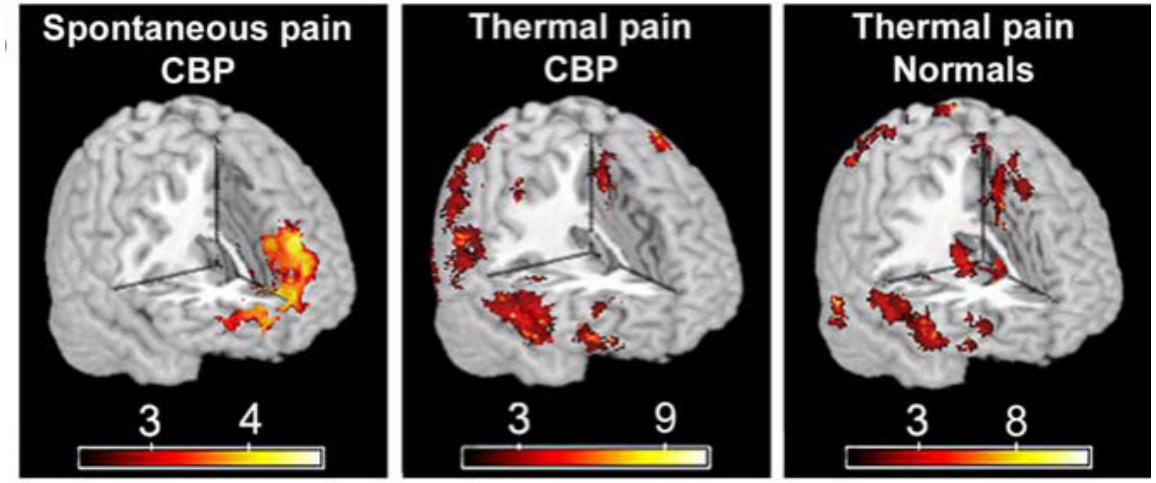
Chronification of Pain Occurs in the Brain





Baliki M N et al. J. Neurosci. 2006;26:12165-12173

Chronic pain **activates different areas** of the brain than acute pain.

People with chronic pain have **brains that are different** than those without pain.

The brain areas affected overlap with brain networks involved in **depression**.

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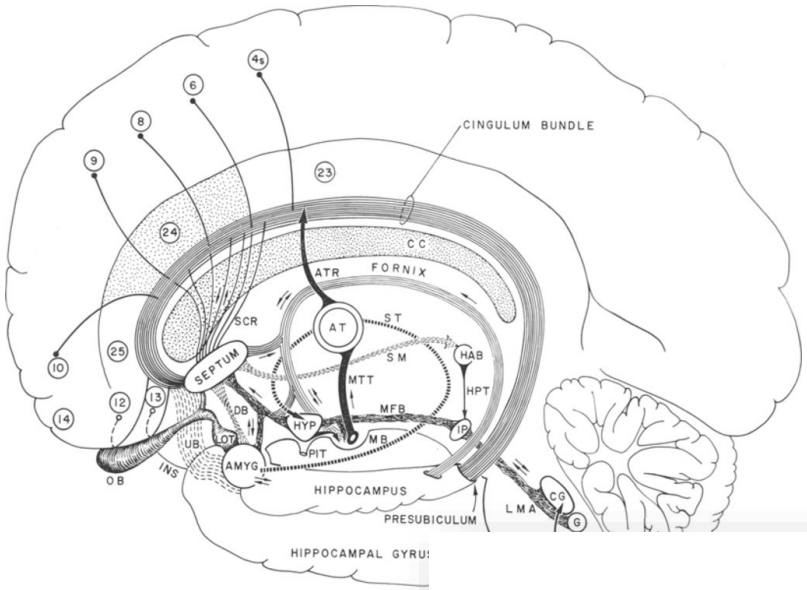
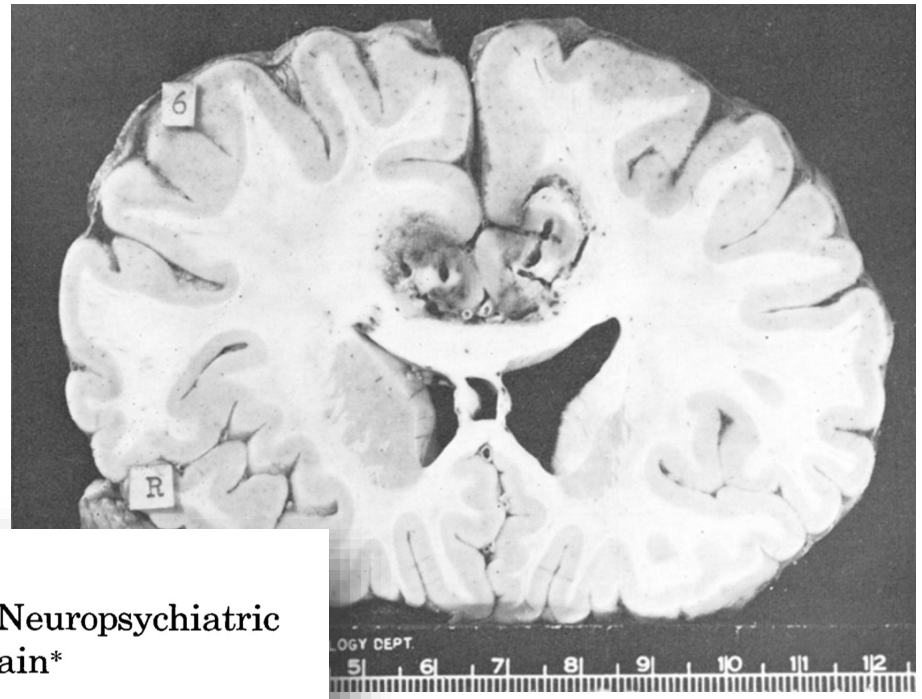
“Historical” Procedures for Pain Targeted the Brain





Stereotaxic Anterior Cingulotomy for Neuropsychiatric Illness and Intractable Pain*

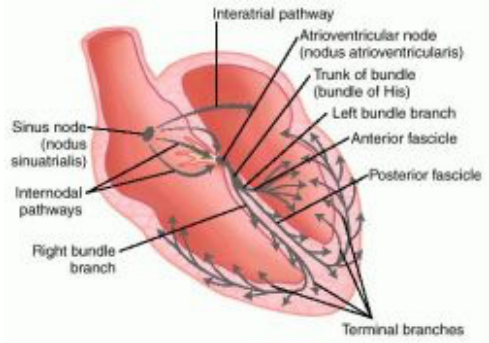
H. Thomas Ballantine, Jr., M.D.,† Walter L. Cassidy, M.D.,‡ Norris B. Flanagan, M.D.,§ and Raul Marino, Jr., M.D.**

Boston and Wellesley, Massachusetts

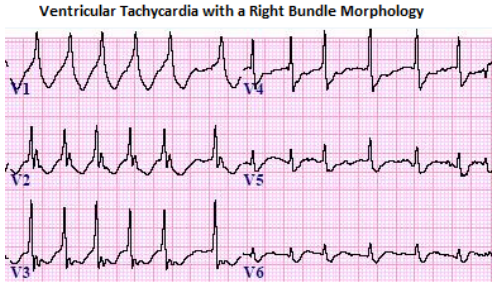
But only 50-60% effective and can lose effectiveness with time

If your heart is sick, you get a cardiac pacemaker

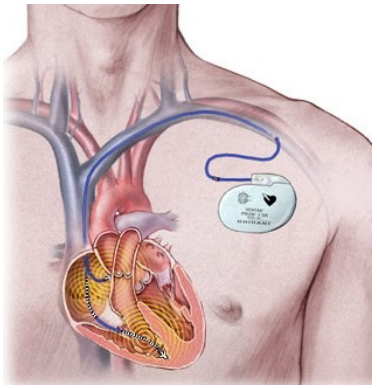
Cardiac Disease



Cardiac Arrhythmia



Cardiac Pacemaker



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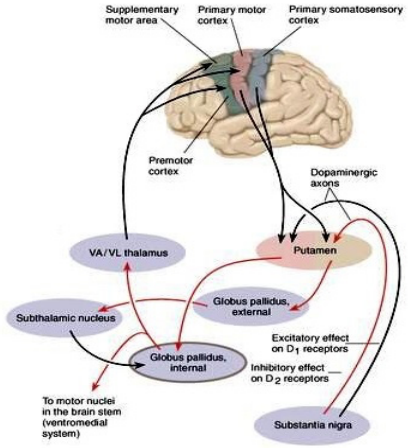
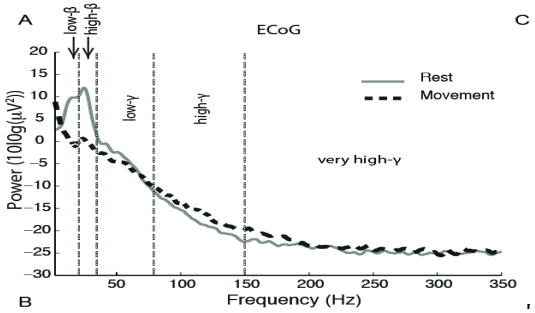
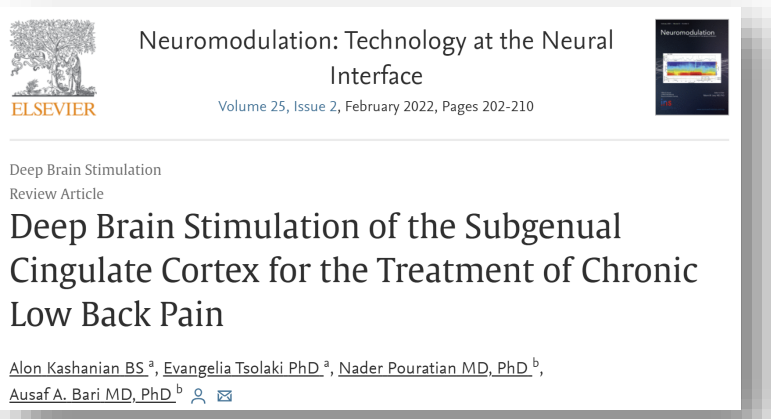
If your brain is sick, should you get a brain pacemaker?

Brain Disease

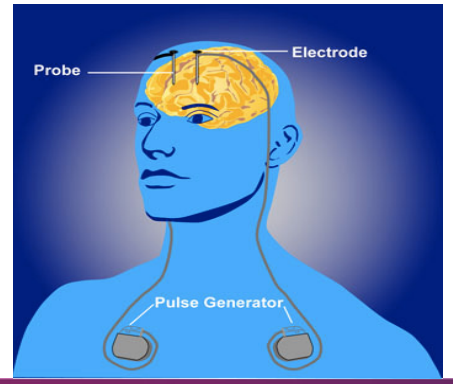


Brain Arrhythmia





Brain Pacemaker



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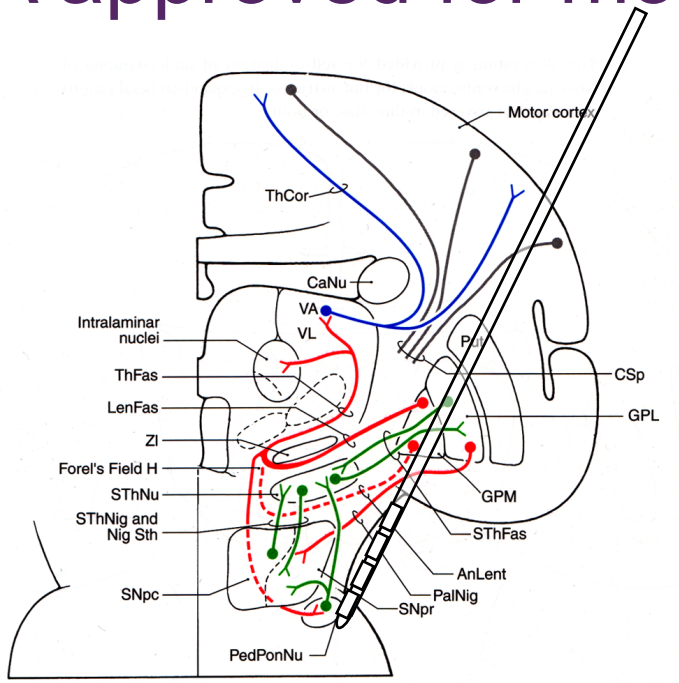
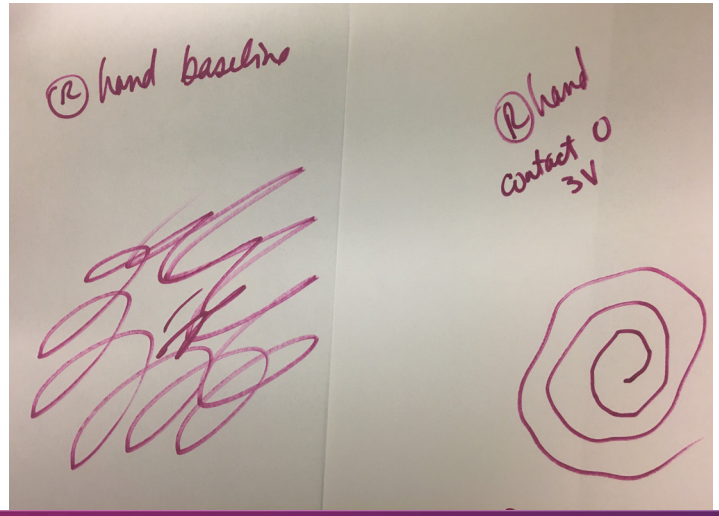
Repurposing Brain Stimulation:
FDA approved for movement disorders for >20 years





Deep Brain Stimulation Facts:
~175,000 implants worldwide
~1,000 implanting centers worldwide
<1% risk of brain injury.

