Drug Abuse and Addiction in America: Challenges and Opportunities

Kurt Rasmussen, Ph.D.
Director
Division of Therapeutics and Medical Consequences
National Institute on Drug Abuse
Disclosures

• No disclosures
THE CRISIS: NATIONAL OVERDOSE DEATH RATES

IN 2017, THERE WERE 70,237 OVERDOSE DEATHS (9.6% HIGHER THAN 2016)

Opioid Prescriptions: 1991-2011

Waves Opioid Crisis: Overdose Fatalities

IMS’s Source Prescription Audit (SPA) & Vector One®: National (VONA)

Other Synthetic Narcotics, 31,335
Heroin, 14,996
Natural and Semi-Synthetic Opioids, 12,552
Helping to End Addiction Long-Term SM (HEAL) Initiative

- Enhancing Pain Management
  - Advance Effective Treatments for Pain Through Clinical Research
  - Accelerate Discovery And Development Of Pain Treatments

- Improving Treatments for Misuse and Addiction
  - Expand Therapeutic Options
  - Enhance Treatments for Infants with NAS/NOWS

- Development New and Improved Prevention & Treatment Strategies
  - Optimize Effective Treatments

- Statistics:
  - 25.3 million American adults suffer from daily pain
  - 23.4 million American adults report a lot of pain

Source: National Institutes of Health, National Center for Complementary and Integrative Health

nci.nih.gov/health/pain
NIH HEAL Initiative

Improving Prevention and Treatment for Opioid Misuse, OUD and Overdoses

THE CRISIS: NATIONAL OVERDOSE DEATH RATES

IN 2017, THERE WERE 70,237 OVERDOSE DEATHS (9.6% HIGHER THAN 2016)

Medications for Opioid Use Disorder (MOUD)

- **Full Agonist**: Methadone (Daily Dosing)
- **Partial Agonist**: Buprenorphine (3-4X week)
- **Antagonist**: Naltrexone (ER 1 month)

**DECREASES**
- OPIOID USE
- OPIOID-RELATED
- OVERDOSE DEATHS
- CRIMINAL ACTIVITY
- INFECTIOUS DISEASE TRANSMISSION

**INCREASES**
- SOCIAL FUNCTIONING
- RETENTION IN TREATMENT
Extended Release (ER) Formulations Facilitate Use in Health Care & Justice Settings and Improve Compliance

**Mu Antagonist: NALTREXONE**

Vivitrol®
Once-month Injection

**Mu Partial Agonist: BUPRENNORPHINE**

SUBLOCADE™
(Buprenorphine ER), Once-Month Injectable
FDA Approval 11.30.2017

CAM2038
Subcutaneous
Buprenorphine ER:
Once-Week Injection
Once-Month Injection

PROBUPHINE®
6 months implant

---

**Percent of Weekly Urine Tests**

- 100%
- 80%
- 60%
- 40%
- 20%
- 0%

**PLACEBO**
- Placebo: N=124

**ER-NTX**
- ER-NTX: N=126

Krupitzky et al., Lancet 2011
<table>
<thead>
<tr>
<th>Early Preclinical Time to Launch: &gt;12 yrs</th>
<th>Late Preclinical 10-12 yrs</th>
<th>Phase I 6-10 yrs</th>
<th>Phase Ib 5-9 yrs</th>
<th>Phase II 4-6 yrs</th>
<th>Phase III 3-5 yrs</th>
<th>New Formulation &lt;3 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ANS6637 ALDH2 inhibitor</td>
<td>Guanfacine α2 adren agonist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C4X3256OX-1 antagonist</td>
<td>Ketamine NMDA antagonist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mor, Her, Oxy, Hydro vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Semiglutide GLP-1R agonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxy/Fentanyl nano-vaccine</td>
<td>Cannabidiol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl vaccine</td>
<td>Heroin Vaccine</td>
<td>Tradip tant NK-1 antagonist</td>
<td>Gabapentin VDCC blocker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heroin/Fentanyl vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Naloxone Hi-dose nasal spray</td>
</tr>
<tr>
<td>Fentanyl mAb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## OUD pipeline AFTER HEAL

