



**NIH
HEAL
INITIATIVE**

HEAL Multi-Disciplinary Working Group

March 2, 2021



NIH National Institutes of Health
HEAL Initiative

NIH HEAL Initiative and Helping to End Addiction Long-term are service marks of the U.S. Department of Health and Human Services.



Welcome and Introductions

Francis Collins, Director, NIH



Helping to End Addiction Long-term Research Overview

Rebecca Baker, Director, NIH HEAL Initiative, Office of the Director, NIH

Meeting Overview

- Day 1, March 2
 - *Open Session:*
 - Welcome, Francis Collins
 - HEAL Initiative: Overview of Current Portfolio and Programs, Rebecca Baker
 - Emerging Issues in the Opioid Crisis: Collision of COVID-19 on Opioid Overdose and Treatment, Nora Volkow
 - *Closed Session:* Discussion of Future Research Concepts
- Day 2, March 3
 - *Open Session:*
 - Patient and Stakeholder Engagement in the NIH HEAL Initiative, Walter Koroshetz
 - Building the HEAL Research Community, Data Platform, and Investigator Meeting
 - *Closed Session:* Discussion of Future Research Concepts

2017 Cutting-Edge Science Meeting Series to End the Opioid Crisis



"With our partners, the NIH will take an 'all hands-on deck' approach to developing and delivering the scientific tools that will help end this crisis and prevent it from reemerging in the future."

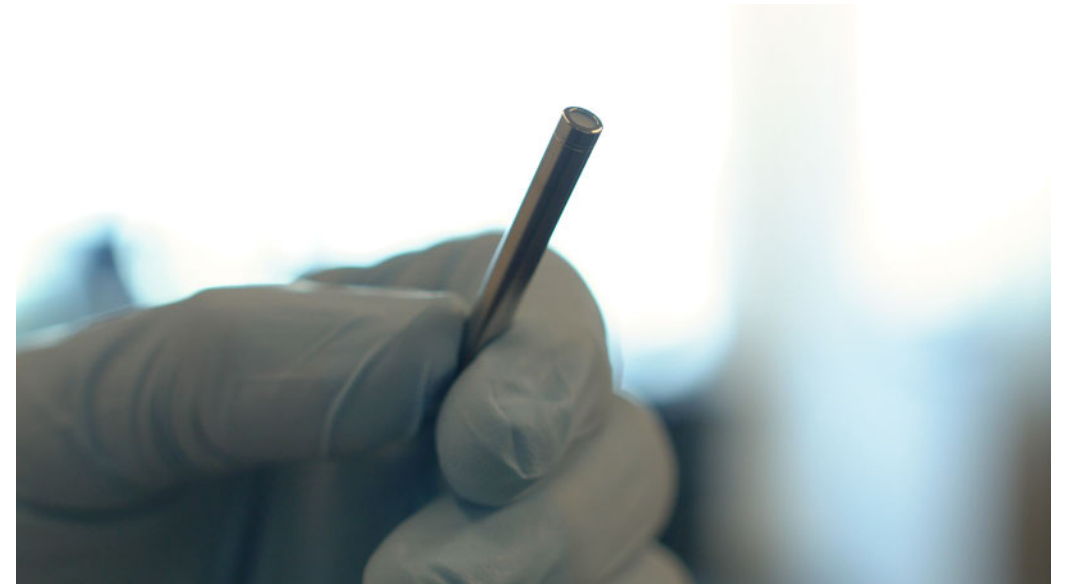
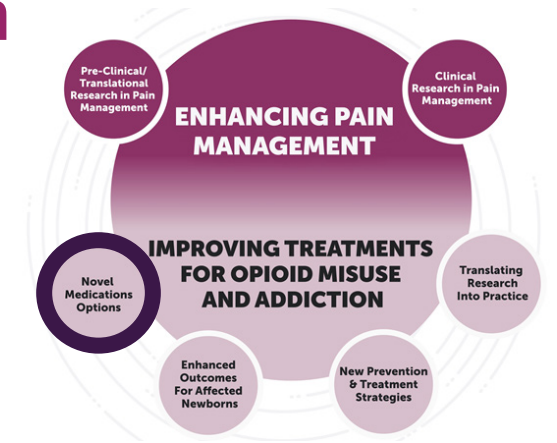
— Nora Volkow, M.D. and Francis Collins, M.D., Ph.D., *New England Journal of Medicine*, 2017

NIH HEAL INITIATIVE RESEARCH OVERVIEW



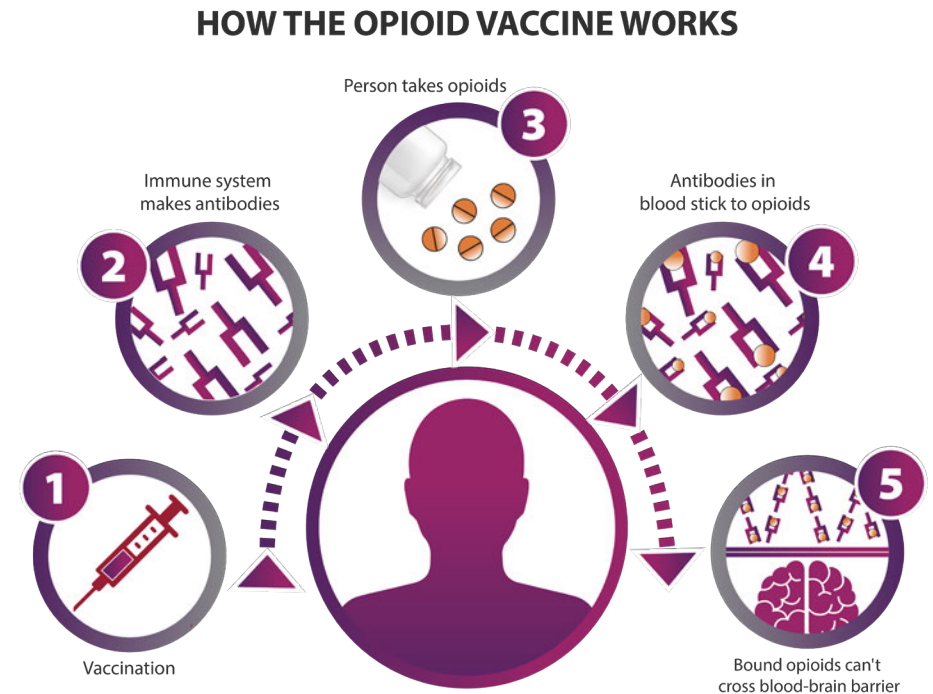
Novel Therapeutic Options for Opioid Addiction and Overdose

- **Focused Therapeutic Development for Opioid Use Disorder and Overdose**
 - 61 projects, \$241M to date, NIDA, NHLBI
 - Novel medications and formulations
 - 32 New Molecular Entities (NME) and 23 repurposed medications.
 - 50+ compounds being developed from early preclinical to late clinical phases
 - Anti-opioid immunotherapies (vaccines and monoclonal antibodies)
- **Novel Immunotherapies to Opioids**
 - 10 projects, \$30M to date; NIAID led in collaboration with NIDA



Therapeutic Development Research Accomplishments:

- 16 Investigational New Drugs (IND) have been filed with FDA
 - HEAL goal to file 15 INDs in 5 years, which has been exceeded in 2 years
- *Biologics*: First study in humans of an opioid vaccine was launched
- *Devices*: One IDE to study Deep Brain Stimulation for Opioid Use Disorder



Enhanced Outcomes for Infants and Children

- **Advancing Clinical Trials in Neonatal Opioid Withdrawal (ACT NOW)**
 - 2 clinical trials –weaning and eat-sleep-console, 1 longitudinal study; \$41M to date; NICHD and OD/ECHO
 - Early survey found significant site to site practice variation in treatment of infants with NOWS;
- **HEALthy Brain and Child Development Study (HBCD)**
 - \$7.8M to date, co-funded together with NIDA with NIMH, NIAAA, NINDS, NIEHS, NIBIB, NICHD, OBSSR, ORWH and NIMHD
 - FY21 FOAs to develop neuroimaging measures in infants and young children

***** NOW OPEN TO APPLICATIONS *****



Research Accomplishments in Enhancing Outcomes for Infants and Children

- ACT-NOW now enrolling for all three studies in 23 sites nationwide
- HBCD researchers designed an MRI compatible crib to increase success rate of imaging sleeping newborns and infants
- 2 small business research projects on non-pharmacological, noninvasive treatments for NOWS received Breakthrough Devices Designation by the FDA



