Director’s Report to the
National Advisory Council on Drug Abuse

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Director
National Institute on Drug Abuse
February 8, 2023
## NIDA BUDGET
(all dollars are in $k)

<table>
<thead>
<tr>
<th></th>
<th>FY 2022 Enacted</th>
<th>FY 2023 President’s Budget</th>
<th>FY 2023 Appropriated**</th>
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</thead>
<tbody>
<tr>
<td><strong>Base</strong></td>
<td>$1,250,828</td>
<td>$1,437,883 *</td>
<td>$1,307,400</td>
</tr>
<tr>
<td><strong>HEAL</strong></td>
<td>$345,295</td>
<td>$405,443</td>
<td>$355,295</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>$1,596,123</td>
<td>$1,843,326</td>
<td>$1,662,695</td>
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</tbody>
</table>

* The FY 23 President’s Budget included a request for $196.3m in support of non-HEAL opioid and pain research.
** NIDA’s FY 23 appropriated budget included a 3.8% general increase as well as a $10m increase for the HEAL program and a $10m increase for research on pain and pain management.
FY 22 Funding Overview

Non-HEAL Research

- Clinical Trials Network, 3%
- Office of the Director, 9%
- Therapeutics and Medical Consequences, 11%
- Epidemiology, Services & Prevention Research, 32%
- Neuroscience & Behavior, 45%

HEAL Research*

- Office of the Director, 8%
- Neuroscience & Behavior, 8%
- Clinical Trials Network, 16%
- Therapeutics and Medical Consequences, 24%
- Epidemiology, Services & Prevention Research, 44%

*Includes all NIDA HEAL projects regardless of funding source
Proposed Changes to RPG Peer Review Criteria

Goal: To facilitate the identification of the strongest, potentially highest-impact research

• Refocus peer review on assessment of scientific/technical merit of grant applications
  • reduce burden of administrative items
• Mitigate reputational bias in the peer review process
  • evaluation of Investigator and Environment in the context of the proposed research

Summary of New Framework
• Reorganize the current five criteria (Significance, Investigators, Innovation, Approach, and Environment) into three factors:
  • Factor 1: Importance of Research (Significance and Innovation) – scored 1-9
  • Factor 2: Feasibility & Rigor (Approach) – scored 1-9
  • Factor 3: Expertise & Resources (Investigator, Environment) each to be rated “appropriate” or “additional resources needed”
• Overall Impact Score (1-9) to be based on Factors 1-3 and “Additional Review Criteria”, e.g. Human Subjects
• Most “Additional Review Considerations”, which have no bearing on overall impact score, removed

NIH seeks additional input via an RFI through March 10, 2023

NIH has invested over $3B in ~1300 BRAIN projects since 2014

1166 PIs across 234 Institutions supported by 952 BRAIN Awards
Join us June 12-13, 2023 for the 9th Annual BRAIN Initiative Meeting!

- Subscribe to the BRAIN Blog
- Visit the NIH BRAIN Initiative website
- Monitor NIH Guide Notices
- Connect with your IC’s BRAIN Program Officer

https://braininitiative.nih.gov/News-Events/event/9th-annual-brain-initiative-meeting
2022 Monitoring the Future Study

Key Findings and Concerns to Watch

• Most prevalences remained at or below pre-pandemic levels of use

• Few rebounds (notable one alcohol 12th graders) from last year’s unprecedented number of decreases in drug use among youth

• How will the decreases impact outcomes longer term?
Changes in Patterns of Cannabis Consumption 1992 to 2020

-- Recreational Marijuana legal in 21 states & DC.
-- Medical marijuana: legal in 38 states & DC

Monthly users quadrupled
Daily users increased 14X
Past year users Tripled

Source: Slide from Caulkins J
Brain Development: Effects of Drugs, ACE and Genetics

HEALthy Brain and Child Development (HBCD) Study
Longitudinal study (n=7,500 infants) to assess normative neurodevelopment from birth to 9-10 years and investigate impact of drug exposures and of genes and environment.

Adolescent Brain Cognitive Development (ABCD) Study
Longitudinal study (11,880 children) from ages 9-10 through early adulthood to assess factors that influence individual brain development trajectories and functional outcomes.

RESEARCH PRIORITIES

- Cannabis (THC, CBD, others) actions at molecular, epigenetic, cellular (neurons, glia, endothelium), circuits, energetics, behavioral levels.
- Risk for cannabis use and CUD (genetic, developmental, SDH).
- Consequences of cannabis use in brain health and behaviors across the lifespan including effects in neurodevelopment (fetal and childhood) and in neurodegeneration.
- Prevention and therapeutic Interventions for CUD.
- Impact of different policies on patterns of cannabis consumption and its consequences.
- Medical cannabis potential in management of SUD, HIV or pain.