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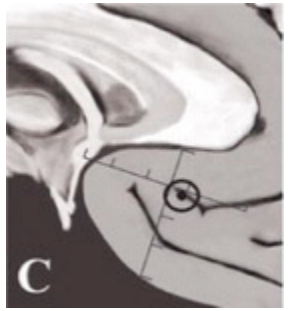
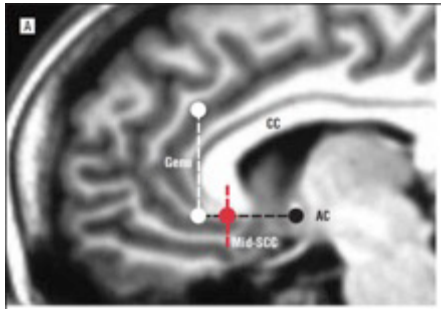
Personalized Targeting of a Central Hub for Pain

Stimulation Target

Anatomical Landmarks

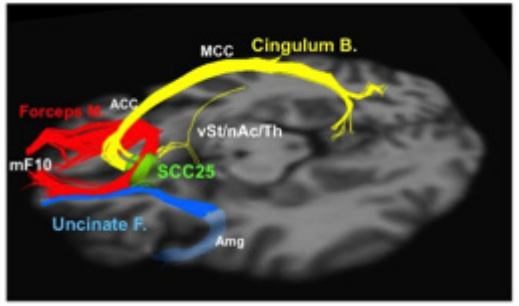


Hamani et al JNS 2009



Holtzheimer et al Arch Gen Psychiatry 2012

Diffusion Tensor Imaging

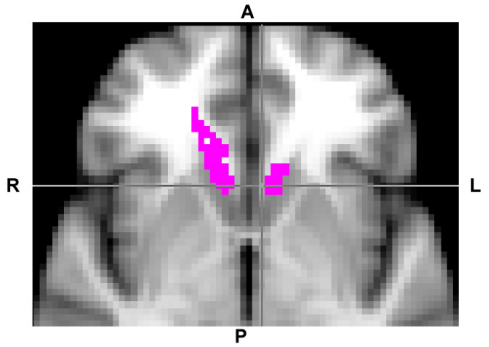


Riva Posse et al. Biol Psychiatry 2014

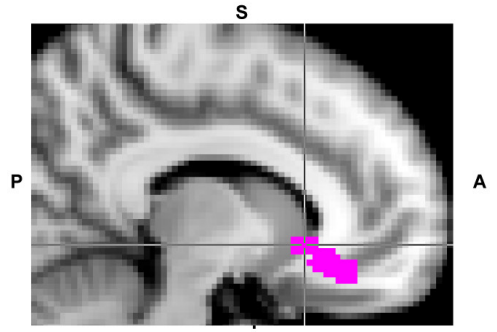
A personalized brain target that connects to the critical areas of the brain affected in depression AND chronic low back pain.

Alternatively, target a brain hub for addiction

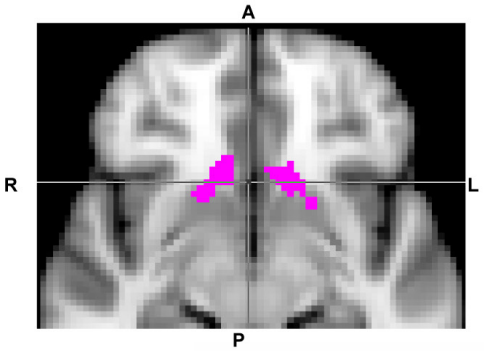
Right Medial Prefrontal Cortex



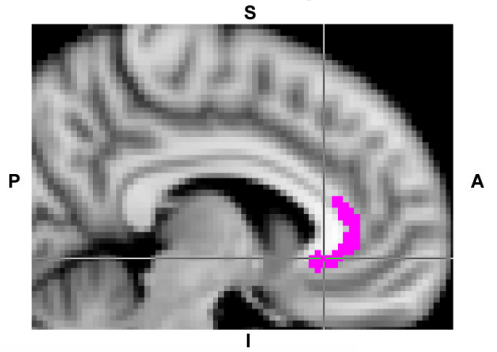
Left Medial Prefrontal Cortex



Ventral Striatum



Anterior Cingulate



Contents lists available at ScienceDirect

Psychiatry Research Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Short communication

Using probabilistic tractography to target the subcallosal cingulate cortex in patients with treatment resistant depression

Evangelia Tsolaki[a,*], Randall Espinoza[b,c], Nader Pouratian[a,d]

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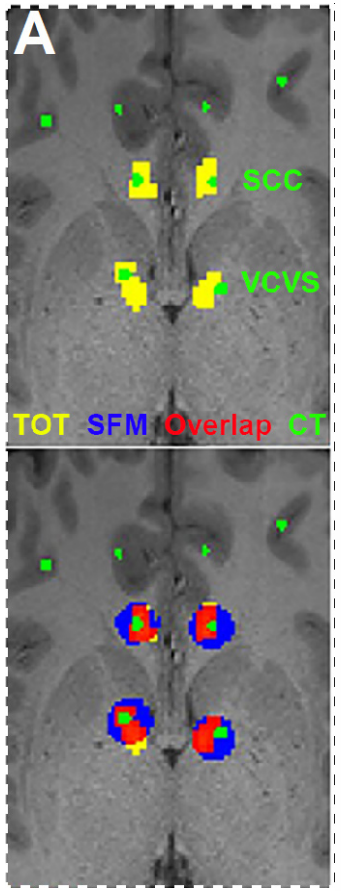
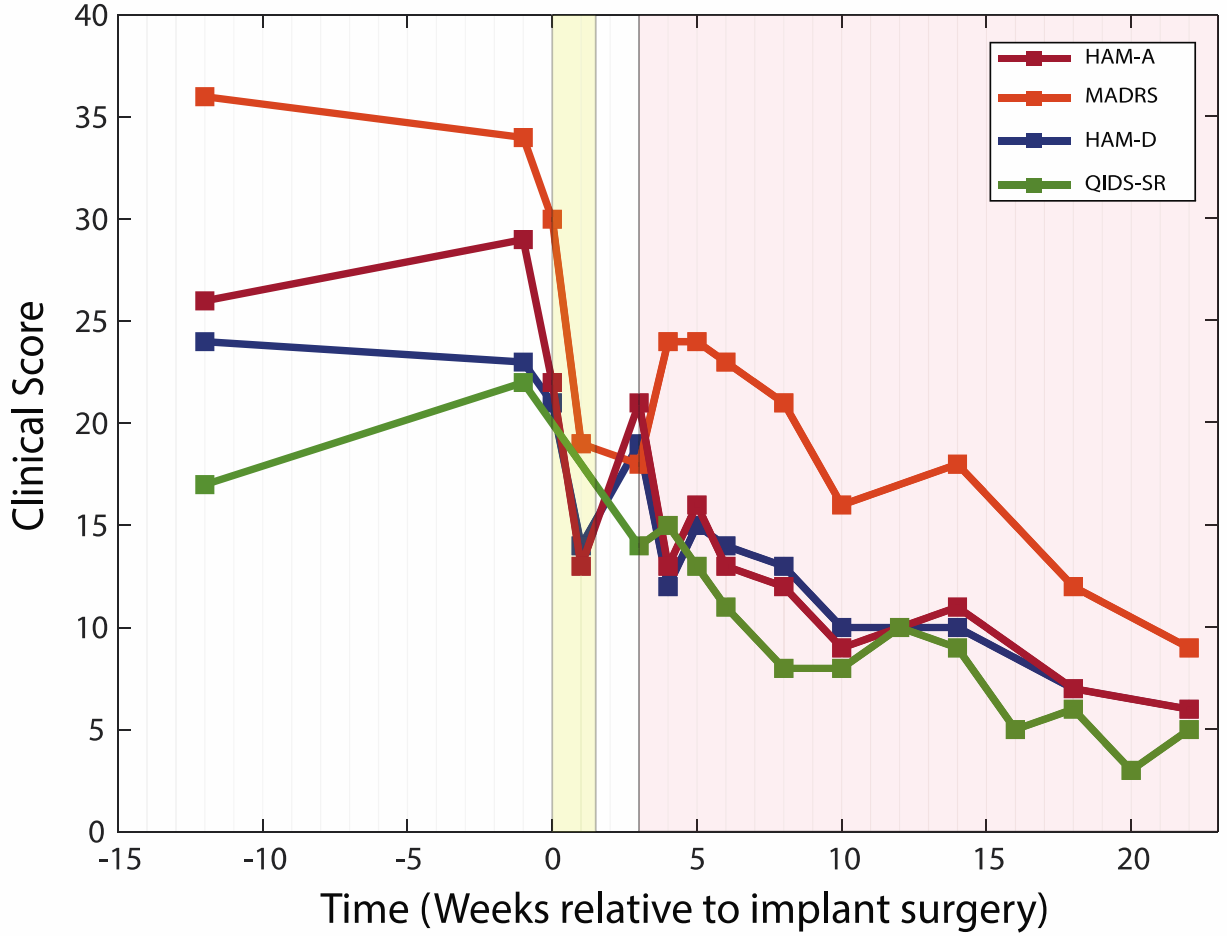
Deep Brain Stimulation for Depression



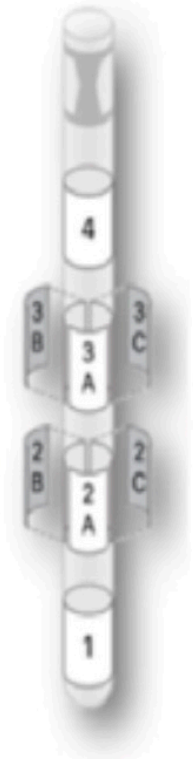


NIH BRAIN Initiative
UH3 NS103549

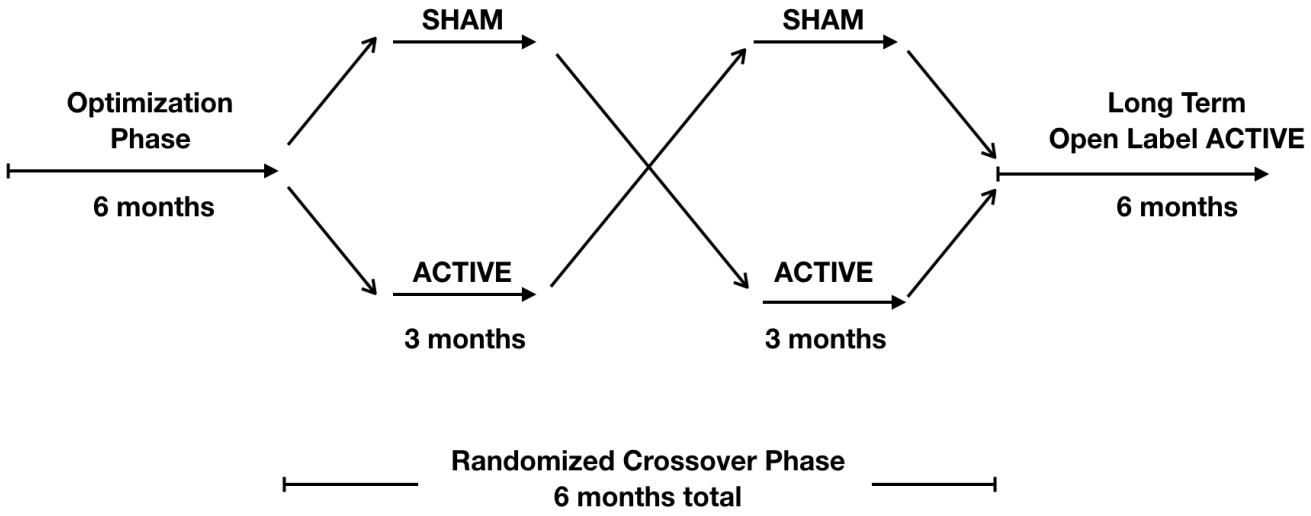
Sheth, Bijanki.... Pouratian. *Biol Psychiatry*. 2021 3223(21)01747-9

Brain Stimulation for Back Pain: First in Human Feasibility Study

“DBS of the SCC for the Treatment of Medically Refractory CLBP”