New Prevention & Treatment Strategies for Opioid Use Disorder

- **Preventing Opioid Use Disorder in At-Risk Populations**

- 9 projects, \$48.5M to date; NIDA, NIAAA, NIGMS
- Research addressing substance use and/or mental health among adolescents transitioning to adulthood, homeless, American Indian/Alaskan Native (AI/AN) communities



New Prevention & Treatment Strategies for Opioid Use Disorder

- **Optimizing Care for People with Opioid Use Disorder and Mental Health Conditions**
 - 13 projects, \$56M to date; NIMH led; NIDA, NIAAA
 - Testing collaborative care model for OUD treatment; improving treatment, management, and services for people with co-occurring conditions and suicide risk
- **Sleep Dysfunction**
 - 10 projects, \$25.6M to date; NIDA, NHLBI
 - Basic mechanistic studies, clinical trials, and supplements for objective assessments of sleep during OUD treatment and recovery



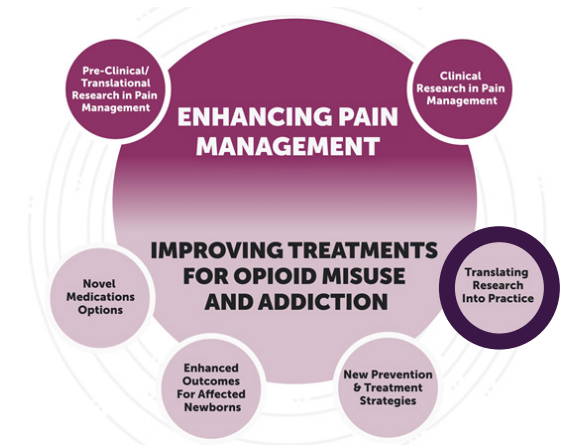
Research Accomplishments in Prevention and Treatment for OUD

- Enhanced Rx opioid registry developed from 10 diverse health systems with harmonized EHR allows for:
 - Monitoring opioid dose reduction, tapering and how this relates to health outcomes
 - Examining changes in opioid Rxs for acute pain, surgery
- PHARMSCREEN tool to provide pharmacists with a validated OUD-risk measure to better identify high risk opioid use patterns for early intervention



Translation of Research into Practice for Effective Treatments for OUD

- **Behavioral Research to Address Medications for the Treatment of OUD (BRIM)**
 - 8 grants, \$26.5M to date; NCCIH led
 - Test if behavioral/social interventions, mHealth, peer delivery help improve long-term outcomes for medication-based OUD treatment
- **HEALing Communities Study**
 - 5 grants, \$209M to date; NIDA led
 - “Communities That Heal” menu of evidence-based interventions, including naloxone distributions, tested in 67 communities in 4 states hit hard by the opioid crisis



“I’m a FIRST RESPONDER” **“I’m a FIRST RESPONDER”** **“I am TOO”**

Carry naloxone (Narcan®). Save a life.

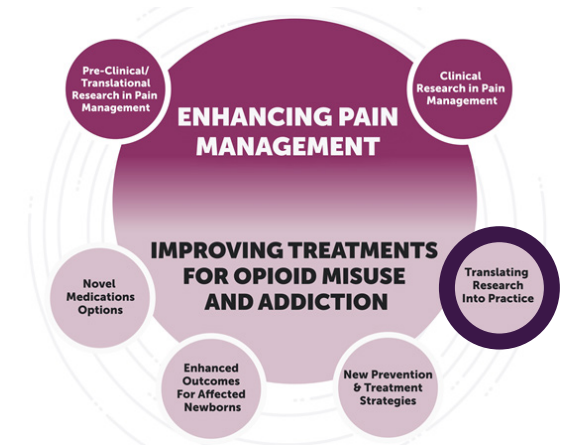
Recognize the signs of an opioid overdose. Learn where to get Narcan® and how to use it.

HealTogetherKY.org/Franklin

NIH HEAL INITIATIVE
HEALing Communities Study
Kentucky

Translation of Research into Practice for Effective Treatments for OUD

- **Expanding the NIDA Clinical Trials Network to address Opioids**
 - 26 study protocols, \$145M to date; NIDA led
 - Test expansion of OUD treatment into primary care and criminal justice settings, among pregnant women
- **Justice Community Opioid Innovation Network (JCOIN)**
 - 15 projects, \$83.6M to date; NIDA led
 - Collaborative with justice systems in 27 states studying the quality care for opioid misuse and OUD in justice populations
 - 13 multi-site clinical trials, 9 modeling projects, 11 surveys



Accomplishments in Translation of Research to Practice for OUD

- Communications campaign for community uptake of medications for OUD and naloxone
- Data tools to monitor overdose spikes, geospatial analyses of opioid misuse risk environment, and service availability
- National opinion surveys tracking perceptions of OUD and stigma
- Compilation of emerging best practices for criminal justice agencies on addressing OUD in the context of COVID-19



Preclinical and Translational Research in Pain Management

- **Discovery and Validation of Novel Targets for Safe and Effective Pain Treatment**
 - 34 projects, \$69M to date; NINDS led; NIDCR, NIAMS, NCCIH, NIA, NCI, NIDDK, NIDA
 - Multiple diverse target types and pain conditions, e.g. neuropathic, post-surgical, osteoarthritis, and chemotherapy induced pain
- **Optimizing Non-Addictive Therapies to Treat Pain***
 - 6 Contracts focused on 4 small molecules and 2 biologics; \$7.5M to date; NINDS-led
- **Translating Discoveries into Effective Devices for Pain Treatment**
 - 11 projects, \$23M to date; NINDS and NIBIB
 - Testing implanted devices, such as electrodes, and noninvasive targeted stimulation of nerve cells and regions of the brain associated with pain perception


*** *Applications open now and more to come****



Preclinical and Translational Research in Pain Management



STEP 1
A participant lies down with their head inside a PET scanner, a kind of imaging machine that looks at activity in the brain.



STEP 2
A needle filled with salty water is inserted into each side of the participant's face, a bit above the corner of the jaw. Over the next 20 minutes, a tiny quantity of salt water trickles through the needle on one side.



STEP 3
Every 20 seconds, the person pushes a button to indicate how much pain they are feeling, on a scale of 0 to 100. (With regular salty water, most people feel very little pain.)



STEP 4
The procedure repeats on the other side with much saltier water, causing about as much pain as a bad toothache. Prossin will compare this to the results from the first side.



STEP 5
Every 10 minutes a blood sample is taken. Eventually, Prossin will use this information to develop a blood test that may help show how sensitive someone is to pain.



- **Human Based Models and Candidate Testing for Nociception, Addiction, and Overdose**

- 5 awards, \$7M to date; Intramural-extramural collaborative projects and prizes \$63M to date; NCATS
- hiPSC-based DRG tissue chip model of acute and chronic nociception and multi-organ human-on-a-chip

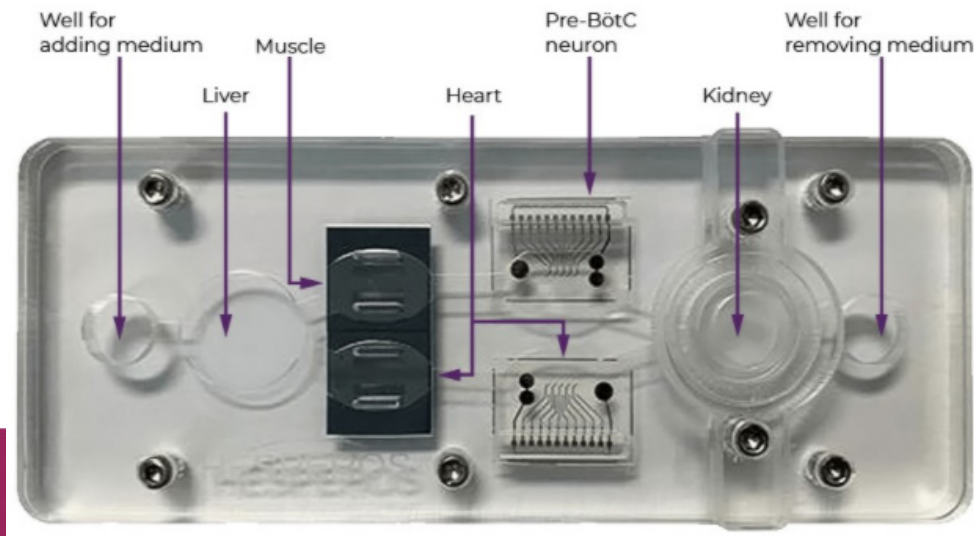
- **Biomarkers, Signatures and Endpoints for Pain**