Hippocampal synaptic density (PET $^{13}$CUCB-J $BP_{ND}$)
HEALthy Brain and Child Development Study

- 22/27 sites cleared for piloting
- Protocol finalized for visits 1-3
- Train the Trainer (visits 4-6) scheduled for April
- Enrollment of study cohort expected in May
- Child Welfare & Research workshop in development

http://hbcdstudy.org
Adolescent Brain Cognitive Development Study

97.6 Percent Retained

As of January 2023

Studies have shown both negative (depression and anxiety with excessive use) and positive (faster reaction times and improved working memory) outcomes from screen use.
<table>
<thead>
<tr>
<th>Date</th>
<th>ALL DRUGS</th>
<th>HEROIN</th>
<th>NAT &amp; SEMI SYNTHETIC</th>
<th>METHADONE</th>
<th>SYNTHETIC OPIOIDS (mainly illicit fentanyl)</th>
<th>COCAINE</th>
<th>OTHER PSYCHO-STIMULANTS (mainly meth)</th>
</tr>
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<tbody>
<tr>
<td>8/2021 *</td>
<td>104,038</td>
<td>10,488</td>
<td>13,970</td>
<td>3,708</td>
<td>67,624</td>
<td>22,571</td>
<td>30,876</td>
</tr>
<tr>
<td>12/2021 *</td>
<td>109,179</td>
<td>9,411</td>
<td>13,906</td>
<td>3,765</td>
<td>72,484</td>
<td>25,174</td>
<td>33,637</td>
</tr>
<tr>
<td>8/2022 *</td>
<td>107,477</td>
<td>6,863</td>
<td>12,272</td>
<td>3,357</td>
<td>73,102</td>
<td>26,786</td>
<td>33,534</td>
</tr>
<tr>
<td>Percent Change 8/21-8/22</td>
<td><strong>3.3%</strong></td>
<td><strong>-34.5%</strong></td>
<td><strong>-12.2%</strong></td>
<td><strong>-9.5%</strong></td>
<td><strong>8.1%</strong></td>
<td><strong>18.7%</strong></td>
<td><strong>8.6%</strong></td>
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* NCHS Provisional drug-involved overdose death counts are PREDICTED VALUES, 12 months ending in select months.
Drug Overdose Deaths: 2019–2020

NIDA Clinical Trials Network

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

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

- 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

- Goal: Reduce opioid-related OD deaths 40%
- OD education and naloxone distribution
- Increase access/utilization MOUD
- Decrease high-risk prescribing

Karisa M et al., MMWR Morb Mortal Wkly Rep, 2022
Synthetics Are Now Linked to Almost 90% of Opioid Overdose Deaths

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

Legend for Drug or Drug Class:
- Cocaine (140.5)
- Fentanyl (140.1)
- Methadone (140.3)
- Natural & semi-synthetic opioids (140.2)
- Opioids (140.0-140.4,140.6)
- Psychostimulants with abuse potential (T33.6)
- Synthetic opioids, excl. methadone (140.4)

Counts:
- 81,231
- 73,102

National Center for Health Statistics. 2022
Why are FENTAYL and 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.
Highly Lipophilic Synthetic Opioids Access MOR Via Two Routes

Fentanyl, But Not Morphine, Can Reassert Its Action (GIRK Currents) After Washout

**FIGURE 8** | Model for the unique pharmacology of fentanyl at the MOPr. In competition with a morphinan ligand (such as morphine or naloxone), fentanyl (green) can access the orthosteric pocket via two binding routes; the canonical aqueous pathway and by the novel lipid pathway. In contrast, the morphinan ligand (orange) only has access to one binding route.

Sutcliffe, et al., 2022
Why have synthetic opioids supplanted other opioids and used to contaminate other illicit drugs?

- Easier to produce than heroin (no opium poppy cultivation) – supply chain issues largely absent
- Synthesis is not complex (3-4 steps)
- More easily transported: a 40 g Altoids tin of illicit fentanyl powder is equivalent to ~ 1 kg of heroin
- Fentanyl high potency makes it easy for drug dealers to mix with other illicit drugs (heroin, cocaine and methamphetamine), which are then diluted to increase profits
- Profits much larger than for other illicit drugs including illicitly manufactured prescription pills (Oxycontin, Vicodin, Aderall, benzodiazepines) such that fentanyl pills are now being disguised and sold as prescription drugs
Fentanyl-involved and non-fentanyl overdose death rates in US youth aged 15-19 prior to and during the COVID pandemic

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.
Xylazine

- Alpha-2 agonist used as a veterinary sedative, muscle relaxant, and analgesic
- Not reversed by naloxone
- Associated with severe tissue injury

Xylazine-involved Deaths (A) And Percentage Of Fentanyl-involved Deaths With Detectable Xylazine (B)
Cook County, Illinois, 2017–2021


Journal of Analytical Toxicology, 46(8), 911-917.
Removal of the DATA-2000 Waiver

• December 29, 2022: President signed into law H.R. 2617, the “Consolidated Appropriations Act, 2023” which included:

  ▪ Mainstreaming Addiction Treatment (MAT) Act – eliminated the X-Waiver and removed the associated patient cap for buprenorphine prescribing
  ▪ Medication Access and Training Expansion (MATE) Act – Established a requirement for training on substance use for practitioners renewing or applying for DEA registration.

• Practitioners prescribing buprenorphine for OUD will still be held to state laws, insurance rules, and other applicable state or local requirements – could lead to heterogeneity in access to buprenorphine across states.
Research to Address Overdose Deaths in 2022

- **Pain** treatments
- **Treatment of opioid use disorder**
  - Implementation and services research to expand MOUD
  - Therapeutic development: medications and immunotherapies
    - New formulations
    - Novel targets
    - Alternative outcomes: craving, sleep, SUD severity
- **Neuromodulation**
- **Combined Treatments**
- **Treatment of other substance use disorders, polysubstance UD, co-morbidities**
- **Overdose treatments**: automatic reversals opioid OD, OD from drug combinations, OD from stimulants
- **Prevention** of drug use including but not limited to opioids
  - Screening and treatment intervention for SUD (mild-severe)
- **DATA**: Timely data of fatal and non-fatal overdoses, patterns of consumption on emerging new drugs and drug mixtures (xylazine)
- **Social Determinants of Health**
THANK YOU!