NCT04085406



Targeted Enrollment: 10 patients

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UH3 NS113661

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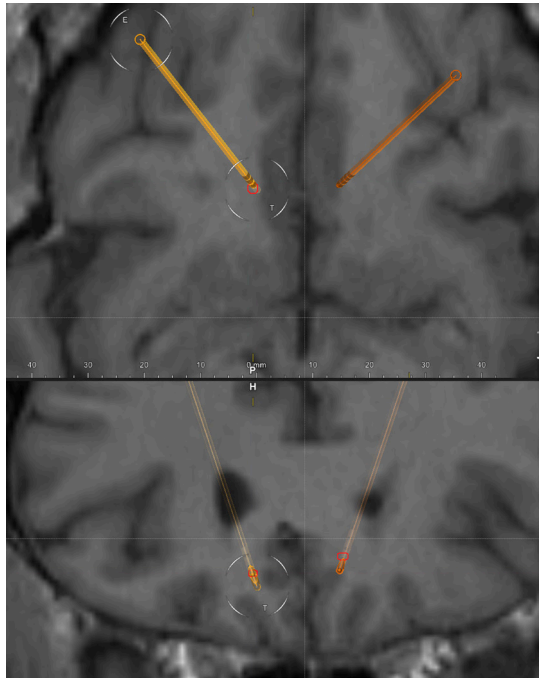
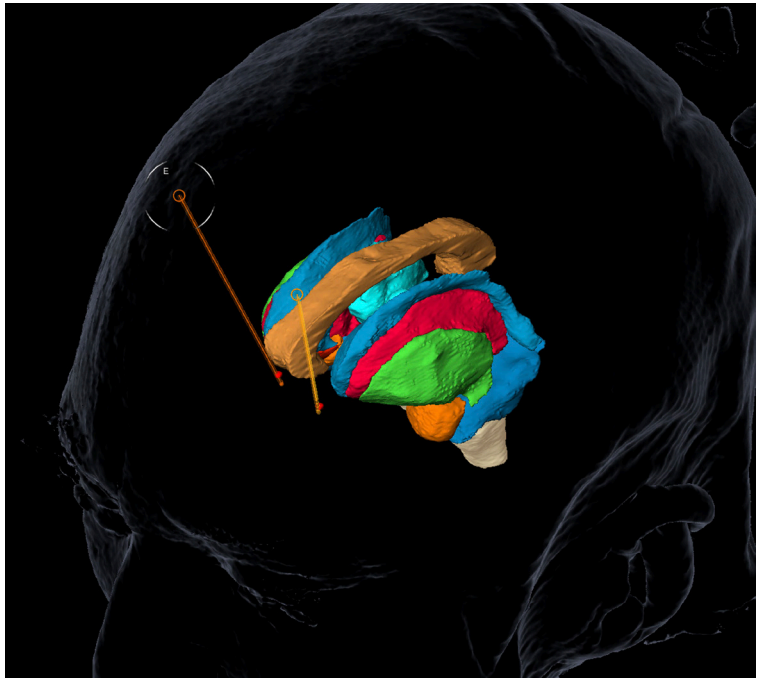
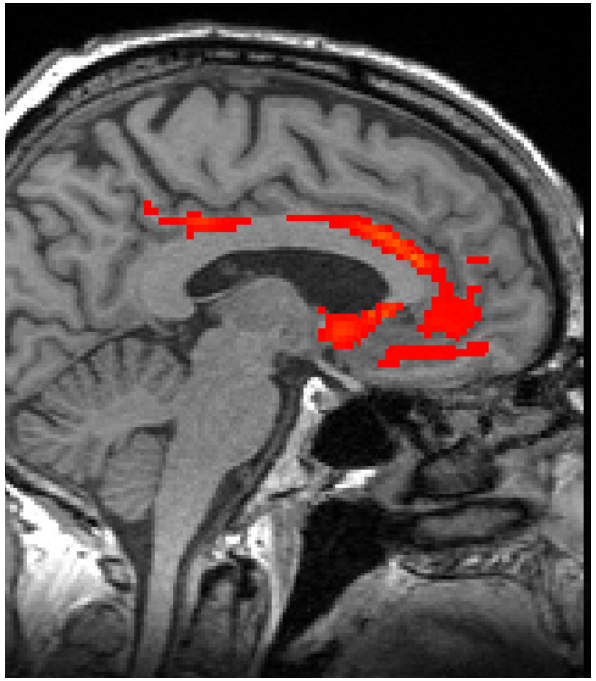
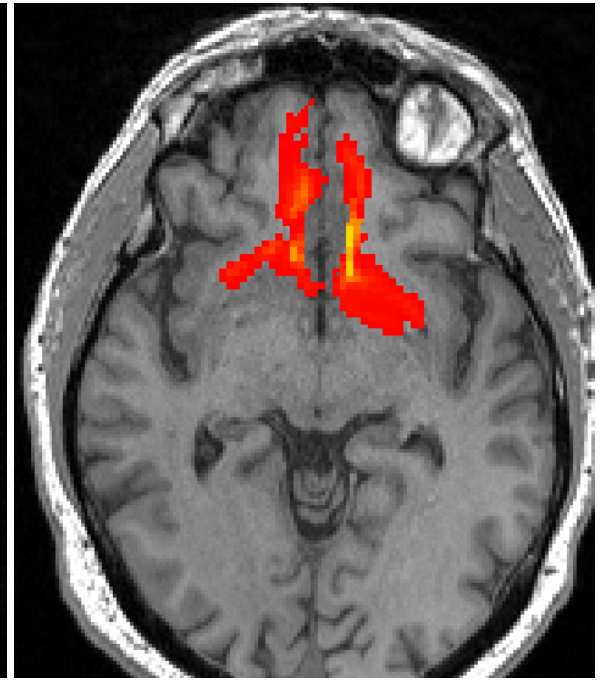
First Enrolled Participant

68 year old male with chronic LBP (8/10).

- *Prior low back surgery and failed spinal cord stimulation.*
- *No operative spinal pathology*

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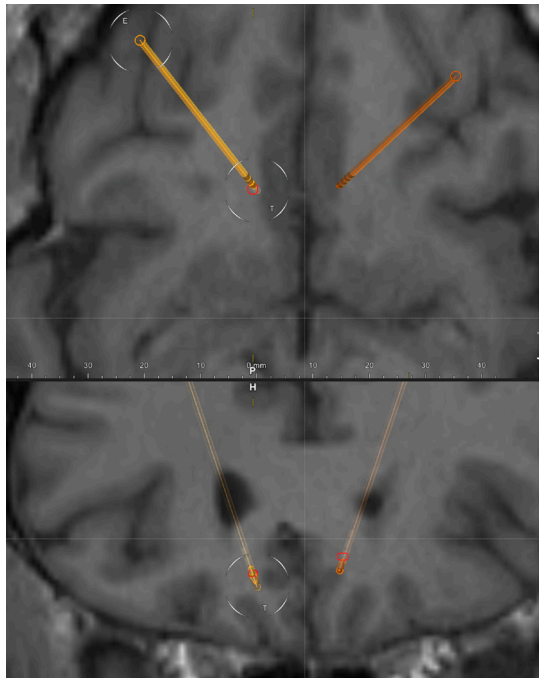
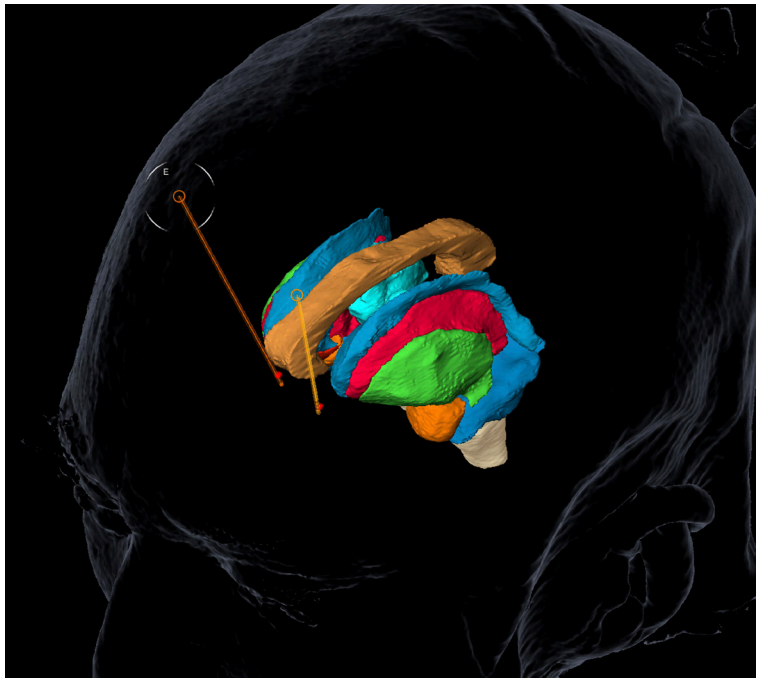
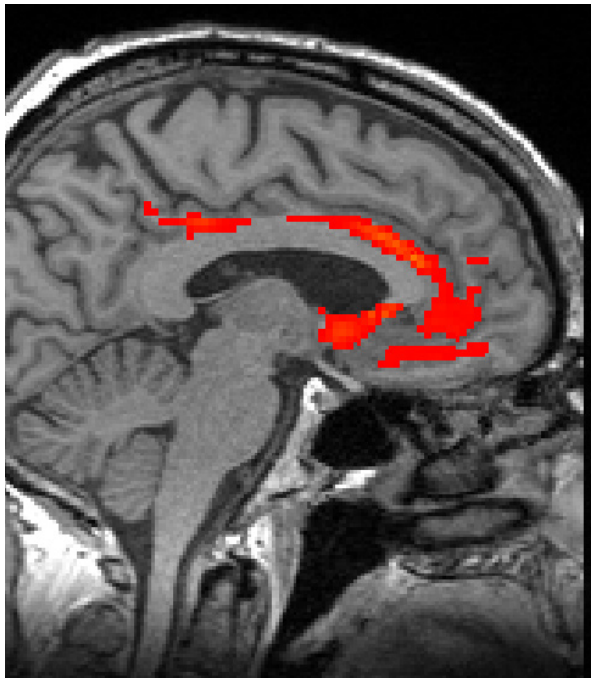
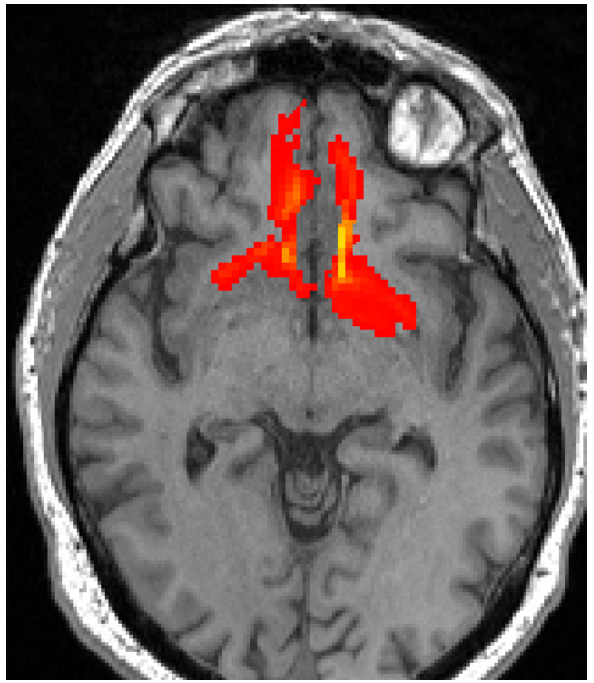
First Enrolled Participant

- *No procedural or stimulation related adverse events.*
- *Tolerated surgery well and discharged on POD 2*
- *30% improvement in pain initially.*
- *Able to start working out again and increased functional status*









Conclusions

***The brain changes with chronic pain*.**

Repurpose a known brain therapy to treat chronic pain.

Pain and Depression networks overlap significantly in the brain.

Therapy is improved with personalized mapping and targeting.

Recruitment ongoing.

Nader Pouratian, M.D., Ph.D.
Ausaf Bari, M.D., Ph.D.

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Xiao Hu, PhD

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Baylor
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Jiaynag Xiao

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Vaselios Christopoulos, PhD

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Ed Clark, MD
Hila Segev

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NIBIB, NINDS, NIGMS, NIMH, BRAIN Initiative, **HEAL Initiative**

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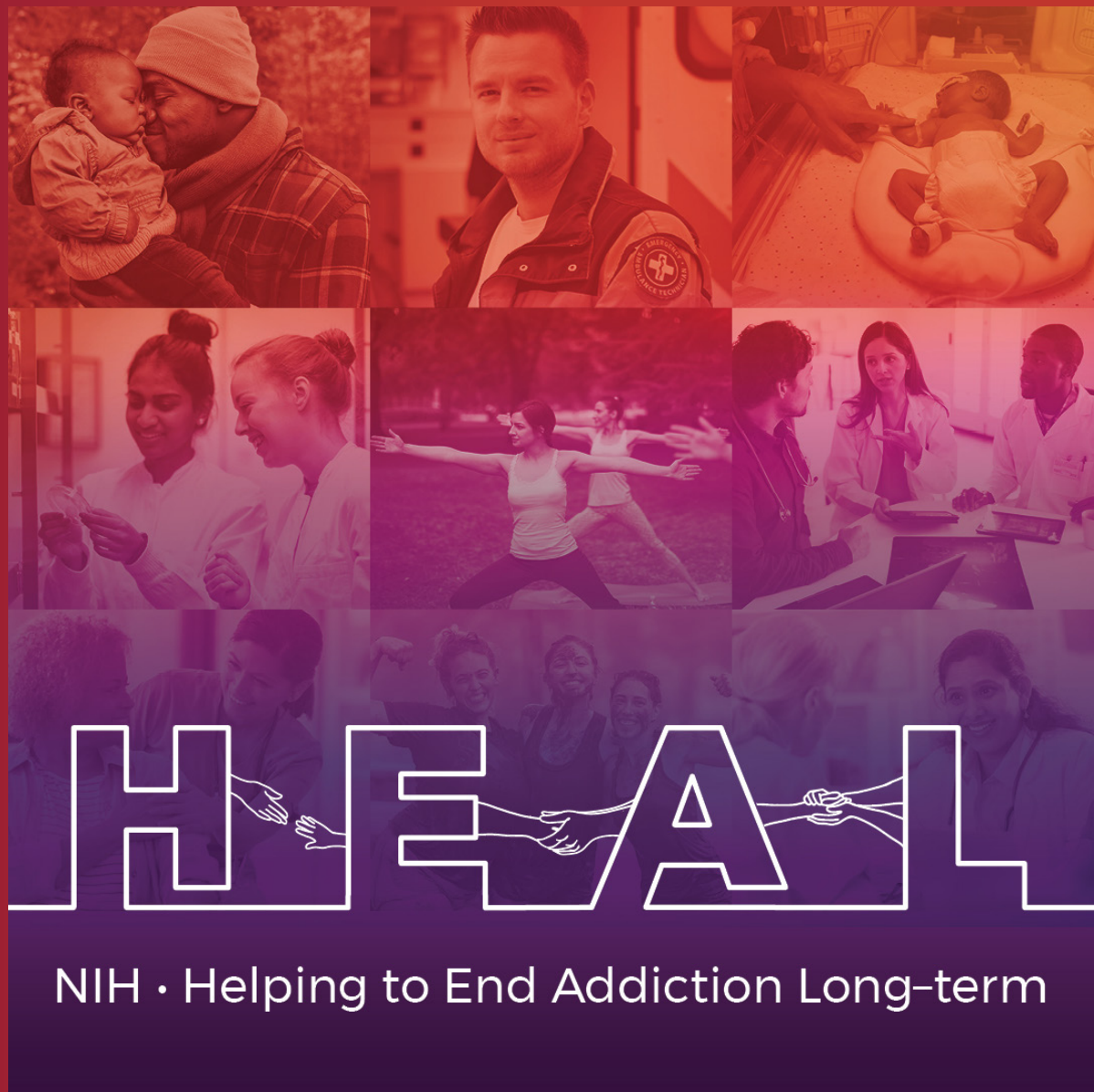
Innovation in Therapeutics to Address Opioid Use Disorder