- 9 projects, \$31.7M to date; NINDS-led
- Pain associated with sickle cell disease, eye pain, musculoskeletal disease, nerve pain and spinal cord injury, persistent headache after concussion

*** *REVISIONING in collaboration with FNIH, more to come* ***

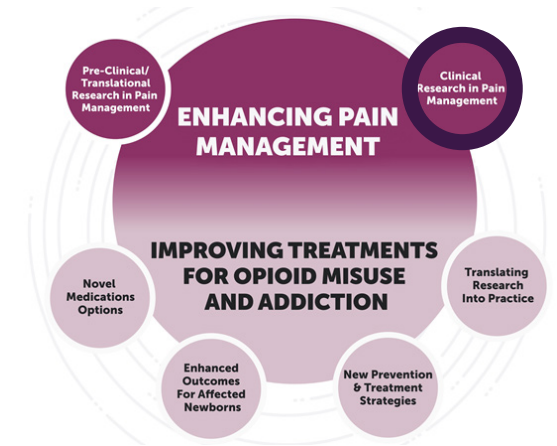
Research Accomplishments in Preclinical and Translational Pain

- 2 separate patents for small molecule modulators of pain receptors; includes chronic pain and migraine therapies
- Validated the ability of a portable thermoelectric device to inhibit pain signals in two different peripheral nerves
- Investigational New Drug (IND) for a first-in-class non-addictive drug candidate for the treatment of chronic pain



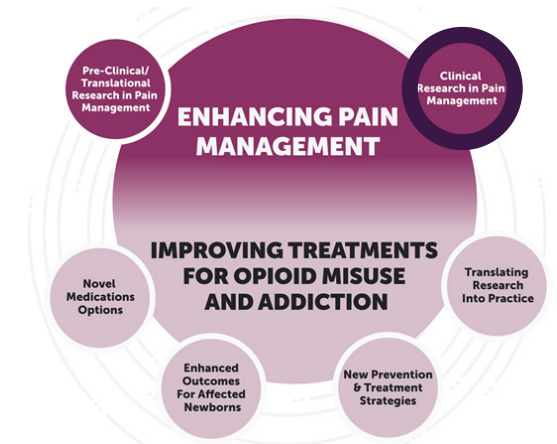
Clinical Research in Pain Management

- **Early Phase Preclinical Investigation Network (EPPIC Net)**
 - 14 grants for infrastructure; \$32M to date; NINDS led
 - Trial under development for CCR2 antagonist for knee osteoarthritis pain
- **Back Pain Consortium**
 - 14 research projects totaling \$117M to date; NIAMS led
 - 3 mechanistic research centers, 7 technology sites, 2 phase II trials, data center, and 1 supplement to study back pain in the context of OUD
- **Hemodialysis Opioid Prescription Effort (HOPE)**
 - 8 clinical sites and data center; \$28M to date; NIDDK led
 - Test non-pharmacological interventions and buprenorphine for pain in patients in kidney dialysis



Clinical Research in Pain Management

- **Pain Effectiveness Research Network (Pain ERN):**
 - 8 projects \$60M to date; NCATS infrastructure with NICHD, NIA, NIAMS, NIDA, NINR, NCI trials
 - Pain conditions studied: knee osteoarthritis, postsurgical pain in adolescents, post-mastectomy pain, acute pain post cesarean, chronic pain in cancer survivors, chronic pain in veterans with OUD
- **Pragmatic and Implementation Studies for Management of Pain to Reduce Opioid Prescribing (PRISM):**
 - 7 projects \$23M to date; NCCIH NIA, NIAMS, NINR
 - Nonpharmacological management of diffuse fibromyalgia pain, post-surgery, sickle cell and chronic low back pain



Clinical Research Accomplishments in Pain Management

- Data harmonization through a set of pain-unique Common Data Elements for HEAL clinical pain studies
- Iterative model to inform precision medicine for chronic low back pain
 - Multiple contributions to chronic low back pain and treatment interventions — from anxiety to tissue damage and from psychotherapy to surgery
- FDA IND for use of buprenorphine for pain management as part of multidisciplinary pain management for patients on dialysis for end stage renal disease



Adapting Research Interventions for COVID-19

- Creative strategies to move parts of the intervention online while still creating the same feelings of social connectedness that in-person experiences provide
 - Investigators successfully engaged individuals in virtual cooking sessions
- Emergency department-based study shifted from recruiting participants in the ED to following up by phone after discharge
 - Choice of communication medium for completing questionnaires (over the phone, video chat, What's App or return forms by mail)



