Scientific Solutions for the OPIOID CRISIS

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Overdose Death Rates

1999

2015

Designed by L. Rossen, B. Bastian & Y. Chong. SOURCE: CDC/NCHS, National Vital Statistics System
Analgesic & Reward Mechanisms of Mu Opiate Drugs (Heroin, Vicodin, Morphine)
NIH OPIOID RESEARCH INITIATIVE

Using Research to End the Opioid Crisis

PAIN MANAGEMENT
Safe, more effective strategies

OPIOID ADDICTION
TREATMENT
New and innovative medications and technologies

OVERDOSE REVERSAL
Interventions to reduce mortality and link to treatment
Biased Mu-Opioid Receptor Ligands: A Promising New Generation Of Pain Therapeutics

Fentanyl-Related Deaths Surpassed Heroin or Rx Opioids in 2016

Graphs from NY Times Article based on CDC MMWR Report 2017
NALOXONE REQUIRES FAST AND EFFICIENT DELIVERY as achieved with IV injection but few know how to inject

Receptor occupancy by INTRANASAL equivalent to INTRAVENOUS Naloxone

Baseline Intranasal Intravenous

Intranasal naloxone reaches blood as fast as Intramuscular naloxone and achieves higher levels

Medication Assisted Treatment (MAT)

**Opioid Effect**

- **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

**But MAT is highly underutilized!**
**Relapse rates are very high!**

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**OUD Cascade of Care in USA**

- Current estimates
- Treatment gap
- 90% goal

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*Williams AR, Nunes E, Olfson M. Health Affairs Blog, 2017*
Extended Release Formulations

- Vivitrol®
- PROBUPHINE®

IM Injection q 4 weeks for 24 weeks

Median % Opioid-Negative Urines

<table>
<thead>
<tr>
<th>Percent of Weekly Urine Tests</th>
<th>PLACEBO</th>
<th>XR-NTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>N=124</td>
<td>N=126</td>
</tr>
<tr>
<td>80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td></td>
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</tr>
</tbody>
</table>

Placebo: N=124
XR-NTX: N=126

Krupitzky et al., Lancet 2011

Rosenthal et al., Addiction 2013;105.

FDA approval – May 26, 2016

Opportunities for Partnership in the Development of Longer Acting Formulations and/or Drug Combinations to Improve Treatment Compliance and Retention
Target Selection on the Basis of the Neurocircuitry of Addiction

Targets to interfere with drug reward

Targets to reduce stress-induced drug seeking and to improve mood

Targets to reduce cue-induced drug seeking and to improve executive function

Compounds targeted to neurocircuitry could be beneficial not just to addiction but also to diseases for which such circuits are disrupted (i.e., ADHD, depression)

2016: First vaccine for fentanyl and fentanyl analogs reported in a mouse model

- Successfully stimulated antibody production
- Reduced fentanyl reaching the brain
- Reduced analgesia and protected against overdose

Bremer et al, 2016; Janda and Treweek, 2012
Emergency Departments
Implementing Medication-Assisted Treatment

- Emergency department-initiated buprenorphine
- Reduced self-reported, illicit opioid use
- Increased engagement in addiction treatment; decreased use of inpatient addiction treatment services

Self-Reported Illicit Opioid Use in the Past 7 Days

<table>
<thead>
<tr>
<th>Days</th>
<th>Baseline</th>
<th>30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>5.4</td>
<td>0.9</td>
</tr>
<tr>
<td>Referral</td>
<td>5.4</td>
<td>2.3</td>
</tr>
<tr>
<td>Brief Intervention</td>
<td>5.6</td>
<td>2.4</td>
</tr>
</tbody>
</table>

D’Onofrio G et al., JAMA April 28, 2015.
Opioid Use and Misuse During Pregnancy

17% of pregnant women are prescribed an opioid during pregnancy

NICU Admissions for Neonatal Abstinence Syndrome NAS
(Number per 1000 Admissions)

Buprenorphine for NAS Tx

Buprenorphine resulted in a shorter duration of NAS treatment and length of hospital stay than treatment with morphine


NIH Public Private Partnership
To Address the Opioid Crisis

Focus Area A: Enhance the range of medication options to treat opioid use disorder and prevent/reverse overdoses

• Develop *new formulations* and *combinations of medications* to treat opioid use disorder and to prevent overdoses.