Marco Pravetoni, Ph.D.
Rick L. Seaver Endowed Professor in Brain Health, Department of Psychiatry & Behavioral Sciences Department of Pharmacology, Center for Medication Development for Substance Use Disorder, University of Washington School of Medicine, Seattle WA



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Drug use and exposure risk: everchanging landscape

Opioid use disorders (OUD), substance use disorders (SUD), and overdose

- Heroin, prescription opioids (e.g., oxycodone), synthetic opioids (e.g., fentanyl)

Unknown street mixtures of opioids and stimulants

- Heroin/fentanyl
- Methamphetamine/fentanyl

New opioid-like synthetic compounds

- Regulatory status evaluated by Drug Enforcement Agency (DEA)

Counterfeit prescription pills can contain a potentially lethal dose of fentanyl

Street tradenames to market illicit drug supply to customers

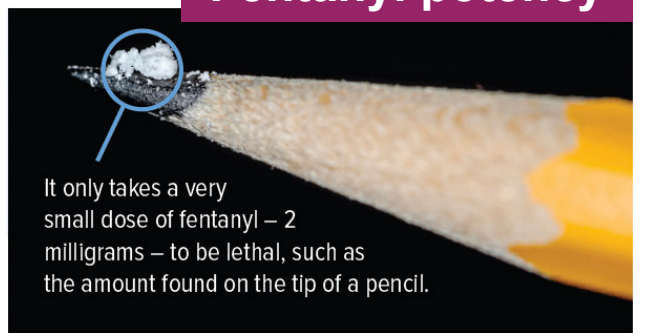
- “Purple heroin”, “rainbow fentanyl”, etc.

Widespread access to potent and toxic synthetic compounds

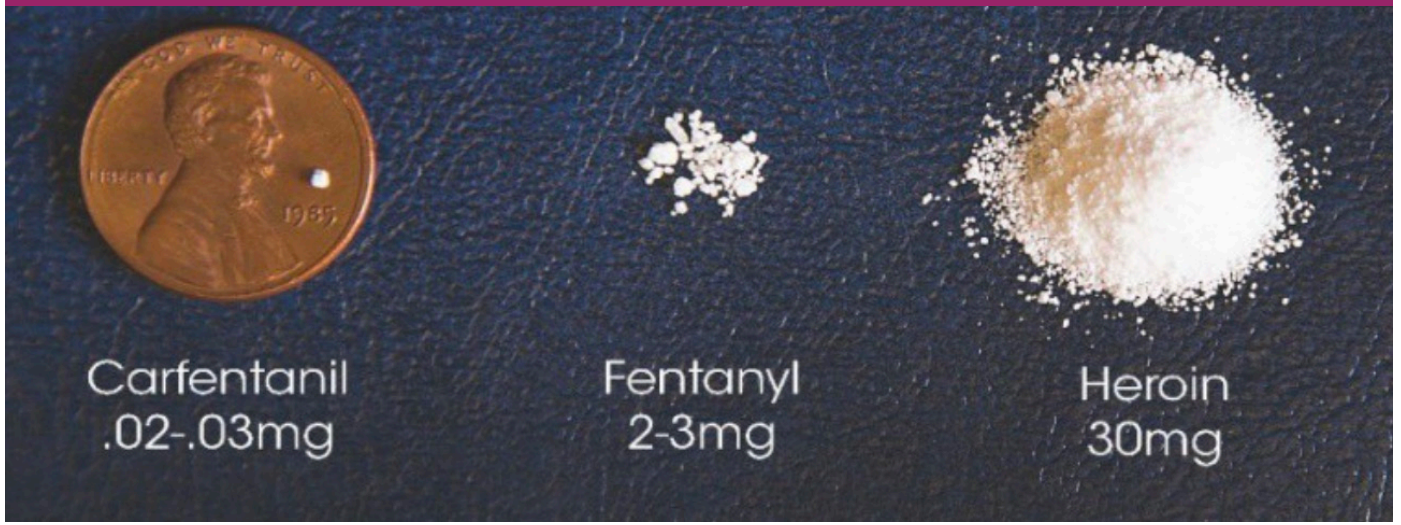
Fentanyl analogs unique pharmacology and pharmacokinetics

- Higher potency (e.g., carfentanil)
- Faster onset and longer half-life
- Target opioid receptors and other non-opioid receptors
- Difficult to counteract with naloxone

Fentanyl potency



LETHAL DOSE: Carfentanil < fentanyl < heroin

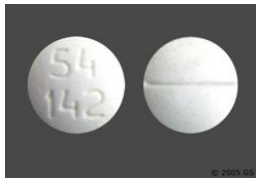


Current FDA-approved treatments are safe, effective, but NOT enough to curb the current opioid overdose epidemic

Very few FDA-approved commercial products consisting of 4 drugs targeting opioid receptors

- Methadone (agonist): replacement therapy
- Buprenorphine (partial agonist)
- Naltrexone (antagonist): antagonism therapy
- Naloxone (antagonist): antagonism therapy
- Combinations (e.g., Suboxone®)
- Extended-release formulations (e.g., Vivitrol®)

Methadone
Daily Tablet



Naltrexone
Monthly Injection

Buprenorphine
Half-year Implant

Naloxone
Nasal Spray for Emergency

Buprenorphine
Daily Tablet

zubsolv® sublingual tablets
(buprenorphine and naloxone) C-III

Suboxone® Sublingual Film
(buprenorphine and naloxone) C-III
2 mg/0.5 mg • 4 mg/1 mg • 8 mg/2 mg • 12 mg/3 mg

BUNAVAIL®

Current FDA-approved treatments are safe, effective, but NOT enough to curb the current opioid overdose epidemic

Only 1 out of 5 patients access treatment for OUD in the United States

- Regulatory or administrative hurdles
- Side effects, sub-optimal efficacy, abuse liability, diversion
  - e.g., naltrexone requires detoxification

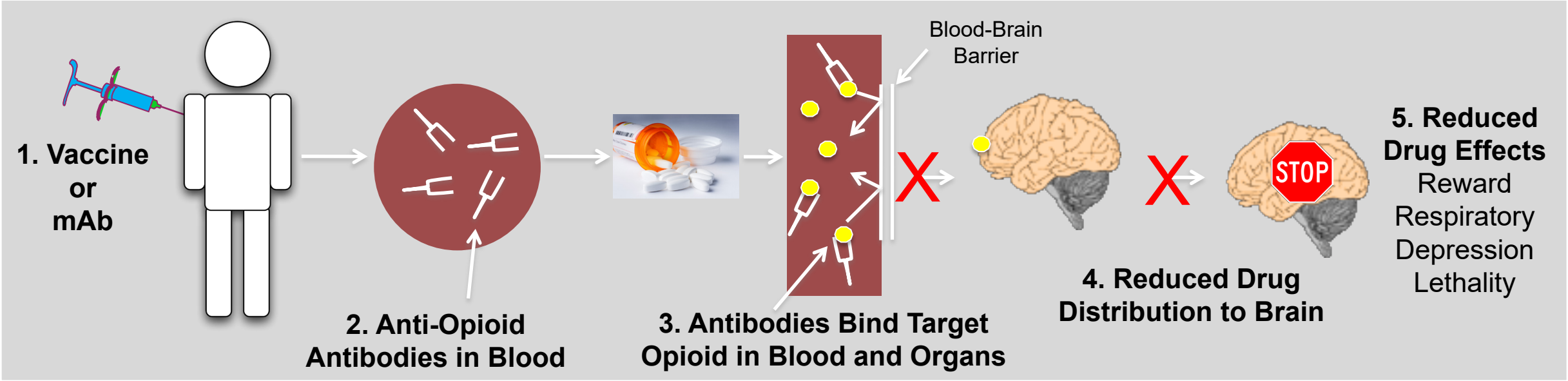
Pharmacotherapies offer limited long-term protection against overdose

- No options for non-drug users and other patient populations at risk of exposure

Naloxone is the only countermeasure for overdose reversal in both drug users and non-users

- Efficacy of naloxone against fentanyl(s) is short-lived and may require multiple doses

Our HEAL solution to treat OUD and prevent overdose: Vaccines and Monoclonal Antibodies (mAb)



- Longer-lasting, safe, and selective interventions for patients diagnosed with OUD, SUD, and other patient populations at high-risk of exposure
- Vaccines and mAb do not interfere with medications for pain, addiction, critical care
- Vaccines and mAb can be combined with current medications (e.g., vaccine + methadone)

Our HEAL pipeline of vaccines for OUD and overdose

Discovery	Pre-clinical R & D	GMP & GLP	IND	Phase I

Oxycodone Vaccine, Adjuvanted

- IND April 2020, completed manufacturing, ongoing Phase I Clinical Trial

Heroin Vaccine, Adjuvanted

- Completed pre-IND 2022, started manufacturing

Fentanyl Vaccine, Adjuvanted

- Completed pre-IND 2021, started manufacturing

Next-Gen Vaccine Formulations

- New technologies
- Target multiple opioids at once
- New targets

Pre-clinical highlights of lead vaccines against oxycodone, heroin, fentanyl, fentanyl analogs, and their combinations

EFFICACY

- Decreased drug distribution to brain and other organs (e.g., lungs, heart)
- Decreased drug-induced pharmacological effects
  - Respiratory depression
  - Cardiovascular depression
  - Lethality
- Decreased drug-induced behavioral effects
  - Motor stimulating effects
  - Intravenous drug self-administration

SELECTIVITY

- Selectively reduced drug effects of target drugs
  - E.g., Fentanyl Vaccine targets fentanyl(s)
- No effect on off-target drugs
  - Methadone, buprenorphine, naltrexone, naloxone
  - Critical care medications

SAFETY

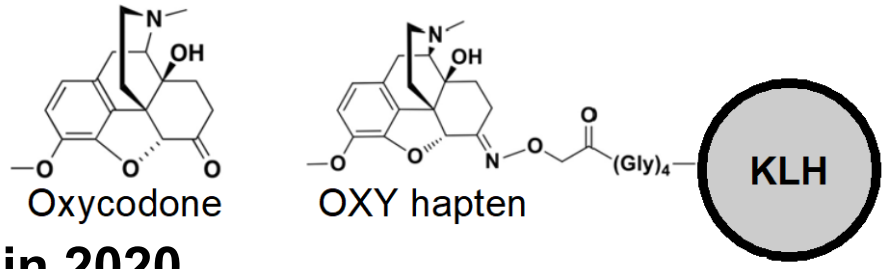
- No adverse or side effects
- No toxicity

References @ PubMed for “Pravetoni M”

Clinical testing of OUD vaccines in human patients: preliminary safety, selectivity, and efficacy

First-in-human Opioid Vaccine (OXY-sKLH)

- Targets oxycodone, hydrocodone, oxymorphone



FDA approved Investigational New Drug (IND) application in 2020

- Completed IND-enabling GMP manufacturing and GLP toxicology studies

Clinical Trial Phase Ia/Ib started in 2020 (NCT04458545)

- Randomized, placebo controlled, 2 active vaccine doses, 2 clinical sites
- Participants diagnosed with an OUD, challenged with intranasal oxycodone or control
- Safe: limited adverse effects
- Selective: antibodies bind oxycodone, but not methadone, buprenorphine, naltrexone, naloxone, or other off-targets
- Effective: vaccine reduced pharmacological and behavioral effects of oxycodone

Our HEAL pipeline of monoclonal antibodies (mAb) to counterACT overdose from opioids