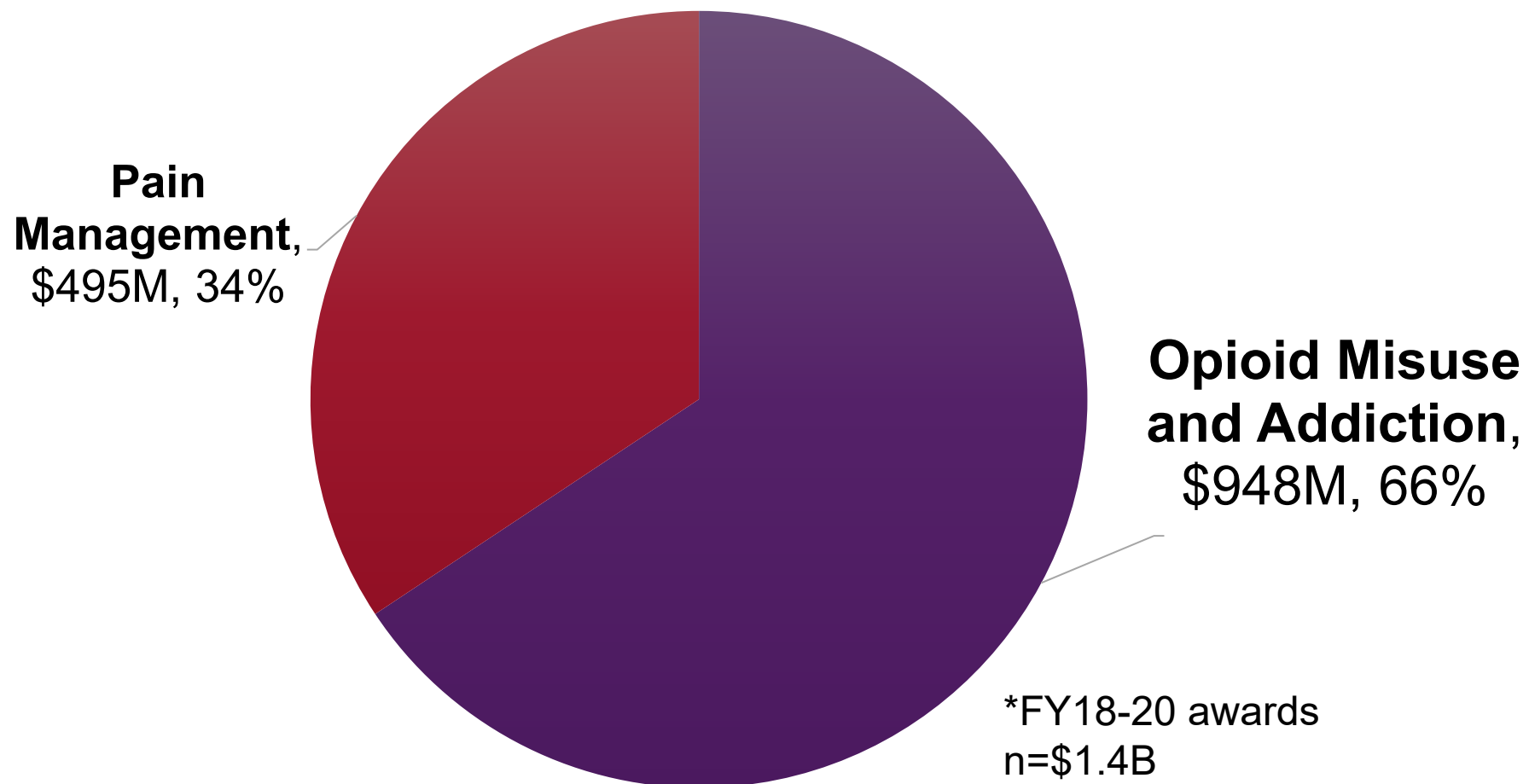
Open Funding Opportunities

- **Analgesic Development Suite of Funding Opportunities**
 - **Non-addictive Analgesic Therapeutics Development [Small Molecules and Biologics] to Treat Pain** (RFA-NS-21-010; NOT-NS-21-033; NOT-NS-21-034)
 - **Development of Therapies and Technologies Directed at Enhanced Pain Management** (RFA-NS-20-008, RFA-NS-20-009, RFA-NS-20-010, RFA-NS-20-011)
- **Enhanced Outcomes for Infants and Children**
 - **Neonatal Opioid Withdrawal Syndrome Pharmacological Treatments Comparative Effectiveness Trial** (RFA-HD-21-031, RFA-HD-21-032)
 - **HEALthy Brain and Child Development Study Consortium** (RFA-DA-21-020, RFA-DA-21-021, RFA-DA-21-022, RFA-DA-21-023)
- **Addressing Co-occurring Pain, Mental Health Conditions and OUD**
 - **Integrative Management of chronic Pain and OUD for Whole Recovery (IMPOWR)** (RFA-DA-21-029, RFA-DA-21-030)
 - **Optimizing Multi-Component Service Delivery Interventions for People with Opioid Use Disorder, Co-Occurring Conditions, and/or Suicide Risk** (RFA-MH-21-145)
- **Research Supplements to Promote Diversity in Health-Related Research** (NOT-NS-20-107)
- **EPPIC-Net Pain Research Asset Application** (OTA-19-008)
- **Small Businesses Build Technologies to Stop the Opioid Crisis** (RFA-DA-19-019, RFA-DA-19-020)