• Develop *more potent* or *longer lasting opioid antagonists* to reverse overdoses from fentanyl or its derivatives.

• *Develop and validate alternative endpoint* other than abstinence that are acceptable to FDA for approval of OUD medications.

Focus Area B: Pain

• Establish *data sharing collaborative* between industry groups
  • *NIH to serve as a neutral broker*

• Determine *objective measures* to understand, predict responses to pain
  • *Biomarkers for pain – and a “Pain-ometer”*

• *Clinical trial network* to accelerate trials on common and rare pain syndromes and to evaluate biomarkers.
Challenges of the Opioid Epidemic

• 25.5 million adults have pain every day
  • Opioids are overprescribed, not effective for chronic pain

• More than 2 million Americans are addicted to opioids
  • Most started with prescription medicines

• Medication Assisted Treatment (MAT) is available for opioid use disorders and to prevent/reverse overdose
  • But MATs are drastically underutilized
  • Duration of treatment needed is not well understood

• Research has revolutionized our understanding of addiction and pain
  • But alternatives to treat addiction and overdose are limited
  • And new, non-addictive pain medicines are urgently needed
Priorities for Future Research

• **Strengthen the connection between research and practice**
  • A learning health care system to translate evidence-based practices
  • Need for large-scale implementation pilot

• **Explore, maximize, and expedite use of all available data sources and study designs**
  • In addition to clinical trials, use observational and secondary data sources as well
  • Consider barriers to using the data, including confidentiality issues

• **Engage citizen scientists to help develop outcome and quality measures**
  • Need standardized metrics that patients and families can use to report on patient experience and treatment outcomes

• **Determine criteria to indicate inpatient vs outpatient treatment**
  • Collect longer-term outcomes data to understand the utility of different treatments settings and modalities

• **Establish which treatment interventions are effective for mild OUD or subclinical opioid misuse**

• **Research to address cost and sustainability**
The purpose of this Funding Opportunity Announcement is to support the discovery and development of medications to prevent and treat opioid use disorders (OUD) and overdose.

The UG3/UH3 Phase Innovation Awards Cooperative Agreement involves 2 phases. The UG3 is to support a project with specific milestones to be accomplished by the end of the 2-year period.

The UH3 is to provide funding for 3 years to a project that successfully completed the milestones set in the UG3. UG3 projects that have met their milestones will be administratively considered by NIDA and prioritized for transition to the UH3 phase. Investigators responding to this FOA must address both UG3 and UH3 phases.
Using Science to Inform Practice and Policy:
A Coordinated Approach to Research Priority Setting

Sponsored by the National Institute on Drug Abuse in Partnership with ECRI Institute

PARTICIPANT AGENCIES

- Academy Health
- Addiction Policy Forum
- Agency for Healthcare Research & Quality
- American Association for the Advancement of Science
- America’s Health Insurance Plans
- American Hospital Association
- American Medical Association
- Bipartisan Policy Center
- Centers for Disease Control & Prevention
- Centers for Medicare & Medicaid Services
- Defense Health Agency
- ECRI Institute
- Health Resources & Services Administration
- National Academy of Medicine
- National Institute on Drug Abuse
- National Institutes of Health
- Office of the Assistant Secretary of Defense
- Office of National Drug Control Policy
- Research!America
- Patient-Centered Outcomes Research Institute
- Substance Abuse & Mental Health Services Administration
- United States Army Medical Research & Materiel Command
- U.S. Department of Health & Human Services
- U.S. Department of Veterans Affairs
- U.S. Food & Drug Administration
In 2016, the age-adjusted rate of drug overdose deaths in the US was more than three times the rate in 1999.

In 2016, 22 states and the District of Columbia had age-adjusted drug overdose death rates that were statistically higher than the national rate.

Community Health Centers (Massachusetts)

**Integrating Buprenorphine Treatment Into Federally Qualified Health Centers (FQHC):**

Integrating BT in a large FQHC network increased retention rates to levels similar to those reported by clinical trials.

_Haddad MS et al., DAD 2013 Jul 1;131(1-2):127-135._