Discovery	Pre-clinical R & D	GMP & GLP	IND	Phase I

Anti-fentanyl mAb, humanized

- Initiated manufacturing, Phase I Clinical Trials planned for 2024-2025

Series of anti-opioid mAb

- heroin, oxycodone, fentanyl analogs

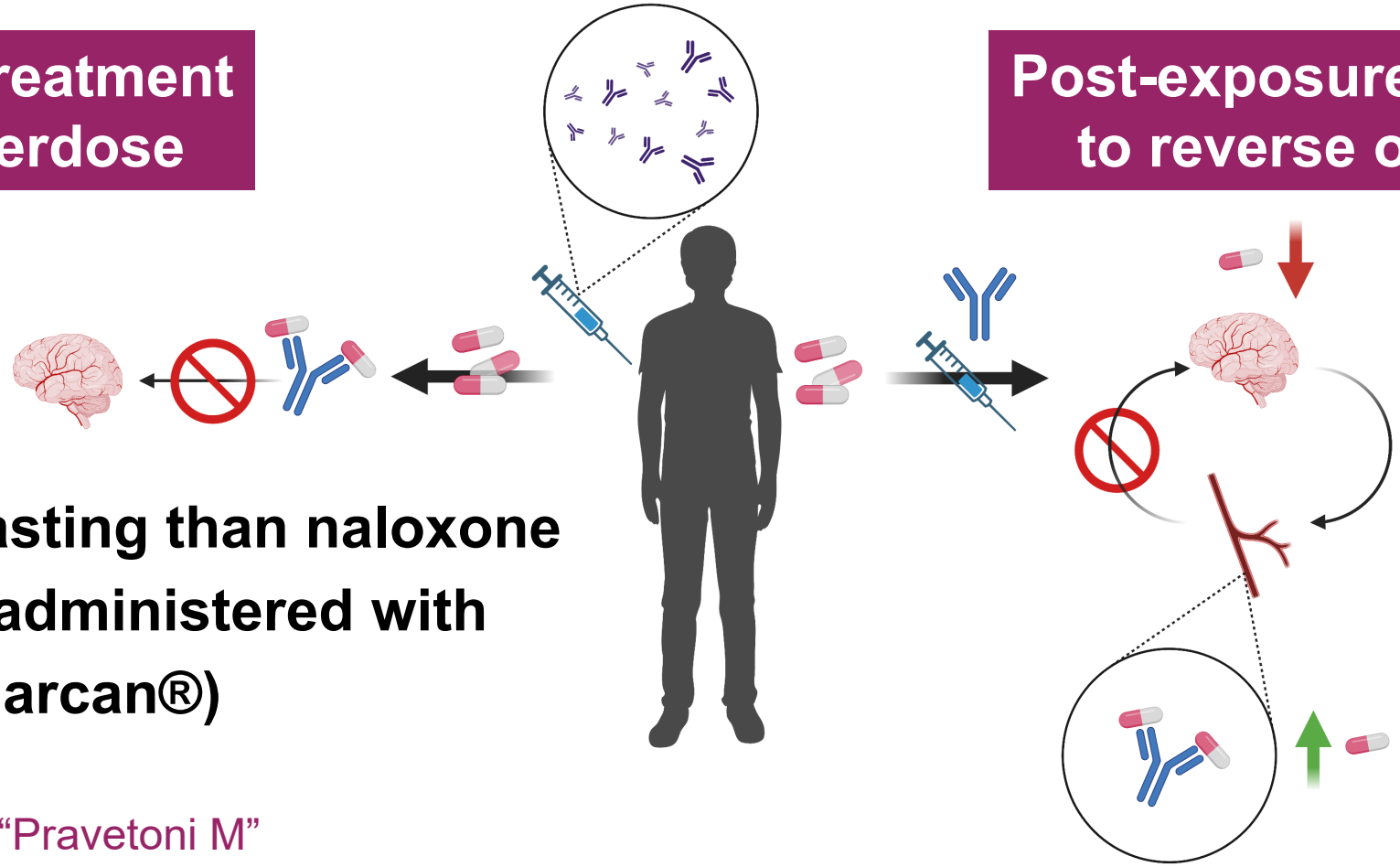
Next-Gen mAb Formulations

- New technologies
- New targets

Monoclonal antibodies (mAb) work similar to vaccines… but mAb work immediately

Pre-exposure treatment to prevent overdose

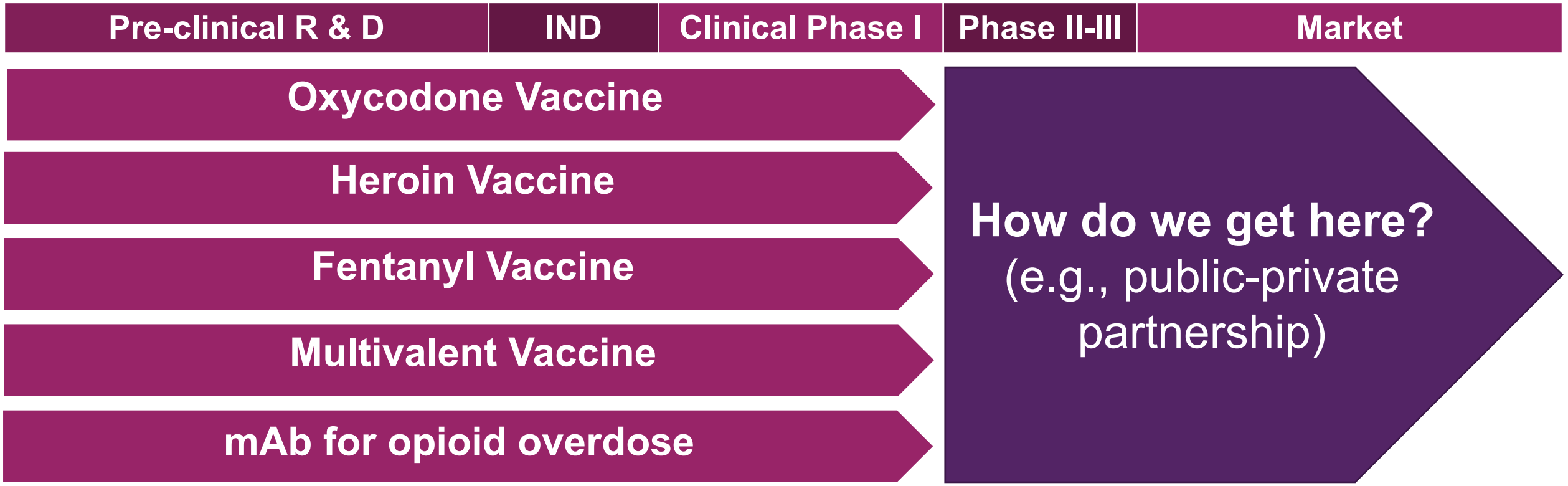
Post-exposure treatment to reverse overdose



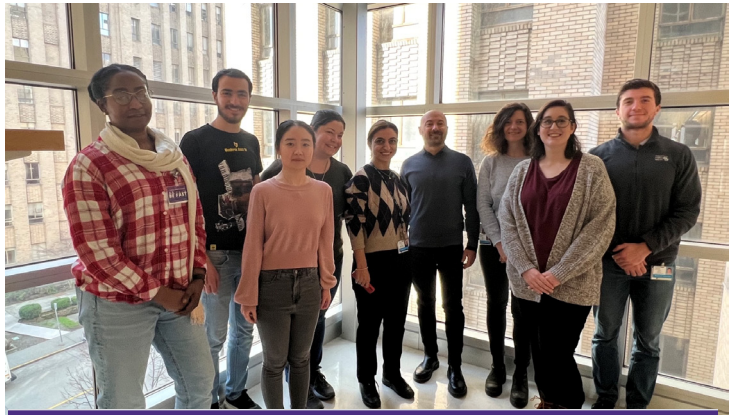
- **mAb is longer lasting than naloxone**
- **mAb can be co-administered with naloxone (i.e., Narcan®)**

References @ PubMed for “Pravetoni M”

Keep momentum to achieve long term impact with vaccines and mAb for OUD and overdose: future directions



Pravetoni Research Group



Margaret Calhoun, PhD; SaraRostamizadeh, PhD; Courtney Marecki, MS; Jamie Valeich; Bryan Hannon; Tyler Phan; Yue Zhang, MS; Fatima Hamid, MS; Davide Tronconi

Carly Baehr, PhD; Michael Raleigh, PhD; Jenny Vigliaturo; Ann Gabo; Dustin Hicks; Aaron Khaimraj, MS; Daihyun Song; Allison Blaskowski; Brandon Steiger

Our Medication Development Consortium

AHN

Columbia University in the City of New York

Fred Hutch Cures Start Here®

University of Montana

UT Health San Antonio

dkfz.

VT

RTI International

nimmune

Thank you to the NIH HEAL initiative

Thanks to NIH for supporting our work

NIH National Institute on Drug Abuse
Advancing Addiction Science

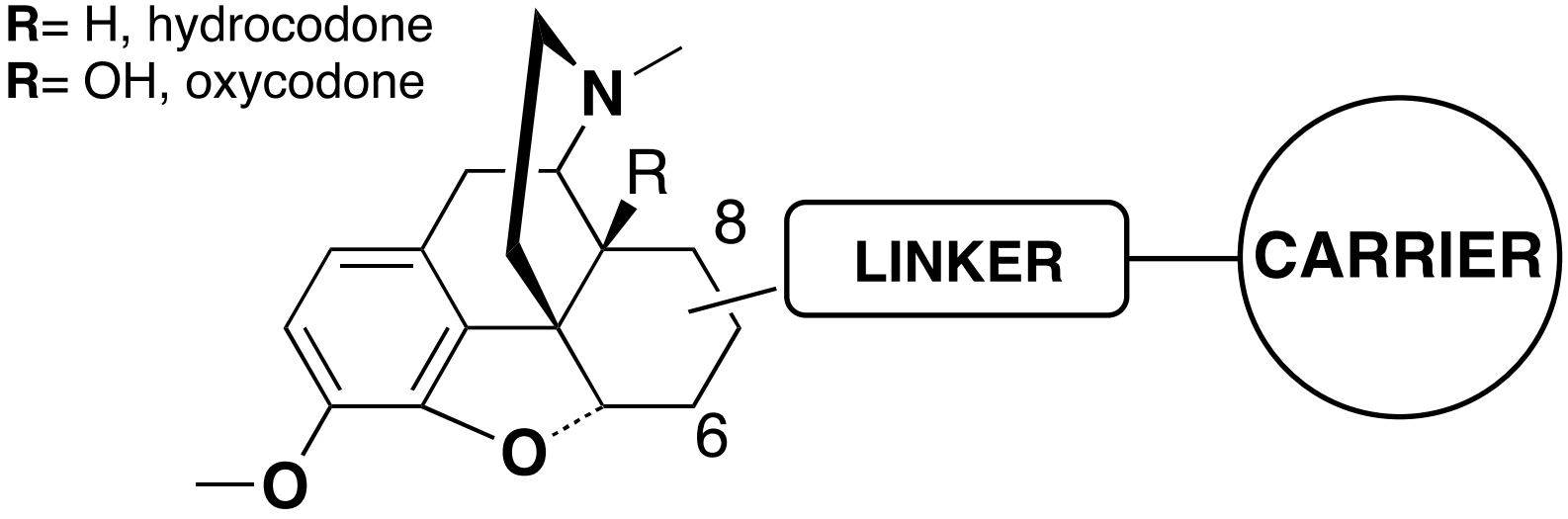
NIH National Institute of Allergy and Infectious Diseases

NIH National Institute of Neurological Disorders and Stroke

National Institutes of Health CounterACT Countermeasures Against Chemical Threats

Appendix

Platform for development of vaccines against opioids other drugs, or chemical threats: components