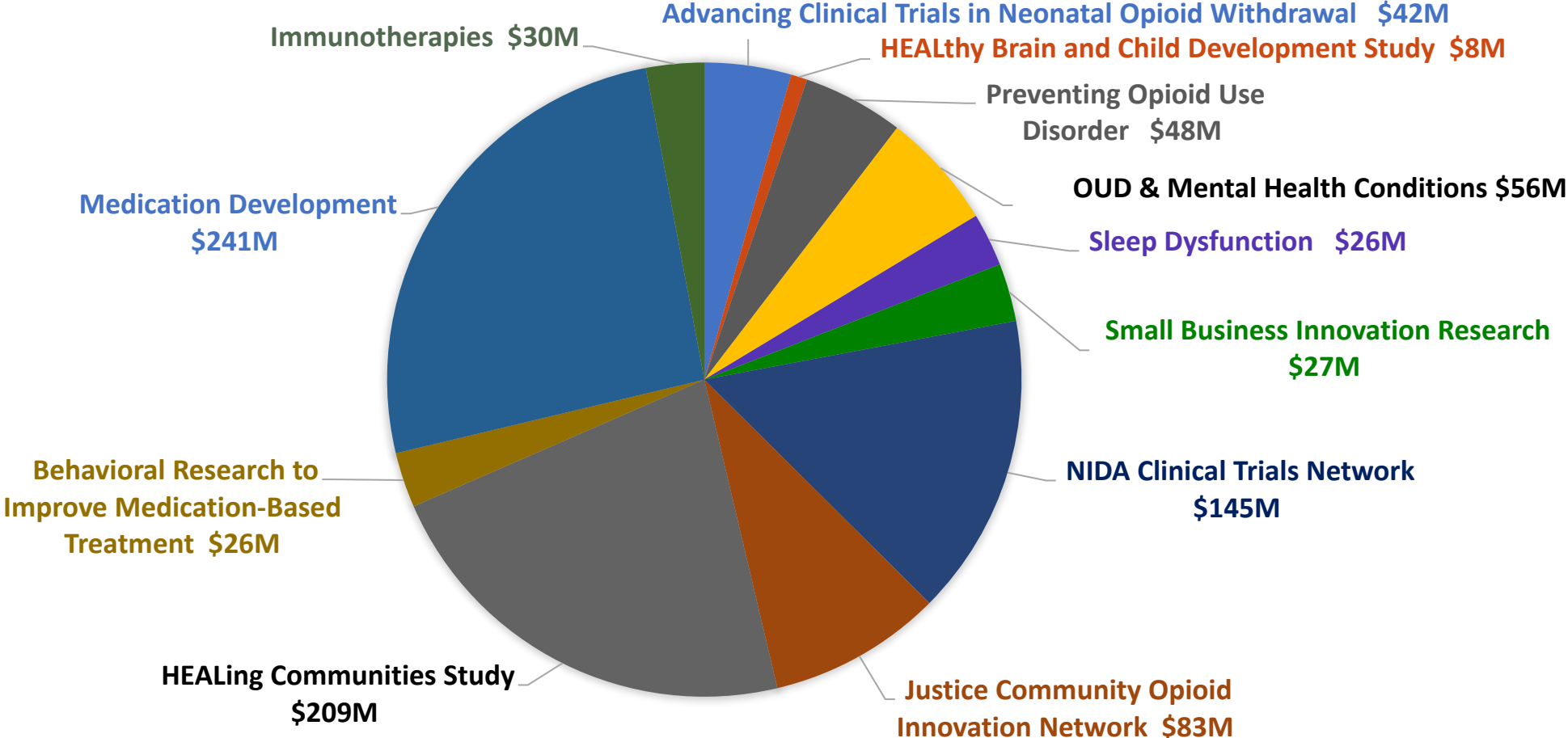


Characterizing Research in the HEAL Portfolio

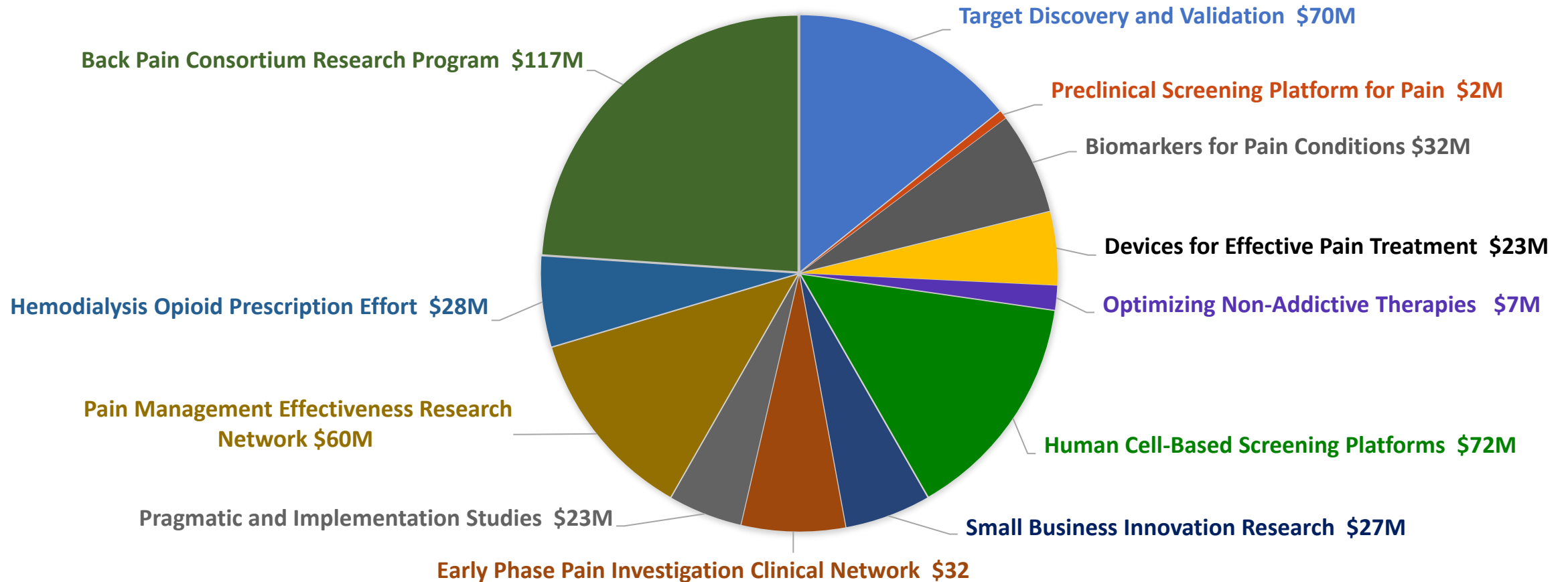
HEAL Research Total Spending to Date



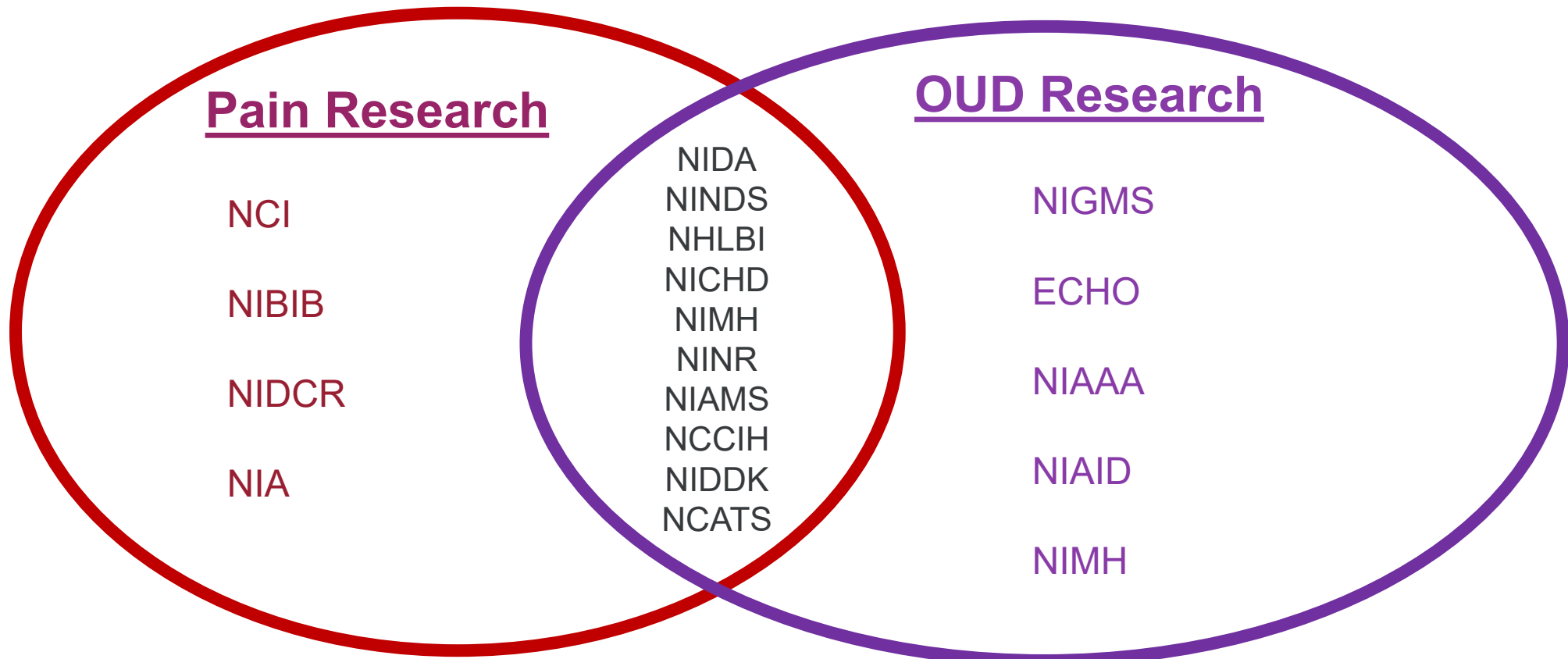
HEAL Research to Date: Opioid Misuse and Addiction



HEAL Research to Date: Enhancing Pain Management



NIH Institutes Leading HEAL Projects



Discussion

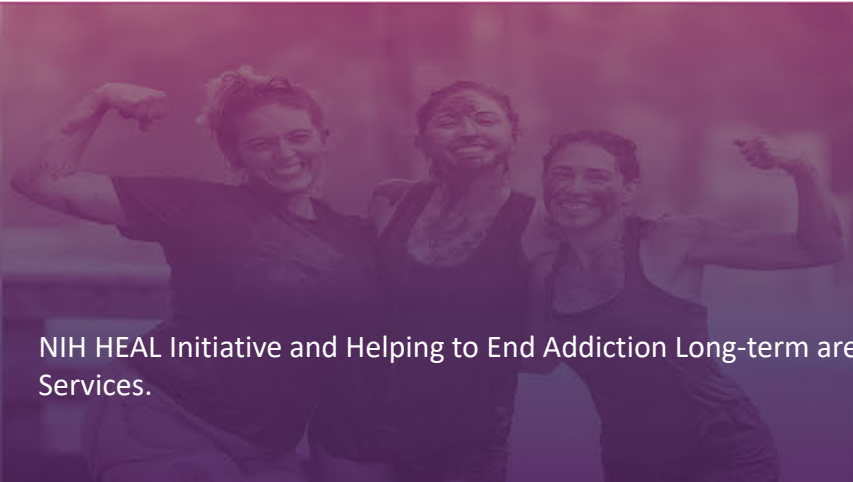


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Emerging Issues in the Opioid Crisis: Collision of COVID-19 on Overdose and Treatment

