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

Nora D. Volkow, M.D.
Director
National Institute on Drug Abuse
May 11, 2021
<table>
<thead>
<tr>
<th></th>
<th>FY 2020 ($k)</th>
<th>FY 2021 ($k)</th>
<th>FY 2022 PB ($k)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base</strong></td>
<td>$1,191,362</td>
<td>$1,210,014</td>
<td>TBD</td>
</tr>
<tr>
<td><strong>HEAL</strong></td>
<td>$266,321*</td>
<td>$270,295*</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>$1,457,683</td>
<td>$1,480,309</td>
<td></td>
</tr>
</tbody>
</table>

*NIH's total HEAL funding is split evenly between NIDA and NINDS*
FY 20 Funding Overview

Non-HEAL Research

- Clinical Trials Network, 4%
- Office of the Director, 8%
- Therapeutics and Medical Consequences, 11%
- Epidemiology, Services & Prevention Research, 32%
- Neuroscience & Behavior, 45%

HEAL Research*

- Office of the Director, 5%
- Neuroscience & Behavior, 0.1%
- Clinical Trials Network, 19%
- Therapeutics and Medical Consequences, 26%
- Epidemiology, Services & Prevention Research, 49%

*Includes all NIDA HEAL projects regardless of funding source
Adolescent Brain Cognitive Development Study

98.5 Percent Retained

As of April 2021
Adolescent Brain Cognitive Development Study (ABCD): Progress up to April 2021

145 papers, half from ABCD, half from non-ABCD investigators
hBCD Study

Longitudinal study to understand normative neurodevelopment from birth to 9-10 years with an emphasis on assessing the impact of in utero exposures to drugs and harmful environments

Phase 1 Accomplishments

- Training for research coordinators
- MRI compatible crib to image newborns and infants
- Summit of families, legal scholars, ethicists, healthcare providers, and relevant agencies to mitigate risk and maximize benefit to women and children enrolled
- Workshop on bioethics
- Motion correction system developed and tested
- Protocols for remotely collecting saliva and stool
- Protocols for MRI data collection in infants with neonatal abstinence syndrome (NAS) created

- Purchased Sprinter van to demonstrate feasibility of scanning remotely
- Developed a multimodal protocol using EEG and MRI to assess brain structure, function, and connectivity.
- Conducted extensive literature review of recruitment and retention with vulnerable populations
- Conducted state by state assessment of legal and ethical issues related to substance use and pregnancy in research
Intersection Between Drug Crisis and COVID-19
COVID-19 risk and outcomes in patients with substance use disorders: analyses from electronic health records in the United States

Quan Qiu Wang, David C Kaelber, Rong Xu, Nora D Volkow

Risk associations between recent SUD diagnosis and COVID-19

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>AOR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUD</td>
<td>COVID-19</td>
<td>7.752 (7.048-8.536)</td>
<td>&lt;1e-30</td>
</tr>
<tr>
<td>CUD</td>
<td>COVID-19</td>
<td>5.296 (4.392-6.388)</td>
<td>&lt;1e-30</td>
</tr>
<tr>
<td>OUD</td>
<td>COVID-19</td>
<td>10.244 (9.107-11.524)</td>
<td>&lt;1e-30</td>
</tr>
<tr>
<td>TUD</td>
<td>COVID-19</td>
<td>8.222 (7.925-8.53)</td>
<td>&lt;1e-30</td>
</tr>
</tbody>
</table>

Death rates among COVID-19 patients with SUD

Wang et al., Mol Psychiatry 2020
Frequency and Comparison Of Number Of Risk Factors For COVID-19 According To Substance Use

The CDC Recognizes Substance Use Disorders as an Underlying Medical Condition Associated with High Risk for Severe COVID-19

Substance use disorders

Having a substance use disorder (such as alcohol, opioid, or cocaine use disorder) can make you more likely to get severely ill from COVID-19.

Get more information:

- How to Recognize a Substance Use Disorder
- Learn more about people who use drugs or have Substance Use Disorder and COVID-19
Drug Use Increase During COVID

Millennium Health Signals Report™ COVID-19 Special Edition: Significant Changes in Drug Use During the Pandemic Volume 2.1 Published July 2020