<table>
<thead>
<tr>
<th>Early Preclinical</th>
<th>Late Preclinical 10-12 yrs</th>
<th>Phase I 6-10 yrs</th>
<th>Phase Ib 5-9 yrs</th>
<th>Phase II 4-6 yrs</th>
<th>Phase III 3-5 yrs</th>
<th>New Formulation &lt;3 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to Launch: &gt;12 yrs</td>
<td>DM24 MOR/DOR het antagonist</td>
<td>SBI-553 NT-1 biased PAM</td>
<td>ITI-333 MOR PA/5HT2a antagonist</td>
<td>KLS13019 CBD analogue</td>
<td>ANS6637 α2 adren agonist</td>
<td>Guanfacine</td>
</tr>
<tr>
<td></td>
<td>PZM21 MOR biased agonist</td>
<td>NAN/NAQ MOR modulator</td>
<td>Nalmefene implant MOR antag</td>
<td>PF5190457 GHS1αR antag</td>
<td>C4X3256 OX-1 antagonist</td>
<td>Ketamine NMDA antagonist</td>
</tr>
<tr>
<td></td>
<td>MOR biased agonist</td>
<td>GPR151 antagonist</td>
<td>N0RS-033 Nalmefene prodrug</td>
<td>Mor, Her, Oxy, Hydro vaccine</td>
<td>Semiglutide GLP-1R agonist</td>
<td>Suvorexant OX-1/2 antagonist</td>
</tr>
<tr>
<td></td>
<td>Oxy/Fentanyl nano-vaccine</td>
<td>AT-121 NOP/MOR partial agonist</td>
<td>LYN-014 Long acting methadone</td>
<td>NYX-783 NMDA modulator</td>
<td>Cannabidiol</td>
<td>Lorcanerin 5HT2c agonist</td>
</tr>
<tr>
<td></td>
<td>Fentanyl vaccine</td>
<td>PTPRD inhibitor</td>
<td>KNX100 Unknown mechanism</td>
<td>Heroin Vaccine</td>
<td>Tradipitant NK-1 antagonist</td>
<td>Gabapentin VDCC blocker</td>
</tr>
<tr>
<td></td>
<td>Heroin/Fentanyl vaccine</td>
<td>R-methadone prodrug</td>
<td>AP007 Extd-release nalmefene</td>
<td>NP10697 GluN2B antagonist</td>
<td>AZD4041 OX-1 antagonist</td>
<td>ASP8062 GABA-B PAM</td>
</tr>
<tr>
<td></td>
<td>Fentanyl mAb</td>
<td>Muscarinic M5 NAM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methocinnamox</td>
<td>MOR antag</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
EXPAND THERAPEUTIC OPTIONS: OUD

ADDICTION CYCLE AND RELEVANT BRAIN REGIONS

Transcranial Magnetic Stimulation (TMS)
Transcranial Direct Current Stimulation (tDCS)
Deep Brain Stimulation (DBS)

Koob and Volkow 2017
EXPAND THERAPEUTIC OPTIONS: OUD

VACCINES AND IMMUNOTHERAPIES

- Vaccines (fentanyl and analogues), heroin/morphine
- Reduced drug reaching brain
- Protection against overdose

Bremer et al, 2016; Janda and Treweek, 2012
Ultimately, we anticipate multiple medications, integrated with devices and psychosocial interventions, employed in an orchestrated fashion, will be needed to achieve truly effective treatments tailored for maximal efficacy for individual patients.
Implementing MOUD in Healthcare Settings

Primary Care: Low Threshold Office-Based Buprenorphine Treatment

- Unobserved induction,
- At most weekly visits,
- No psychosocial treatment.

- Treatment retention at 38 weeks equivalent to office-based opioid treatment.

Emergency department-initiated buprenorphine

- Reduced self-reported illicit opioid use
- Increased engagement in treatment
- Decreased use of inpatient services

D’Onofrio G et al., JAMA April 28, 2015.

IMPLEMENTING MEDICATIONS FOR OUD IN HEALTHCARE

- Optimizing Retention, Duration and Discontinuation MOUD
- Subthreshold OUD Trial
- ED-Initiated Buprenorphine
- MOUD for OUD Expecting Mothers
- Rural Expansion MOUD
- Hospital Initiation MOUD

CTN Node Expansion

- Appalachian Node – Univ. of Pittsburgh & WV Univ.
- Great Lakes Node – Rush University
- Greater Intermountain Node – Univ. of Utah
- Greater Southern CA Node – UCLA
- Southwest Node – Univ. of New Mexico
IMPLEMENTING MEDICATIONS FOR OUD IN JUSTICE SETTINGS

MOUD REDUCED MORTALITY BY 75% IN THE FIRST MONTH POST RELEASE

18 States + Puerto Rico
88 communities
>25,000 justice-involved individuals

Justice Community Opioid Innovation Network

Coordination and Translation Center: George Mason University
Methodology and Advanced Analytics Resource Center: University of Chicago

13 Hubs
- Each 5+ Communities
- Cascade of Care Focus
- Justice & Treatment Partner
- Diversity of Justice Setting, Geography, and Intervention

Novel Studies
- STATE POLICY ROLLOUTS
- LEVERAGING TECHNOLOGY
- PEER NAVIGATION SUPPORT
- INTER ORGANIZATIONAL LINKAGES
- MOUD COMPARATIVE EFFECTIVENESS
The HEALing Communities Study: Integrating Evidence Based interventions across Settings

Healthcare
- Primary care
- Emergency departments
- Inpatient hospital care
- Behavioral health

Criminal Justice
- Jails
- Prisons
- Parole/Probation
- Drug courts

Community
- Families
- Schools
- Police and fire departments
- Faith-based organizations
- Local industry