Drug-based haptens

Immunomodulators
- Adjuvants
- Cytokines

Formulation & Delivery
- Biopolymers
- Nanoparticles

Vaccination strategy
- Monovalent
- Multivalent

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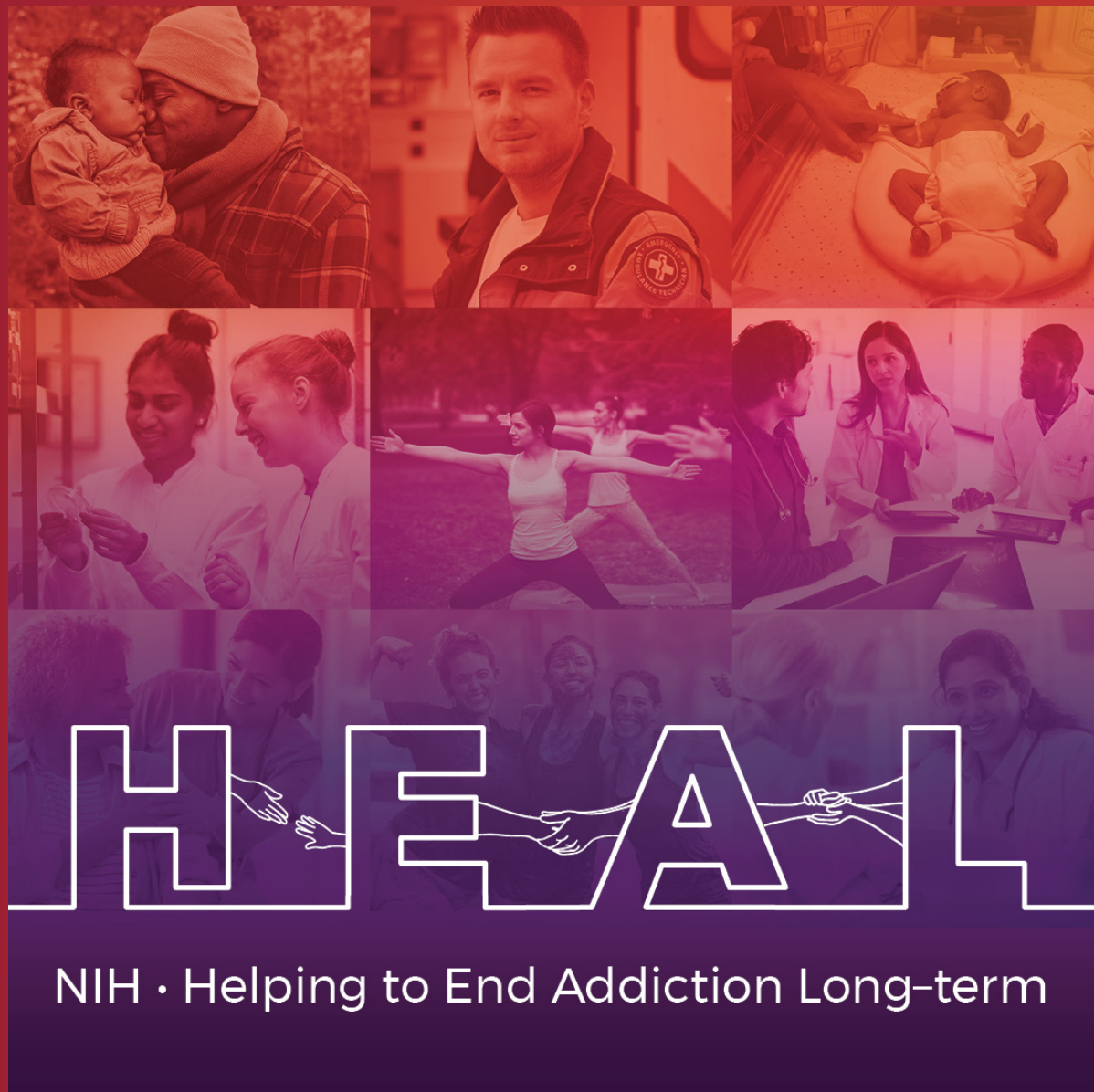
How HEAL is Enhancing Outcomes for Infants Exposed to Opioids

Diana Bianchi, M.D.
Director, *Eunice Kennedy Shriver N*ational Institute of Child Health and Human Development

Matthew Gillman, M.D., S.M.
Director, NIH Environmental influences on Child Health Outcomes (ECHO) Program



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Advancing Clinical Trials in Neonatal Opioid Withdrawal (ACT NOW) Collaborative

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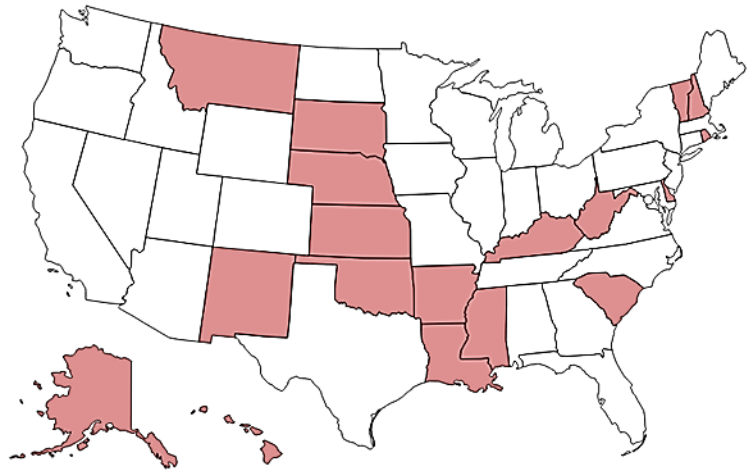
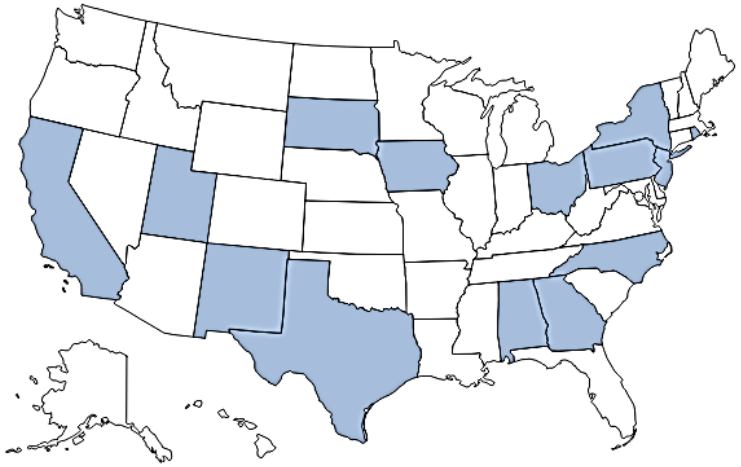


- Started in 2016
- 18 sites, many rural
- Sites overlap with areas of high prevalence of NOWS

NICHD
NEONATAL RESEARCH NETWORK



- Started in 1986
- 15 sites, mostly urban
- Many sites without high prevalence of NOWS

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Matthew Gillman, M.D., S.M, *Director*, ECHO

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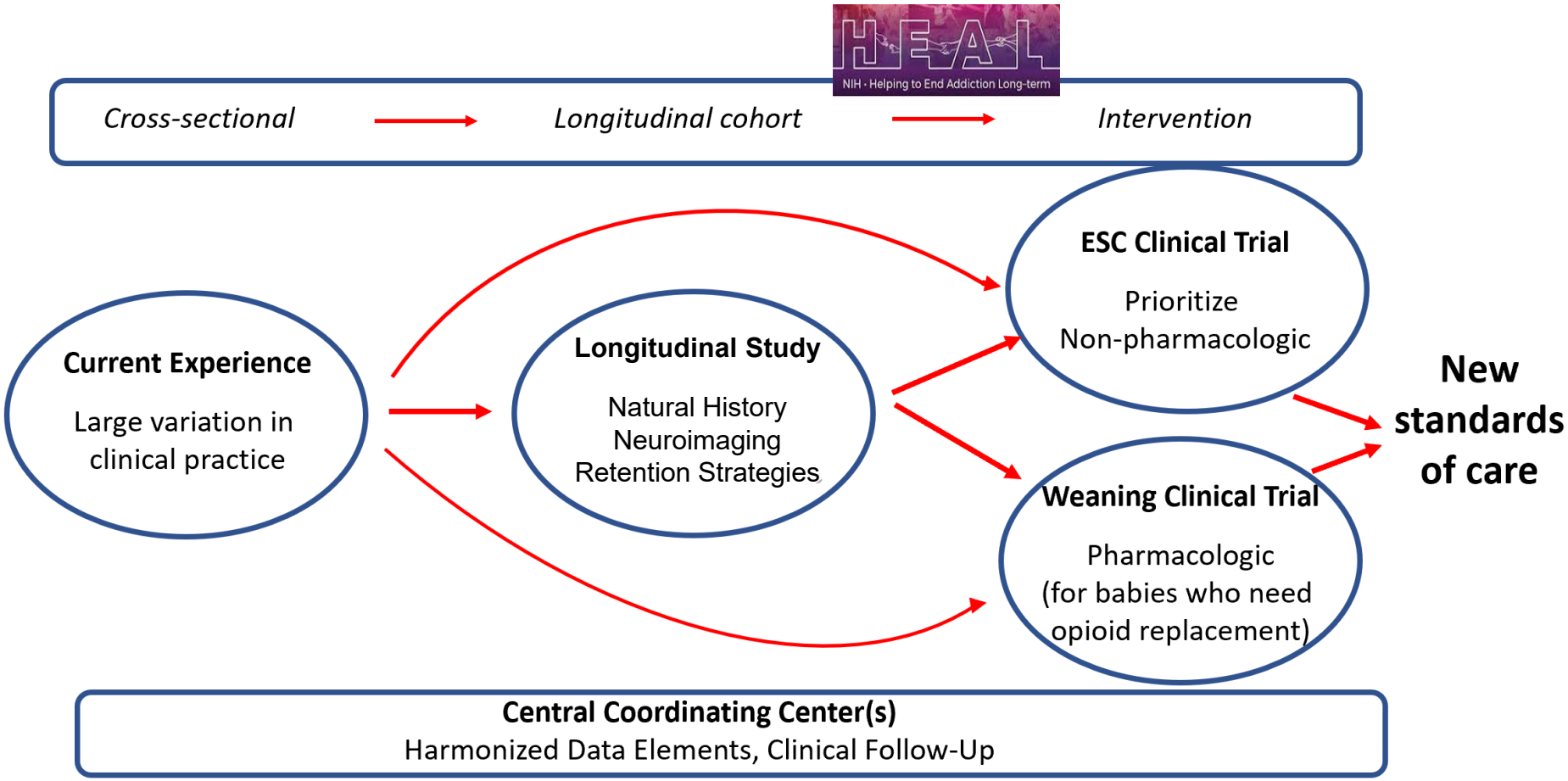
Advancing Clinical Trials in Neonatal Opioid Withdrawal (ACT NOW)

From no standard of care to evidence base for best practices



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Neonatal Research Network

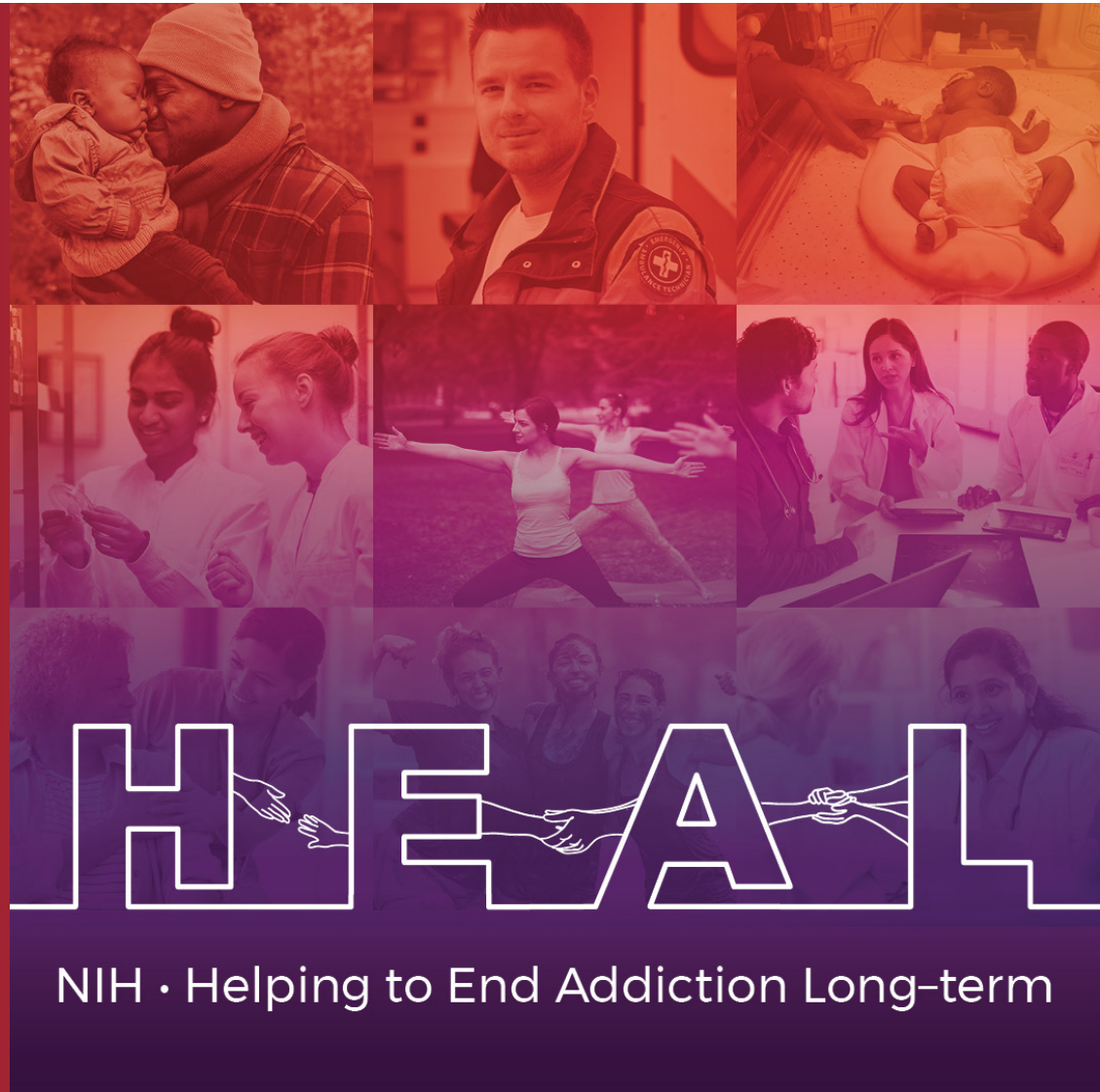
IDeA States Pediatric Network
ECHO A program supported by the NIH

Early Foundations for HEALing: Improving the Care for Opioid-Exposed Infants through the ACT NOW Program

Dr. Lori Devlin, D.O., Professor, University of Louisville

Dr. Leslie Young, M.D., Associate Professor, University of Vermont Larner, College of Medicine