March 2, 2021

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

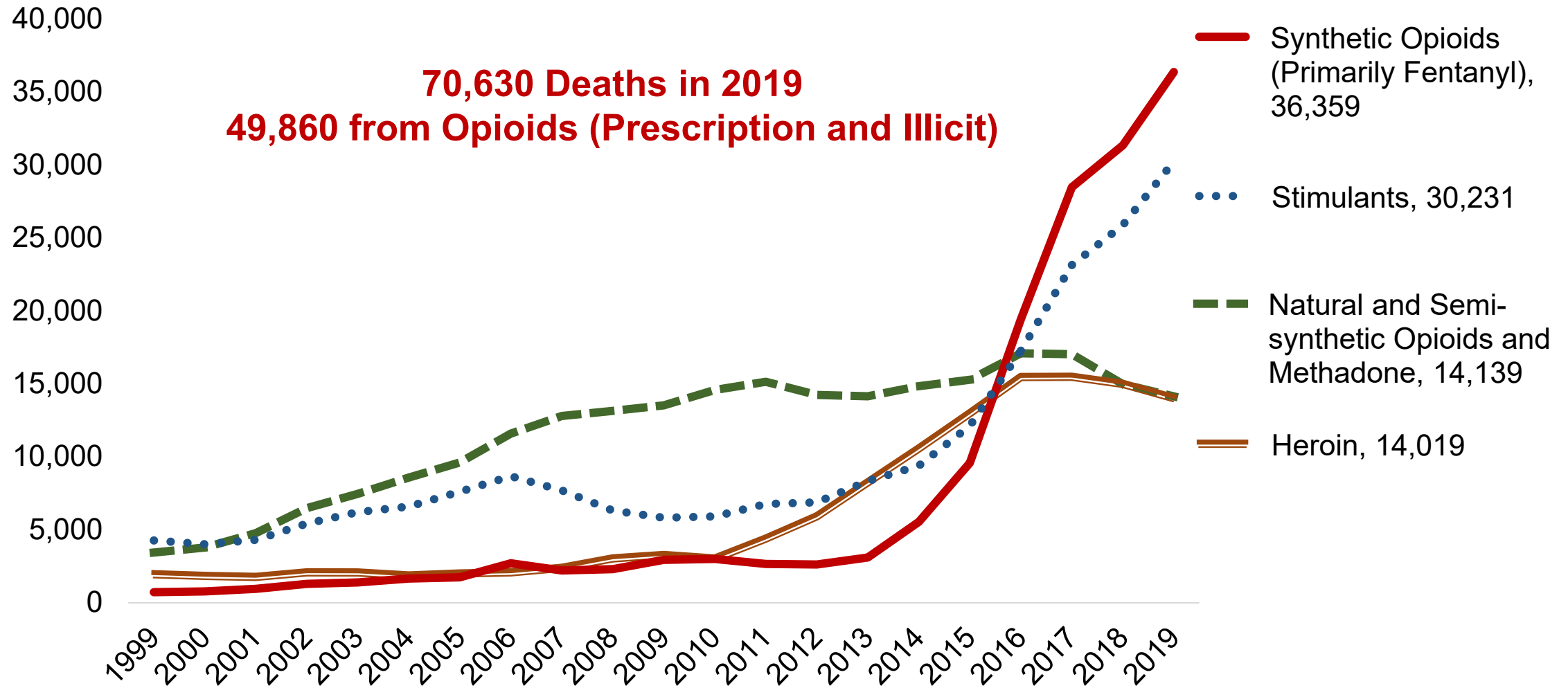


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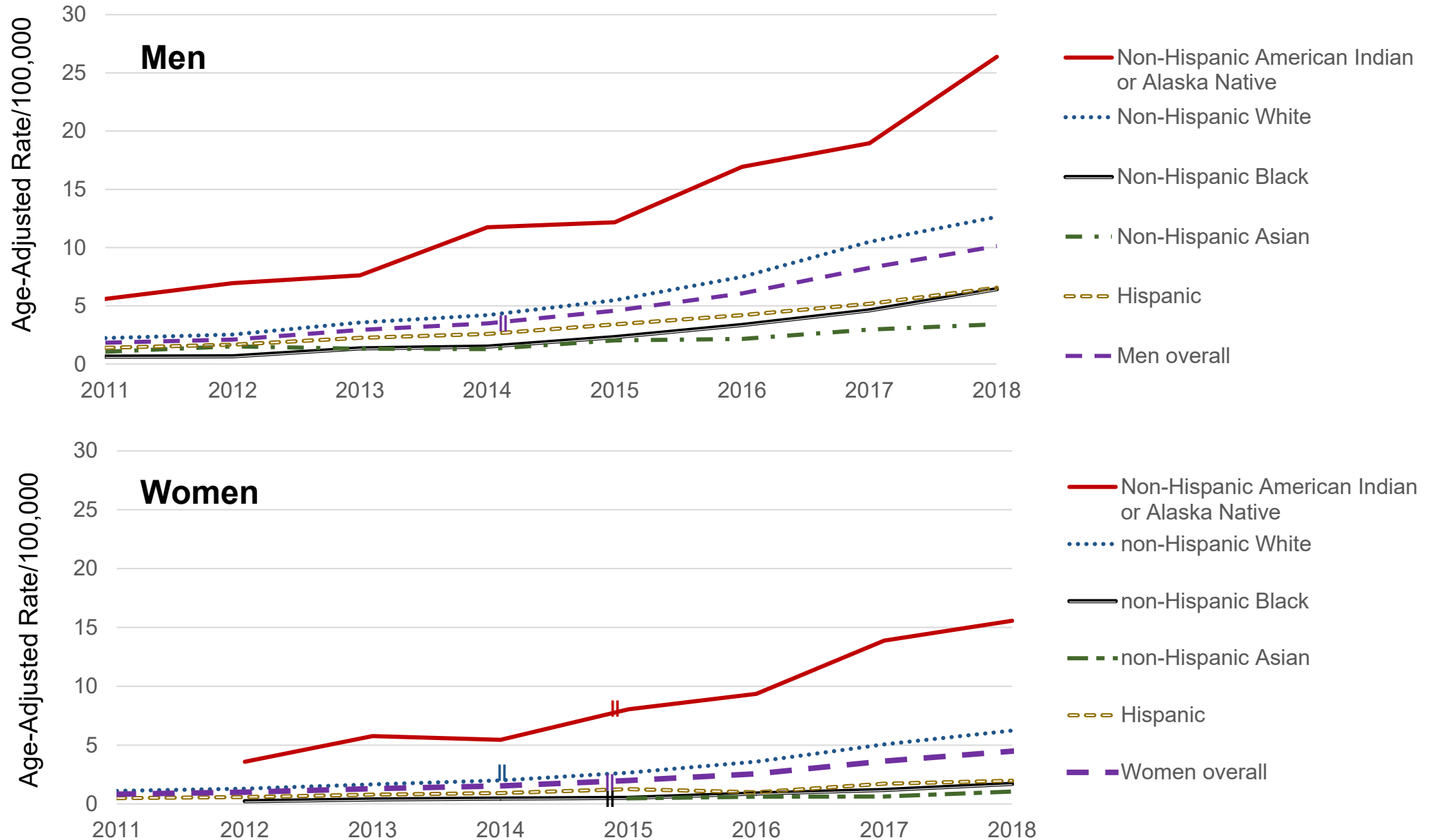
Evolution of Drivers of Overdose Deaths, All Ages

Analgesics → Heroin → Fentanyl → Stimulants

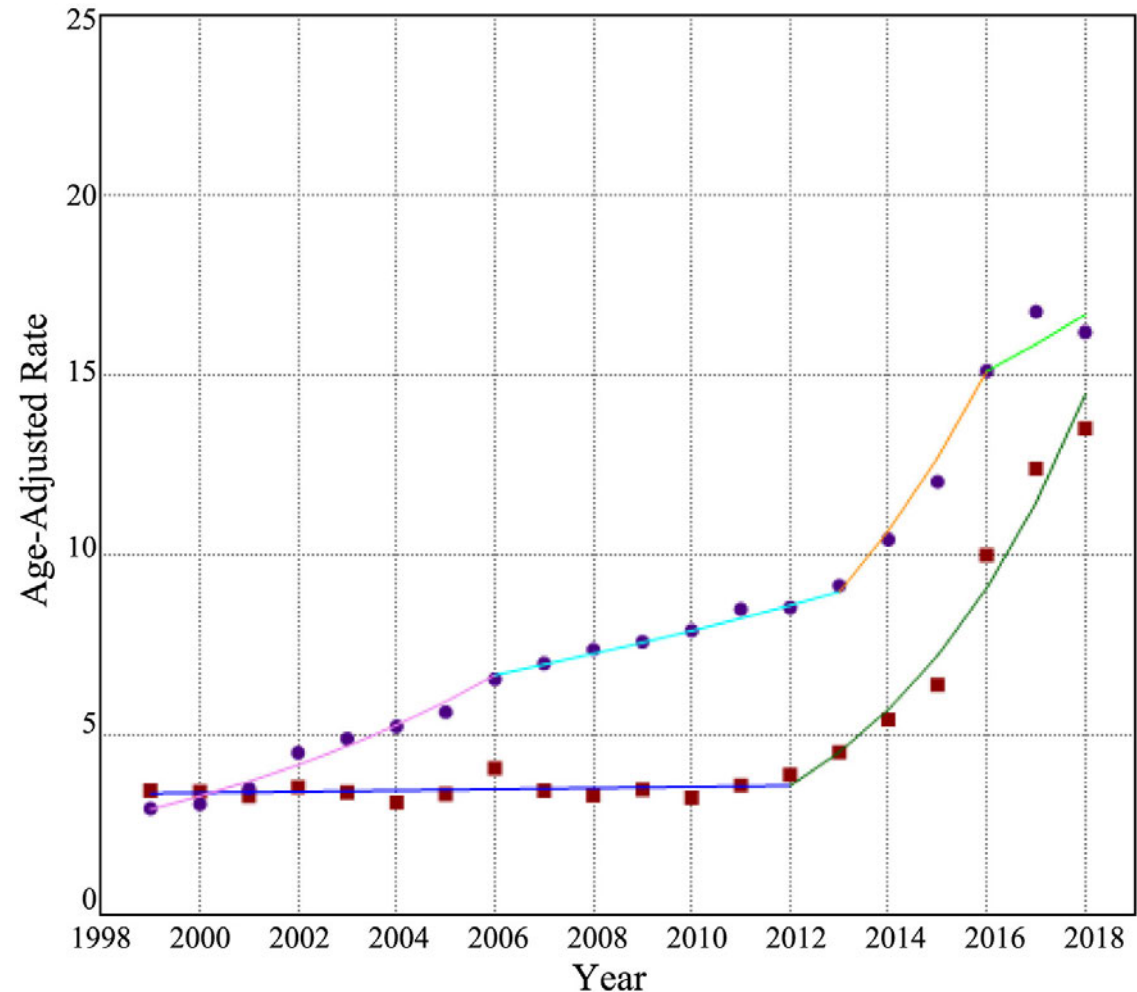
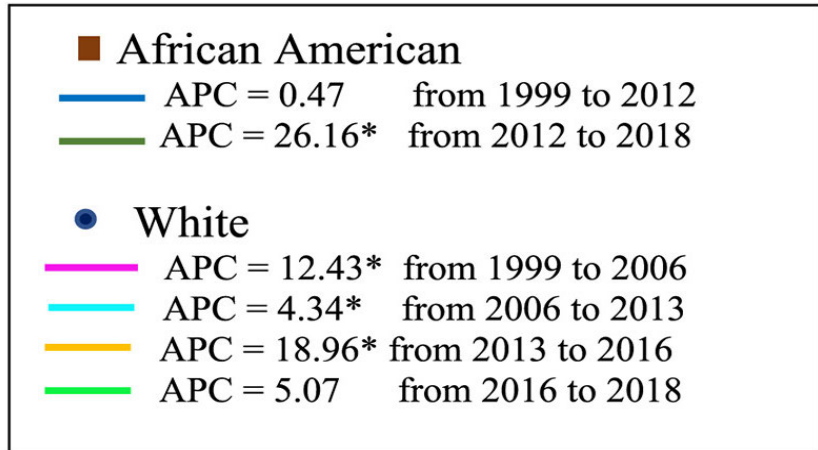


Source: The Multiple Cause of Death data are produced by the Division of Vital Statistics, National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC), United States Department of Health and Human Services (US DHHS).