Ohio State University
PI: Rebecca Jackson

Columbia University
PI: Nabila El-Bassel

Boston Medical Center
PI: Jeffrey Samet

University of Kentucky
PI: Sharon Walsh
PRESENTATION TITLE

Centers for Disease Control and Prevention

PSYCHOSTIMULANTS

SYNTHETIC OPIOIDS

OD Deaths: Provisional Data 3/2018 – 2/2019
Source: CDC National Vital Statistics System, September 12, 2019

OVERDOSE MORTALITY BY CLASS OF DRUG
ADAPTED FROM NCHS STATISTICS

CDC National Vital Statistics System, January 15, 2020

<table>
<thead>
<tr>
<th></th>
<th>HEROIN</th>
<th>NAT &amp; SEMI - SYNTHETIC</th>
<th>METHADONE</th>
<th>SYNTHETIC OPIOIDS</th>
<th>COCAINE</th>
<th>OTHER PSYCHO-STIMULANTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>JUNE 2018 *</td>
<td>15,408</td>
<td>13,703</td>
<td>3,226</td>
<td>30,817</td>
<td>15,408</td>
<td>11,667</td>
</tr>
<tr>
<td>JUNE 2019 *</td>
<td>14,973</td>
<td>12,275</td>
<td>2,883</td>
<td>33,752</td>
<td>15,391</td>
<td>14,687</td>
</tr>
<tr>
<td>Change</td>
<td>-2.82%</td>
<td>-10.42%</td>
<td>-10.63%</td>
<td>9.52%</td>
<td>-0.11%</td>
<td>25.88%</td>
</tr>
</tbody>
</table>

* Number of predicted deaths for the 12 months ending in June of the indicated year

Source: CDC National Vital Statistics System, September 12, 2019

OVERDOSE MORTALITY BY CLASS OF DRUG
ADAPTED FROM NCHS STATISTICS

CDC National Vital Statistics System, January 15, 2020

<table>
<thead>
<tr>
<th></th>
<th>HEROIN</th>
<th>NAT &amp; SEMI - SYNTHETIC</th>
<th>METHADONE</th>
<th>SYNTHETIC OPIOIDS</th>
<th>COCAINE</th>
<th>OTHER PSYCHO-STIMULANTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>JUNE 2018 *</td>
<td>15,408</td>
<td>13,703</td>
<td>3,226</td>
<td>30,817</td>
<td>15,408</td>
<td>11,667</td>
</tr>
<tr>
<td>JUNE 2019 *</td>
<td>14,973</td>
<td>12,275</td>
<td>2,883</td>
<td>33,752</td>
<td>15,391</td>
<td>14,687</td>
</tr>
<tr>
<td>Change</td>
<td>-2.82%</td>
<td>-10.42%</td>
<td>-10.63%</td>
<td>9.52%</td>
<td>-0.11%</td>
<td>25.88%</td>
</tr>
</tbody>
</table>

* Number of predicted deaths for the 12 months ending in June of the indicated year

Source: CDC National Vital Statistics System, September 12, 2019
Intersection between Opioid crisis and COVID-19
COVID-19: Potential Implications for People with SUD

- SUD-related lung impairment may increase risk for serious effects from COVID-19 (smoking/vaping, opioids, methamphetamine)
- Stress on health systems may be a barrier to care for those with SUD
- Populations experiencing homelessness or incarceration at higher risk for SUD; may have increased exposure to COVID-19
- Difficulties in accessing medications (including methadone clinics)
- Restriction of community support system like syringe exchange programs
- Challenges of stress and social isolation to sustain recovery
COVID-19: Potential Implications for SUD Research

- Lab closures
- IRB closures
- Halted recruitment/enrollment/patient interaction in clinical trials
- Healthcare system overwhelmed with clinical needs and research delays
- Public health partners for HEALing Communities overwhelmed
- Researchers not permitted into correctional facilities
Notice of Special Interest (NOSI) regarding the Availability of Administrative Supplements and Urgent Competitive Revisions for Research on the 2019 Novel Coronavirus Notice Number: NOT-DA-20-047

• Key Dates
  **Release Date:** March 19, 2020  
  **First Available Due Date:** March 19, 2020  
  **Expiration Date:** March 31, 2021

• Related Announcements
  - PA-18-935 Urgent Competitive Revision to Existing NIH Grants and Cooperative Agreements (Urgent Supplement - Clinical Trial Optional)
  - PA-18-591 Administrative Supplements to Existing NIH Grants and Cooperative Agreements (Parent Admin Supp Clinical Trial Optional)

• Issued by
  National Institute on Drug Abuse (**NIDA**)

• Purpose
  NIDA is issuing this Notice of Special Interest (NOSI) to highlight the urgent need for research on the 2019 Novel Coronavirus (2019-nCoV, also known as COVID-19). NIDA is especially interested in research collecting and examining data on the risks and outcomes for COVID-19 infection in individuals suffering from SUD.
Analgesic & Reward Mechanisms of Mu Opiate Drugs (Heroin, Vicodin, Morphine)
Social Interaction Favored over Heroin Unless Social Interaction is Punished

Venniro et al., Nature Neuroscience 2018
Plethora of new targets for pain therapy development

Ajay S et al  Nature Reviews Drug Discovery  16, 545-564, 2017