NIH’s Efforts to Reduce the Opioid Epidemic

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National Institute on Drug Abuse
@NIDAnews
Prescription Drug Misuse/Abuse is a Major Problem in the US

Current Drug Use Rates in Persons Ages 12+

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Numbers in Millions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Illicit Drug</td>
<td>27.1</td>
</tr>
<tr>
<td>Marijuana</td>
<td>22.2</td>
</tr>
<tr>
<td>Psychotherapeutics</td>
<td>6.4</td>
</tr>
<tr>
<td>Cocaine</td>
<td>1.9</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>1.2</td>
</tr>
<tr>
<td>Inhalants</td>
<td>0.5</td>
</tr>
<tr>
<td>Heroin</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Past Year Nonmedical Use of Psychotherapeutic Drugs Persons Ages 12+

<table>
<thead>
<tr>
<th>Year</th>
<th>Pain Relievers</th>
<th>Tranquilizers</th>
<th>Stimulants</th>
<th>Sedatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>4.7</td>
<td>2.1</td>
<td>1.2</td>
<td>0.3</td>
</tr>
<tr>
<td>2005</td>
<td>4.9</td>
<td>2.2</td>
<td>1.4</td>
<td>0.3</td>
</tr>
<tr>
<td>2006</td>
<td>5.1</td>
<td>2.1</td>
<td>1.2</td>
<td>0.4</td>
</tr>
<tr>
<td>2007</td>
<td>5.0</td>
<td>2.2</td>
<td>1.1</td>
<td>0.2</td>
</tr>
<tr>
<td>2008</td>
<td>4.8</td>
<td>2.2</td>
<td>1.1</td>
<td>0.4</td>
</tr>
<tr>
<td>2009</td>
<td>4.9</td>
<td>2.2</td>
<td>1.3</td>
<td>0.2</td>
</tr>
<tr>
<td>2010</td>
<td>4.8</td>
<td>2.3</td>
<td>1.3</td>
<td>0.2</td>
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<tr>
<td>2011</td>
<td>4.8</td>
<td>2.2</td>
<td>1.4</td>
<td>0.3</td>
</tr>
<tr>
<td>2012</td>
<td>4.3</td>
<td>2.3</td>
<td>1.4</td>
<td>0.6</td>
</tr>
<tr>
<td>2013</td>
<td>4.2</td>
<td>2.2</td>
<td>1.3</td>
<td>0.3</td>
</tr>
<tr>
<td>2014</td>
<td>3.9</td>
<td>2.3</td>
<td>1.4</td>
<td>0.6</td>
</tr>
<tr>
<td>2015</td>
<td>4.7</td>
<td>2.3</td>
<td>1.4</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Opioid Prescriptions have started to Decrease but Opioids Fatalities are still Increasing

Opioid morphine milligram equivalents (MME) dispensed fell by over 15% from 2010-2015

Source: IMS Health, U.S. Outpatient Retail Setting
Heroin Price Has Decreased in Recent Years

"Retail" Price Per PureGram

$3,500
$3,000
$2,500
$2,000
$1,500
$1,000
$500
$-


Emerging Illicit Synthetic Opioids

- Increasing reports of fentanyl laced-heroin and prescription pills
- Other synthetic opioids emerging i.e., Carfentanil

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
Safe, More Effective Strategies for Pain Management

Non-Opioid Analgesics
- Cannabinoids;
- Inflammatory mediators;
- Ion channel blockers

Targeted Opioid Analgesics
with reduced potential for addiction and overdose

Biologics
- e.g. antibodies that bind to pain producing cytokines

Biased Mu-Opioid Receptor Ligands:
New Generation Of Pain Therapeutics

Knowledge of Pain Pathways –

New Biomarkers for Pain?