Methamphetamine Deaths by Sex, Race, Ethnicity (25-54 years old)



African Americans Now Outpace Whites in Opioid-Involved Overdose Deaths

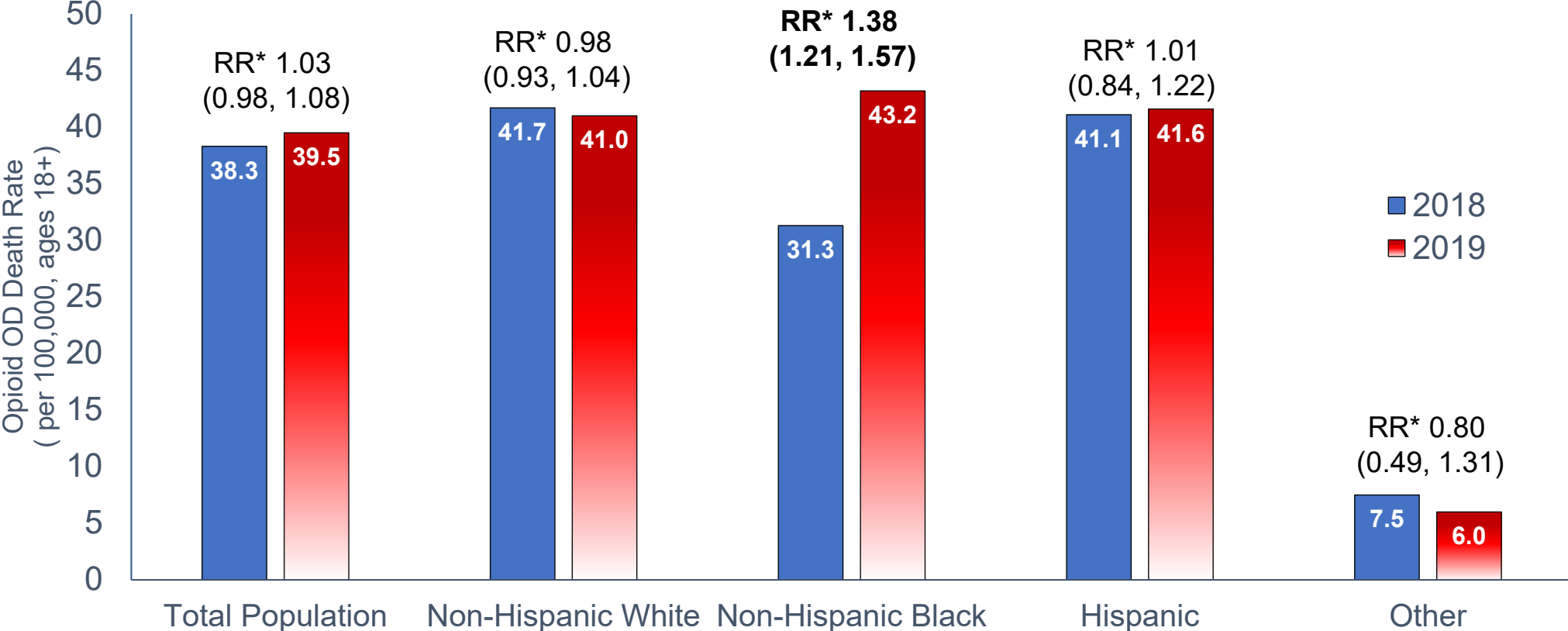


*Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.

Furr-Holden, et al., Addiction, 2021

HEALing Communities Study: Opioid Overdose Death Rate Trends

All Study Communities By Race/Ethnicity, 2018-2019



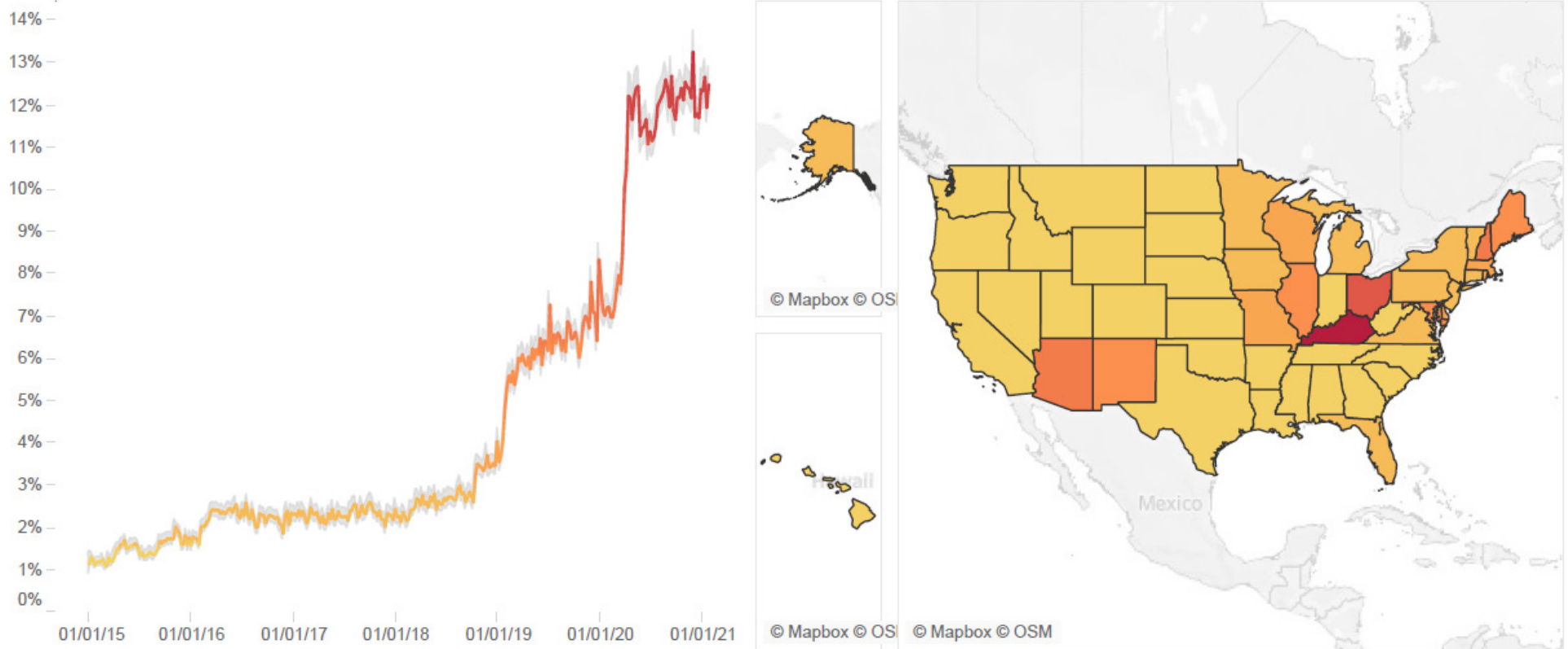
* Rate Ratio for 2019 vs 2018 with 95% Confidence Interval