Dr. Stephanie Merhar, M.D., M.S., Associate Professor, Division of Neonatology, Cincinnati Children's Hospital Medical Center



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HEAL Initiative

In 2019 - 7% of US women self-reported the use of prescription opioid pain relievers during pregnancy

1 in 5 pregnant women who used prescription opioids reported opioid misuse

Opioid-related diagnoses at delivery increased by 131% between 2010 and 2017

Hirai AH. JAMA. 2021. DOI 10.1001/jama.2020.24991

Ko JY. MMWR Morb Mortal Wkly Rep 2020. DOI 10.15585/mmwr.mm6928a1

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Neonatal Opioid Withdrawal Syndrome (NOWS)

- **In the US at least 1 infant is diagnosed with NOWS every 18 minutes**
- Withdrawal syndrome that occurs following opioid exposure during pregnancy
- Symptoms typically appear in the first few days of life and include irritability, tremors, poor sleeping, and difficulty feeding

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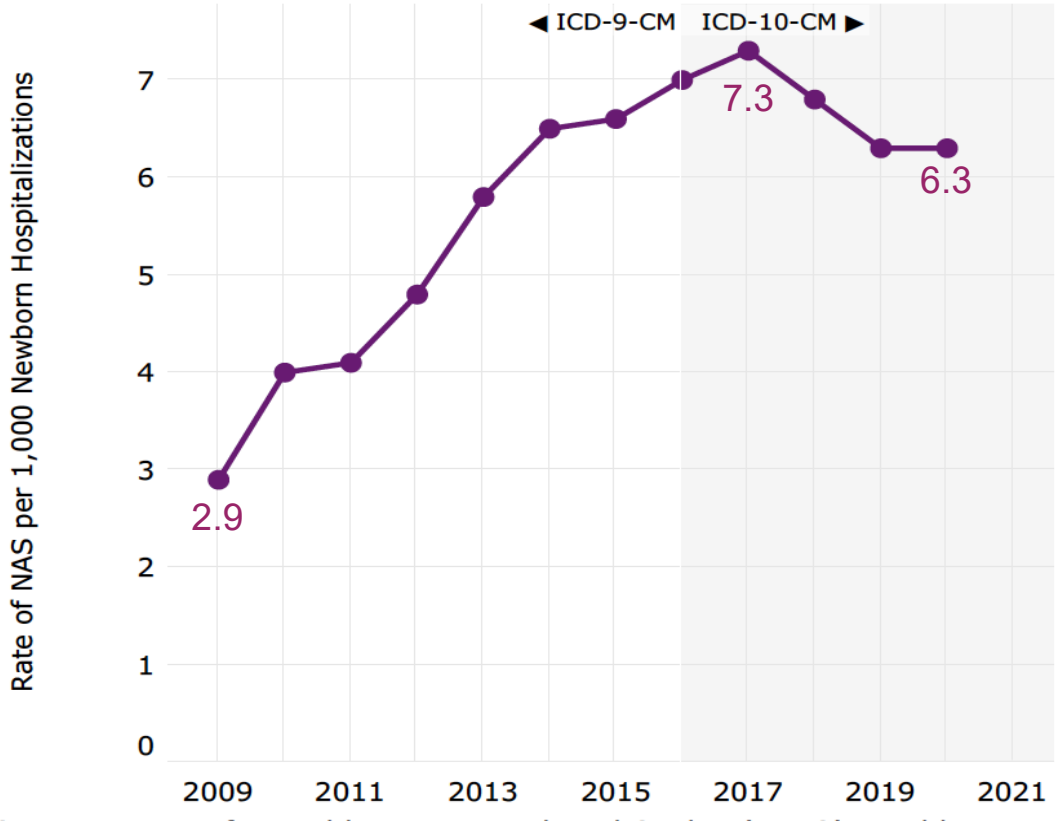
Stephanie Merhar, M.D.

A Significant Public Health Concern

National Rate/1000 Newborn Hospitalizations



- Prolonged Hospital Stays:
  - Average hospital stay is 11.6 days
  - Average hospital stay for infants who receive opioid treatment is 23 days
- Resource Intensive Care:
  - Many infants with NOWS are treated in NICUs
  - Limited ability for families to stay with infants

Substantial burden on healthcare systems, families, and communities

Agency for Healthcare Research and Quality (AHRQ), Healthcare Cost and Utilization Project (HCUP), National (Nationwide) Inpatient Sample (NIS) 2009 to 2020 (all available data as of 10/18/2022)

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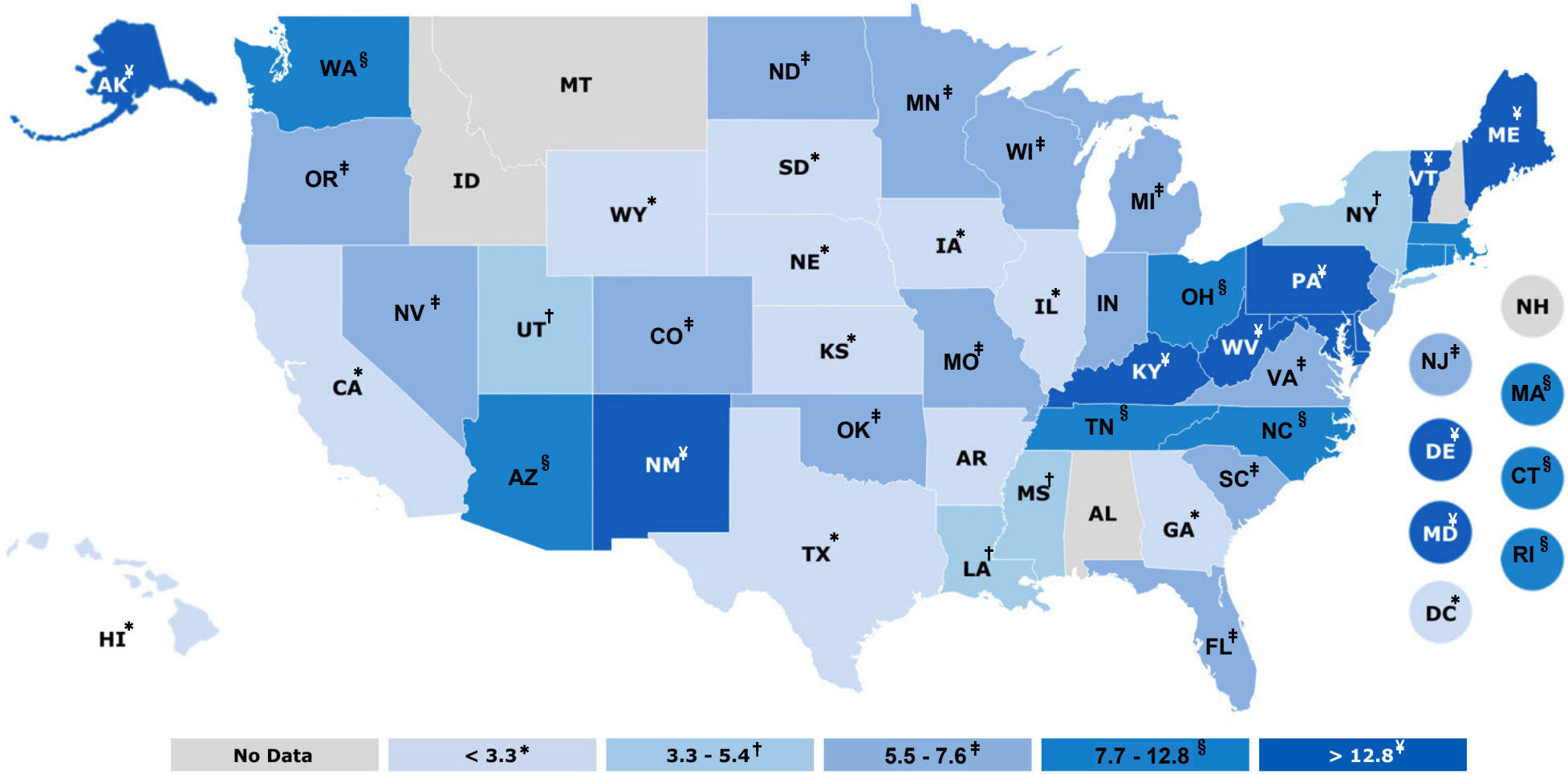
National Rates of NOWS Across States



HCUP Fast Stats. Healthcare Cost and Utilization Project (HCUP). December 2022. Agency for Healthcare Research and Quality, Rockville, ME. https://datatools.ahrq.gov/hcup-fast-stats

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Opioid Use in Pregnancy, Neonatal Abstinence Syndrome, and Childhood Outcomes: Executive Summary of a Joint Workshop by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, American Congress of Obstetricians and Gynecologists, American Academy of Pediatrics, Society for Maternal-Fetal Medicine, Centers for Disease Control and Prevention, and the March of Dimes Foundation

Uma M. Reddy, MD, MPH, Jonathan M. Davis, MD, Zhaoxia Ren, MD, PhD, Michael F. Greene, MD, and **for the Opioid Use in Pregnancy, Neonatal Abstinence Syndrome, and Childhood Outcomes Workshop Invited Speakers***

In 2016 experts from across the field came together to identify **knowledge gaps and research opportunities**

What is the…

- Optimal assessment tool?
- Optimal duration and location for monitoring?
- Optimal approach to treatment with medication?
- Optimal timing for follow-up?

Obstet Gynecol. July 2017. doi:10.1097/AOG.0000000000002054

Advancing Clinical Trials in Neonatal Opioid Withdrawal (ACT NOW) Collaborative

- Designed to inform a standard approach to caring for infants with NOWS through large multicenter studies intentionally developed to address knowledge gaps in the field
  - **Leveraging two established networks uniquely poised to address this crisis quickly and clinician scientists in highly affected areas who were excited for the opportunity to come together and improve care**
- Evidence-based approach to care → reduced variation → improved outcomes for infants and families

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Obstet Gynecol. July 2017. doi:10.1097/AOG.0000000000002054

Approach to Assessing Infants With NOWS

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Obstet Gynecol. July 2017. doi:10.1097/AOG.0000000000002054

Finnegan Neonatal Abstinence Scoring Tool

- Developed in the 1970s
- A list of the signs and symptoms of withdrawal
- Scores dictate medication use
- Many clinicians believe that it overestimates the need for medication

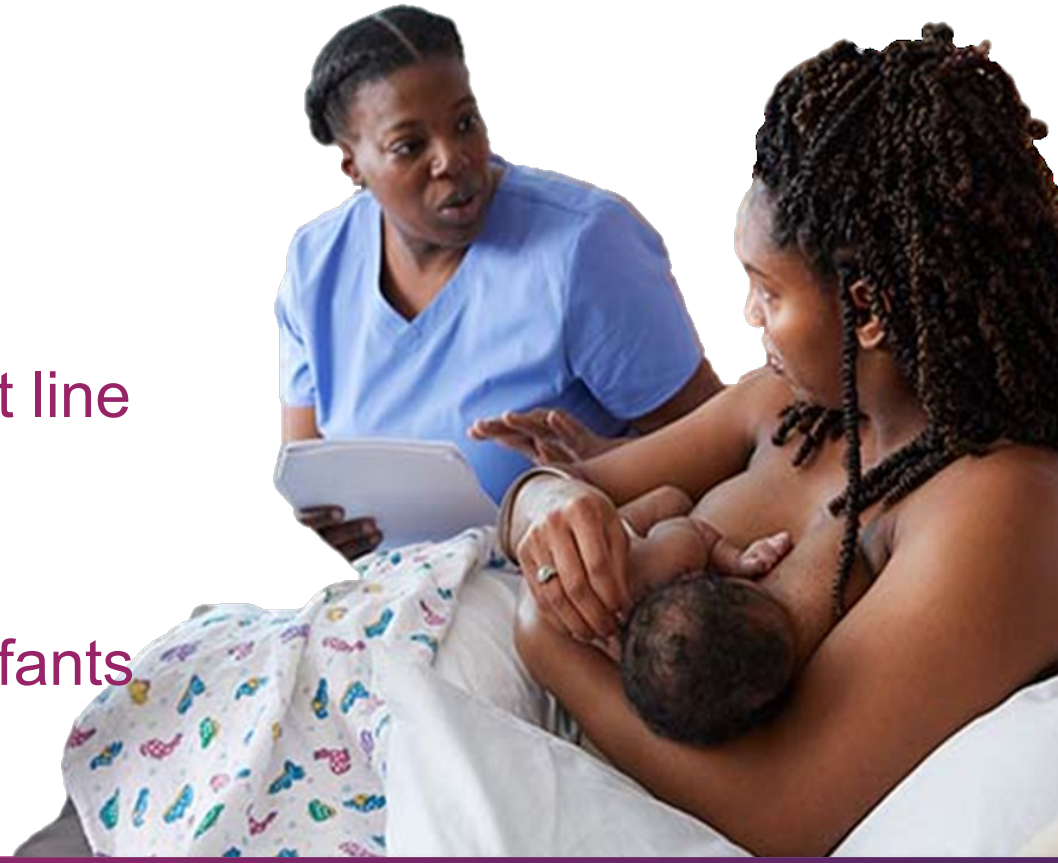
"One nurse would score him for sneezing three times in a row, and the other wouldn't. One nurse would score him for a poopy diaper. The other one wouldn't."