Fentanyl Positivity with Other Drugs Before and During COVID

## Overdose Deaths Increased Again in 2019 (and 2020*)

<table>
<thead>
<tr>
<th></th>
<th>ALL DRUGS</th>
<th>HEROIN</th>
<th>NAT &amp; SEMI – SYNTHETIC</th>
<th>METHADONE</th>
<th>SYNTHETIC OPIOIDS</th>
<th>COCAINE</th>
<th>OTHER PSYCHO-STIMULANTS (mainly meth)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>September 2019</strong></td>
<td>70,036</td>
<td>14,548</td>
<td>12,136</td>
<td>2,832</td>
<td>34,758</td>
<td>15,389</td>
<td>15,600</td>
</tr>
<tr>
<td><strong>March 2020</strong></td>
<td>75,687</td>
<td>14,145</td>
<td>12,349</td>
<td>2,837</td>
<td>40,756</td>
<td>17,465</td>
<td>18,033</td>
</tr>
<tr>
<td><strong>September 2020</strong></td>
<td>90,237</td>
<td>14,201</td>
<td>13,649</td>
<td>3,501</td>
<td>53,877</td>
<td>19,952</td>
<td>22,791</td>
</tr>
</tbody>
</table>

| **Year end September 2019-September 2020 Change** | +28.8% | -2.4% | +12.5% | +23.6% | +55.0% | +30.0% | +46.0% |

HEALing Communities Study: Opioid Overdose Death Rate Trends

All Study Communities By Race/Ethnicity, 2018-2019

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>2018 Opioid OD Death Rate (per 100,000, ages 18+)</th>
<th>2019 Opioid OD Death Rate (per 100,000, ages 18+)</th>
<th>RR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Population</td>
<td>38.3</td>
<td>39.5</td>
<td>1.03 (0.98, 1.08)</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>41.7</td>
<td>41.0</td>
<td>0.98 (0.93, 1.04)</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>31.3</td>
<td>43.2</td>
<td>1.38 (1.21, 1.57)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>41.1</td>
<td>41.6</td>
<td>1.01 (0.84, 1.22)</td>
</tr>
<tr>
<td>Other</td>
<td>7.5</td>
<td>6.0</td>
<td>0.80 (0.49, 1.31)</td>
</tr>
</tbody>
</table>

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

Under review, Am. J. Public Health
Treating Fentanyl OUD and Overdoses

Limited data on efficacy of MOUD to treat fentanyl OUD

- Methadone is effective in fentanyl OUD.
  - Methadone protected against death, but relapse rates were high (Stone, et al., 2018, Stone, et al. 2020).
- Buprenorphine is effective in fentanyl OUD (Wakeman, et al., 2019).
  - Harder to initiate patients on buprenorphine
- Naltrexone no published data

Deaths from fentanyl are increasing despite naloxone (Torralva and Janowsky, 2019).

- OD from fentanyl require multiple naloxone doses (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
- Chest wall rigidity from fentanyl
Treating Psychostimulant Use Disorder and Overdoses

• No FDA approved medications. Though promising results from combinations (Naltrexone + Bupropion, Naltrexone + Buprenorphine)

• Behavioral therapies: Most effective intervention is contingency management (uses rewards for evidence of abstinence) combined with a community reinforcement approach (uses recreational, familial, social, and vocational reinforcers, to make non-drug-using lifestyle more rewarding than substance use) (De Crescenzo et al., 2018).

• No overdoses reversal medications currently available
Treating Polysubstance Use Disorders
Reverting Polysubstance Overdoses
How Do We Address the Failure To Implement Evidence Based Treatments?

- Develop and promote sustainable models of care (use of pharmacies)
- Economic research (costs of not intervening; cost of relapse; Averted cost with extended-release formulations)
- Integrated healthcare interventions
- Telehealth
Conclusions
A collaborative care model for people with OUD that involves buprenorphine-waivered physicians and community pharmacists appears to be feasible in the US and has high acceptability to patients.
The Practice Guidelines for the Administration of Buprenorphine for Treating Opioid Use Disorder provide an exemption from certain certification requirements under 21 U.S.C. § 823(g)(2)(B)(i)-(ii) of the Controlled Substances Act (CSA). Specifically, the Practice Guidelines provide that:

- … buprenorphine, practitioners, defined as physicians, physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists, and certified nurse midwives, who are licensed under state law, and who possesses a valid DEA registration, may be exempt from the certification requirements related to training, counseling and other ancillary services.
- Practitioners utilizing the exemption are limited to treating no more than 30 patients at any one time.
## Stimulant (Cocaine and Methamphetamine) Use Disorder Medication Pipeline