Under review, Am. J. Public Health

Positive Urinalysis for Non-Prescribed Fentanyl Increased Sharply in Early 2020

Analysis of 6 Year Non-Prescribed Fentanyl Positivity

Insights below are based on specimens collected between 1/1/2015 and 1/23/2021

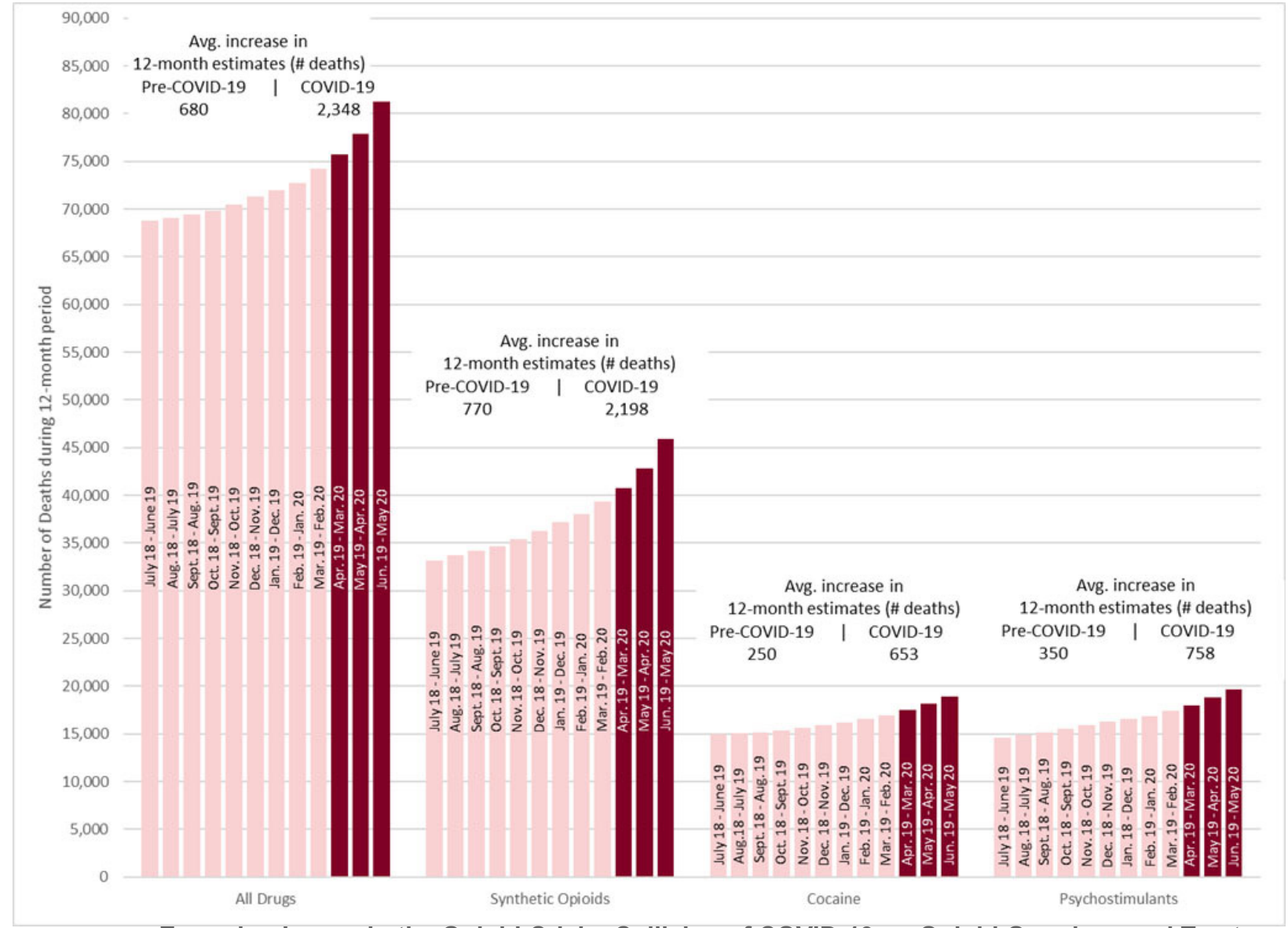


The graphs above display the positivity rate for non-prescribed fentanyl, where the total positivity rate is 4.2% [4.2% - 4.2%]. Gray bands show 95% confidence interval values. The legend shows the positivity rate color scale. States with less than 50 tests performed are not shown.



Twelve Months Provisional Drug Overdose deaths: June 2019 to May 2020

CDC Health Alert Network, December 17, 2020



Emerging Issues in the Opioid Crisis: Collision of COVID-19 on Opioid Overdose and Treatment

Increased Overdose Death Rates During COVID-19 Pandemic

12-months Ending July 2020 Compared to 12-months Ending July 2019

| | ALL DRUGS | HEROIN | NAT & SEMI-SYNTHETIC | METHADONE | SYNTHETIC OPIOIDS | COCAINE | OTHER PSYCHO-STIMULANTS (mainly meth) |
|----------------------------|---------------|--------------|----------------------|---------------|-------------------|---------------|---------------------------------------|
| July 2019 * | 69,266 | 14,793 | 12,203 | 2,875 | 33,704 | 15,031 | 14,941 |
| March 2020* | 75,687 | 14,145 | 12,349 | 2,837 | 40,756 | 17,465 | 18,033 |
| July 2020* | 86,001 | 14,427 | 13,259 | 3,315 | 50,122 | 19,542 | 20,406 |
| July 2019-July 2020 Change | +24.2% | -2.5% | +8.7% | +15.3% | +48.7% | +30.0% | +36.6% |

*Predicted Number of Deaths

Source: NCHS Provisional Drug Overdose Death Counts:

<https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm> (Accessed on 2-18-2021)

Fentanyl Overdoses (OD): Reversal with Naloxone

- Deaths from fentanyl or analogs are increasing in spite of naloxone ([R Torralva and A Janowsky, 2019](#)).
- OD from fentanyl frequently requires multiple naloxone administrations ([Schumann et al., 2007](#), [Somerville et al., 2017](#))
 - Shorter duration of naloxone ($t_{1/2}$ 1.3–2.4 h) than fentanyl ($t_{1/2}$ 7-8 h)
 - Slower clearance of fentanyl in frequent users
- Rapid injection of fentanyl can result in chest wall rigidity, which is not MOR-mediated and might reflect noradrenergic and cholinergic effects.

MOUD for Fentanyl

- Limited data on methadone or buprenorphine or naltrexone on fentanyl associated OUD
- Methadone maintenance therapy (MMT) is effective in fentanyl OUD.
 - Retrospective study in RI showed that 6 months of MMT protected against death and promoted abstinence, but relapse rates were high ([Stone, et al., 2018](#)).
 - Repeated exposure to fentanyl common while in MMT, but no deaths for those who remained in treatment, 4 deaths in those who left treatment ([Stone, et al. 2020](#)).
- Buprenorphine is effective in fentanyl OUD ([Wakeman, et al., 2019](#)).
 - Harder to initiate patients on buprenorphine
- MOUD can reduce demand for fentanyl in rats ([Hammerslag, et al., 2020](#)).

Stimulant (Cocaine and Methamphetamine) Use Disorder Medication Pipeline

| Early Preclinical T2L: (> 12 years) | Late Preclinical (10 – 12 years) | Phase I (6 – 10 years) | Phase Ib (5 – 9 years) | Phase II (4 – 6 years) | Phase III (3 – 5 years) |
|--|--|--|--|--|----------------------------|
| ① ● SBI-0069330 / SBI-0801315 mGluR2 PAM | ③ ○ IXT-m200 Long-duration anti-meth mAb | ③ ● dAdGNE Anti-cocaine vaccine | ② ○ Mirtazapine NE/5HT antagonist | ① ● NS2359* DAT/NET/SERT inhibitor | |
| ① ● NOP/Kappa/Mu ligands | ③ ○ Methamphetamine conjugate vaccine | ④ ● Cocaine hydrolase gene therapy | ② ○ Duloxetine & Methylphenidate NET/SERT inhibitor & CNS stimulant | ③ ○ IXT-m200 Anti-meth mAb | |
| ① ● PTPRD ligands | ③ ○ IXT-v100 Methamphetamine vaccine | ③ ● h2E2 Anti-cocaine mAb | ① ○ Pomaglometad methionil mGluR2/3 agonist prodrug | ② ● Bupropion DAT/NET inhibitor | |
| ① ● Peptidic KOR agonists | | | ② ● Clavulanic acid GLT-1 activator | ① ● Mavoglurant* mGluR5 non-competitive antagonist | |
| ① ● GLT-1 up-regulator | | | ② ● Ketamine NMDA antagonist | ① ● EMB-001 Metyrapone & oxazepam GC synth inhibitor & benzodiazepine | |
| ③ ○ Methamphetamine vaccine | | | ② ● Pioglitazone PPAR-γ agonist | ② ● Guanfacine α2A agonist | |
| ③ ● Cocaine catabolic enzyme | | | | ② ○ Naltrexone SR injection & oral Bupropion Mu antagonist & DAT/NET inhibitor | |
| ① ○ VMAT-2 inhibitor | | | | | |

KEY:

① – NME ② – New Indication ③ – Biologic ④ – Gene Therapy ● – cocaine ○ – meth ●○ – both cocaine and meth

* Not currently supported by NIDA

Discussion

END OF OPEN SESSION

Adjourn