SYSTEMS	SIGNS AND SYMPTOMS	SCORE
CENTRAL NERVOUS SYSTEM DISTURBANCES	High Pitched Cry	2
	Continuous High Pitched Cry	3
	Sleeps < 1 Hour After Feeding	3
	Sleeps < 2 Hours After Feeding	2
	Hyperactive Moro Reflex	2
	Markedly Hyperactive Moro Reflex	3
	Mild Tremors Disturbed	2
	Moderate Severe Tremors Disturbed	3
	Mild Tremors Undisturbed	1
	Moderate Severe Tremors Undisturbed	2
	Increased Muscle Tone	2
	Excoriation (specify area): _____	1
	Myoclonic Jerks	3
	Generalized Convulsions	3
METABOLIC VASOMOTOR/ RESPIRATORY DISTURBANCES	Sweating	1
	Fever < 101°F (39.3°C)	1
	Fever > 101°F (39.3°C)	2
	Frequent Yawning (> 3-4 times/interval)	1
	Mottling	1
	Nasal Stuffiness	1
	Sneezing (> 3-4 times/interval)	1
	Nasal Flaring	2
	Respiratory Rate > 60/min	1
	Respiration Rate > 60/min with Retractions	2
GASTROINTESTINAL DISTURBANCES	Excessive Sucking	1
	Poor Feeding	2
	Regurgitation	2
	Projectile Vomiting	3
	Loose Stools	2
	Watery Stools	3
SUMMARY	TOTAL SCORE	
	SCORER'S INITIALS	
	STATUS OF THERAPY	

Finnegan LP. Addictive Diseases. 1975

Eating, Sleeping, Consoling Care Approach

- Function based assessment of NOWS severity
  - **A novel and simplified approach**
  - Emphasis on the functional components of withdrawal
    - Is the infant able to eat, sleep and be consoled?
- Optimization of supportive interventions as first line treatment
- Emphasis on education, support, and empowerment of families in the care of their infants



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Is the ESC Care Approach a Better Way to Care For Babies?

Initial quality improvement work has shown promise with improved hospital outcomes but a multicenter clinical trial was needed

- Questions remained -

Would this approach be safe and work well when used by different types of hospitals to care for infants across our diverse communities?

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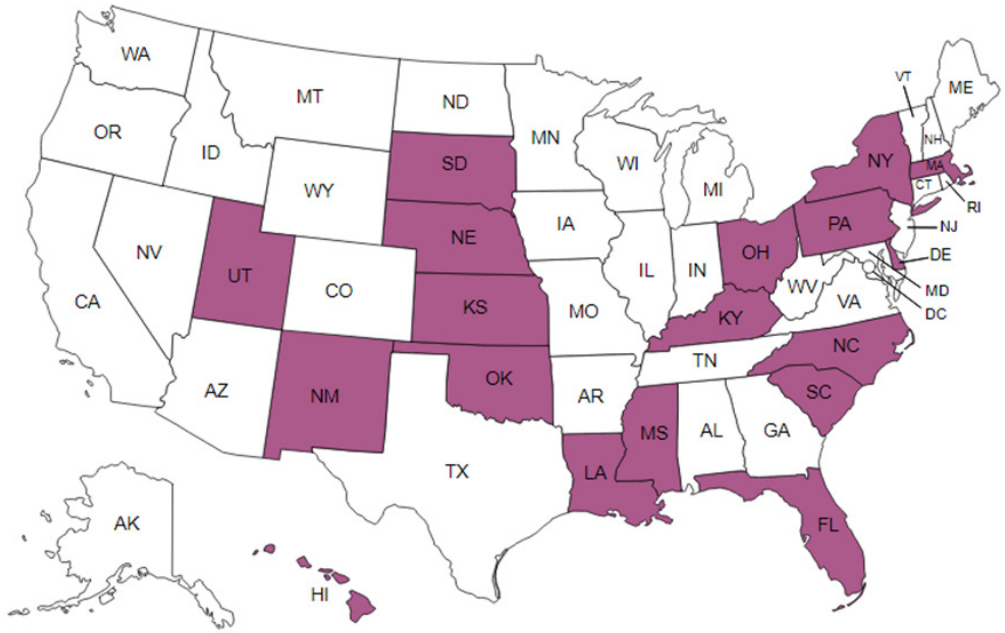
Eating, Sleeping, Consoling for Neonatal Opioid Withdrawal (ESC-NOW) Randomized Controlled Trial

- Conducted between Sept 2020 - March 2022
- 26 sites in 18 states
  - **Sites selected to optimize the generalizability of the study results**
- 1306 infants were enrolled
- >5000 nurses were trained



■ States with ESC Study Sites

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ESC Care Approach Improves Outcomes

- When compared to usual care, the ESC care approach
  - **Decreased the time until infants were medically ready for discharge**
  - **Reduced the receipt of medication**
  - **No difference in safety outcomes through early infancy**
- Our results provide strong evidence to support the use of ESC as a safe and effective approach to caring for infants with NOWS
  - Long-term follow-up will further inform use of this approach

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“I had a baby born 5 years ago and they were more rigid on their scoring at that time, following the protocol more. I was less fearful this time”

It’s really nice when it’s genuine you get asked your opinion… and that just made me feel like I had a part and say in how things went with her.”

“They’ve told us multiple times [mom’s] the best medication for him, skin to skin or mil and just being here in the room.”

“They were on my side and they said that I was doing the best for him as a recovering addict going through this program. It was very nice--addicts just don’t get enough praise for what they’re really doing.”

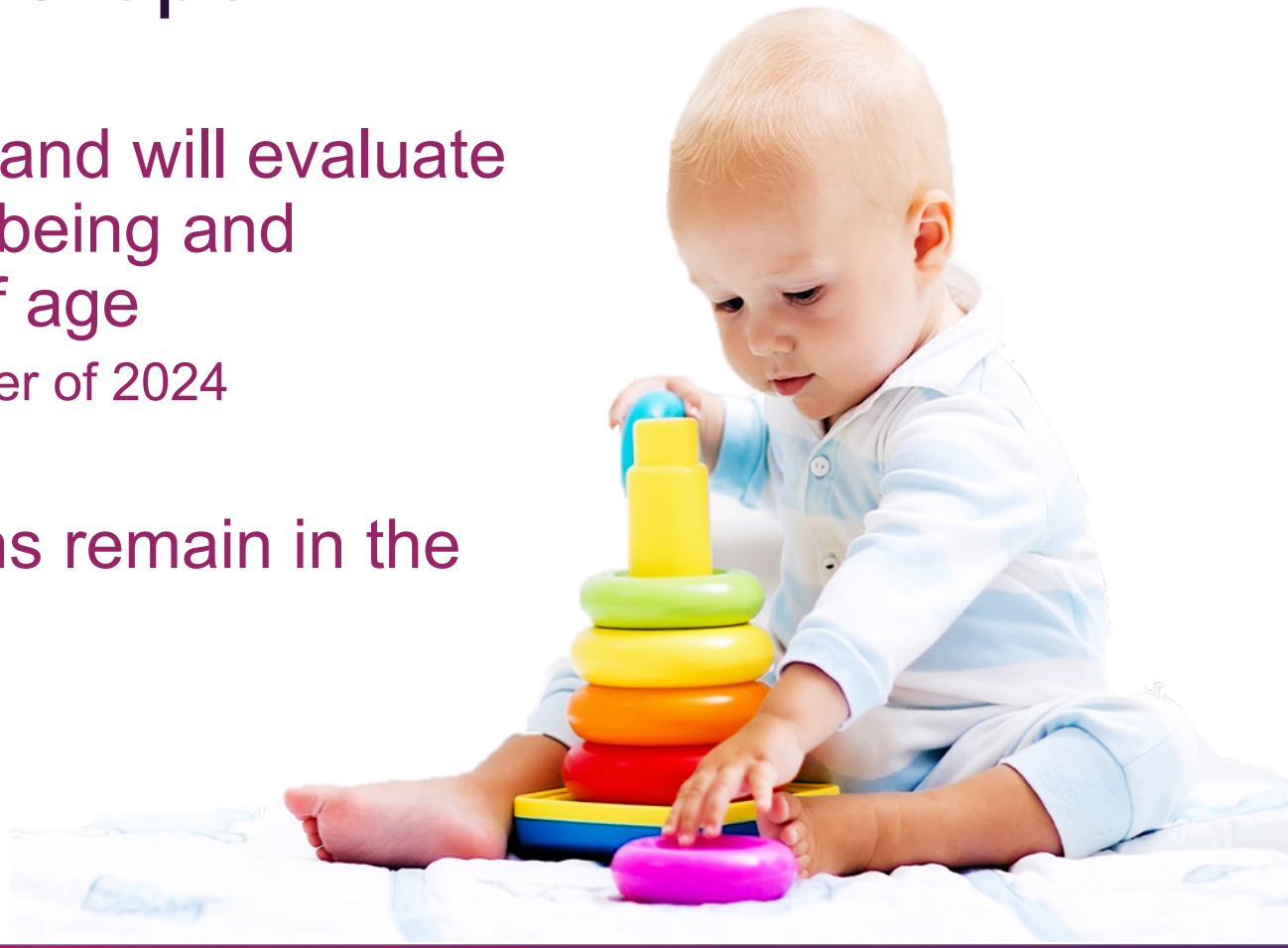
“For me, it’s been huge to be treated like every other patient, just a mom and a baby.”

Provided through the qualitative research of K.MacMillan and colleagues, Dartmouth

Next Steps

- Long-term follow-up is ongoing and will evaluate impact on infant and family wellbeing and development through 2 years of age
  - Anticipate completion during the summer of 2024

- Still many unanswered questions remain in the field



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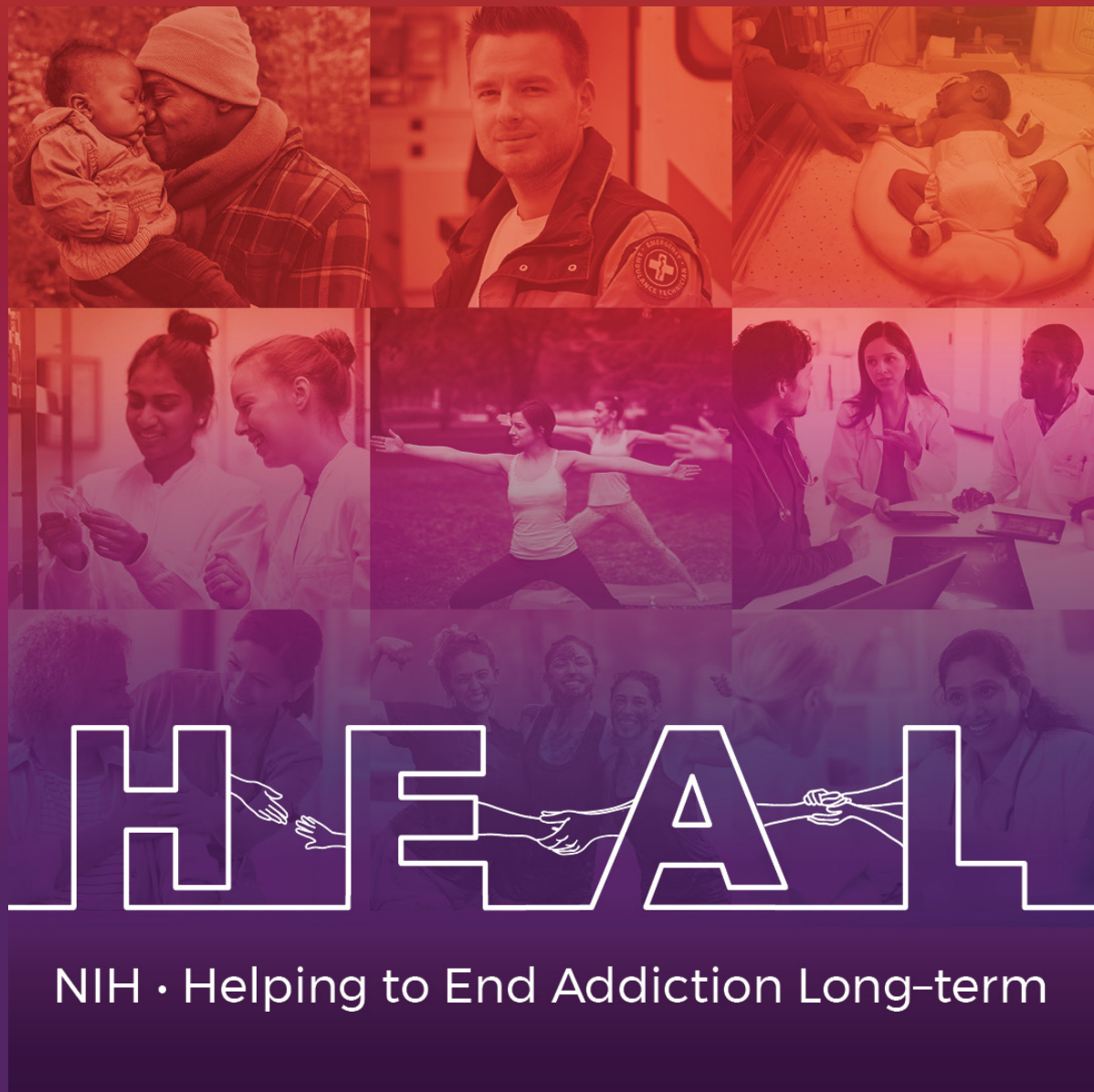
Making an Impact: How the NIH HEAL Initiative's Research is Finding Solutions to the Opioid Crisis

Questions & Answers



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