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

**KEY:**
- NME
- New Indication
- Biologic
- Gene Therapy
- cocaine
- meth
- both cocaine and meth

* Not currently supported by NIDA
<table>
<thead>
<tr>
<th>Early Preclinical</th>
<th>Late Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>New Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to Launch: &gt;12 yrs</td>
<td>10-12 yrs</td>
<td>8-10 yrs</td>
<td>4-5 yrs</td>
<td>3-5 yrs</td>
<td>&lt;3 yrs</td>
</tr>
<tr>
<td><strong>D24M MOR/DOR</strong></td>
<td>SBI-553 NT-1 biased PAM</td>
<td>R-methadone prodrug</td>
<td>PF5190457 GHS1aR antagonist</td>
<td>INDV-2000 OX-1 antagonist</td>
<td>Ketamine NMDA antagonist</td>
</tr>
<tr>
<td><strong>Oxy/Fentanyl nano-vaccine</strong></td>
<td>NAN/NAQ MOR modulator</td>
<td>NRS-033 Nalmefene prodrug</td>
<td>NYX-783 NMDA modulator</td>
<td>Liraglutide/Semiglutide GLP-1R antagonist</td>
<td>Suvorexant OX-1/2 antagonist</td>
</tr>
<tr>
<td><strong>Fentanyl vaccine</strong></td>
<td>GPR151 antagonist</td>
<td>KNX100 Unknown mech</td>
<td>NP10697 GluN2B antagonist</td>
<td>Cannabidiol (CBD)</td>
<td>ASP8062 GABA-B PAM</td>
</tr>
<tr>
<td><strong>Carfentany mAb</strong></td>
<td>AT-121 NOP/MOR partial agonist</td>
<td>BTRX-246040 NOPr antag</td>
<td>Tezampanel AMPA antag</td>
<td>Oxycodone vaccine</td>
<td>Cannabidiol (CBD)</td>
</tr>
<tr>
<td><strong>PTPRD inhibitor</strong></td>
<td>P1A4 Fen mAb</td>
<td>Heroin Vaccine</td>
<td>Brexpiprazole D2/5HT1A par. ago.</td>
<td>ITI-333 MOR PA/5HT2a antagonist</td>
<td>Lemborexant OX-1/2 antagonist</td>
</tr>
<tr>
<td><strong>Methocinnamox MOR antag</strong></td>
<td>Mitragynine analogs</td>
<td></td>
<td>Brexpiprazole D2/5HT1A par. ago.</td>
<td>Mitragynine analogs</td>
<td>CVL-936 D3/D2 antag</td>
</tr>
<tr>
<td><strong>PZM21 MOR biased agonist</strong></td>
<td></td>
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</tbody>
</table>

**Key:** Red – Non-MOR  Black – MOR  Blue – Biologic
HCS and COVID Impact

• OD fatalities increased in 2020
• Virtual platforms deployed to work with coalitions and communities
• Telehealth focus:
  o Provide training to communities to facilitate telehealth
  o Distributed cell phones for patient use
  o Worked with communities to enhance broadband and other access issues
  o Greater emphasis on peer services and remote virtual outreach
  o Develop phone apps for overdose training
• Expanded data collection to include COVID-19
• Increased Health communications campaigns on social media
• Adapted study design and timeline
  o Fast-tracked OD education and naloxone before other EBPs to respond to releases from jail and prison
  o **Extended intervention period for Wave 1 communities due to delays in healthcare and justice settings**
JCOIN -- COVID Impacts

• **Relationships with practitioners** gave us real-time understanding of how the field was responding to the pandemic
  - Opportunities & challenges re: telehealth & MOUD initiation/continuation
• **Most clinical trials delayed by ~1 year in launch**
  - 9 of 13 now underway; 2 pilot testing; 2 imminent
• Investigators were able to **adapt protocols and explore interesting questions around COVID impacts** (e.g., OD associated with rapid decarceration in 2020)
• **RADX-UP:** funded 3 new studies of COVID-19 testing in CJ populations
• Shifted resources to develop **on-line training resources** that can be used post-pandemic

Tisha Wiley, Ph.D., Chief, Services Research Branch, tisha.wiley@nih.gov
Notice of Information:
Establishment of a Standard THC Unit to be Used in Research


Notice Number: NOT-DA-21-049

Key Dates:
Release Date: May 7, 2021

Issued by: National Institute on Drug Abuse (NIDA); National Heart. Lung and Blood Institute (NHLBI); National Institute of Mental Health (NIMH); National Cancer Institute (NCI)

Purpose:
.... Inconsistency in the measurement and reporting of THC exposure has been a major limitation in studies of cannabis use, making it difficult to compare findings among studies. A standardized measure of THC in cannabis products is necessary to advance research by providing greater comparability across studies of both its adverse effects and potential medical uses. ...this Notice informs research applicants of a new requirement to measure and report results using a standard THC unit in all applicable human subjects’ research, beginning May 7, 2021. A standard THC unit is defined as any formulation of cannabis plant material or extract that contains 5 milligrams of THC.
NIDA Racial Equity Initiative Research Priorities

- Develop interventions to improve health disparities (HD) by addressing structural racism
- Assess vulnerabilities & progression of substance use and addiction in HD populations
- Develop and test targeted efficacious and scalable, culturally-specific interventions
- Assess and address stigma and discrimination in the context of SUD and treatment
- Conduct HD research in the CJS, with focus on linkage to SUD & HIV treatments
- Build partnerships with state/local agencies and private health systems to develop models to eliminate barriers to addiction care
- Advance basic science to understand racial disparities
THANK YOU!