New study assess glial role in human pain

- Patients with low back pain (LBP) versus controls
  - Uses PET to detect levels of glial protein (TSPO)
  - Demonstrates role of glial activation in human pain
  - Possible biomarker
  - May suggest new treatments for chronic pain

Loggia et al., Brain 2015;138.
Limiting Abuse by Predicting Addiction

- **OPRM1** encodes for the target of opioids
- Can variants predict likelihood of addiction?
- **OPRM1** variant
  - Affects receptor levels in brain
  - Associated with increased risk for addiction, overdose severity

Hancock et al., Biol Psychiatry 2015; 78.
Peciña et al., Neuropsychopharmacology 2015; 40.
Overdose Treatment: Saving Lives for Future Recovery

- New stronger, longer acting formulations to address more potent opioids (e.g. fentanyl)
- Stimulation devices to prevent respiratory depression
- Overdose detection and alert technologies
- Post-overdose interventions to ensure engagement in treatment

An early prototype of a device students at the University of British Columbia have created to detect drug overdoses. (THE CANADIAN PRESS/HO-Courtesy of Sampath Satti)
User Friendly Naloxone

NARCAN® Nasal Spray device-- $37.50 per 4mg
Approved by FDA November 2015

- Naloxone Px increased 3.5X in past year
- NARCAN® Nasal Spray is the most prescribed naloxone
- 900,000 NARCAN® Nasal Spray doses distributed since launch in 2/16

Opioid Overdose Reversal
By Narcan® Nasal Spray

Avetian GE et al., Current Medical Research and Opinion, 23 May 2017.
Medications Assisted Therapies for OUD

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

**Log Dose**

**DECREASES:**
- Opioid use
- Opioid-related OD deaths
- Criminal activity
- Infectious disease transmission

**And INCREASES**
- Social functioning
- Retention in treatment
- Outcomes in NAS

MAT is **highly underutilized**
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

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

Abstinence from Illicit Opioids over 12 Weeks with Interim Buprenorphine

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

Improving Treatments for Addiction:  
**Naltrexone Trial in CJ Populations**

- **Participants:** parolees/probationers with opioid addiction – all volunteers – received either
  - Monthly injections of extended release naltrexone for 6 months
  - Community treatment, including methadone or Suboxone (encouraged)

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**Relapse Frequency**

- Probability of No Relapse over Weeks

Overdoses in 78 weeks:
- Control: 7
- Naltrexone: 0
Extended Release Formulations

**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>0%</td>
<td>80%</td>
</tr>
<tr>
<td>80%</td>
<td>20%</td>
<td>60%</td>
</tr>
<tr>
<td>60%</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>40%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>20%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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

*Krupitzky et al., Lancet 2011*

**PROBUPHINE®**

*FDA approval – May 26, 2016*

*Placebo XR-NTX*

*Kruepitzky et al., Lancet 2011*

Rosenthal et al., Addiction 2013;105.
Innovative Opioid Addiction Treatments: Fentanyl Vaccine

- 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

Cutting Edge Science Meeting Series to End the Opioid Crisis

1. Medications Development for Opioid Use Disorders and for Overdose Prevention and Reversal -- June 5, 2017

2. Development of Safe, Effective, Non-Addictive Pain Treatments -- June 16, 2017

3. Understanding the Neurobiological Mechanisms of Pain -- July 7, 2017
Goal: Improve pain treatment through education

Goal: Prevent SUD and improve outcomes in addiction through education of health care providers
### Scientific Strategies for Combating the Opioid Epidemic

#### Overdose Prevention & Reversal
- Stronger opioid antagonist formulations
- Novel medications (e.g., 5-HT1A agonists, ampakines)
- Phrenic-nerve stimulation devices
- Technologies to detect overdose & alert help or autoinject naloxone

#### Treatment of Opioid-Use Disorders
- New formulations of existing medications
- Repurposing approved therapies (e.g., lorcaserin)
- Novel medications targeting neurobiology (e.g., lofexidine)
- Vaccines and monoclonal antibodies
- Brain-stimulation technologies

#### Treatment of Chronic Pain
- Opioid formulations with abuse-deterrent properties
- MOR-biased agonists
- Cannabinoids
- Novel or repurposed medications targeting pathophysiology (e.g., sodium-channel blockers)
- Monoclonal antibodies
- Brain-stimulation technologies
- Gene therapies
- Progenitor cell therapies
- Precision medicine
- Biomarkers

Adapted from Volkow & Collins, NEJM, 2017.