Opioids: An Epidemic and Alternatives

Michael B. Marlin, M.D.
Senior Toxicology Fellow
Rocky Mountain Poison and Drug Center
Learning Objectives

- Discuss brief history of opioids and their abuse
- Understand the pharmacology opioids and their clinical presentation
- Understand the current prescription opioid epidemic and its effect on illicit opioid use
- Learn the role of oral health occupations in helping to curb abuse and addiction
- Gain knowledge in alternative treatments and possible avenues of future research
History of Opioid Abuse

- **Pre-500** C.E.
  - Mentioned as soma in the Rig Veda
- **400-1200** C.E.
  - Arab and Persians introduce opium to China
- **1400** C.E.
  - Chinese epidemic
  - Opium Wars
1803 – Morphine isolated from opium
1827 – E. Merck & Co. manufacture opium
1847 – Heroin is synthesized
  - San Francisco bans opium use
1898 – Bayer manufactures heroin
1905 – U.S. Congress bans opium
1910 – Britain dismantles Indo-Chinese opium trade
1923 – All narcotics sells banned in U.S.
1948 – imported by Mafia in NYC
1950s – production and import from “Golden Triangle”
1965-1970 – Air America
- French connection
- Estimated 750K heroin addicts

1973 – Nixon creates DEA
- Mid 70s – opium production begins in Mexico

1992 – introduced from Colombia

2007 – Afghanistan accounts for 95% of the world’s opium production

2008 – Switzerland: legalized heroin program

2009 – Rx opioid deaths > MVC in Florida

2016 – heroin / fentanyl deaths on the rise
Pharmacology

- Bind to $\mu$, $\kappa$, and $\delta$ receptors
  - CNS
    - Brain
    - Spinal cord
  - GI tract ($\mu$)
- $\mu_1$ - euphoria
- $\mu_2$ - respiratory depression
κ – named for binding of ketocyclazocine
- predominantly spinal cord

- $K_1$: Supraspinal analgesia, miosis, diuresis
- $K_2$: Psychotomimesis
- $K_3$: Supraspinal analgesia
- **Analgesia**
  - Mu receptors
    - Periaqueductal gray
    - Nucleus raphe magnus
    - Locus ceruleus
    - Medial thalamus
  - Kappa receptors
    - Spinal cord
- **Euphoria**
  - μ-δ complex in ventral segmental area $\rightarrow$ *dopamine* release in mesolimbic system
  - μ receptors in mesolimbic system
  - Naloxone reverses “runner’s high”
  - κ may cause dysphoria
Opioid Toxicity

- Miosis
- Respiratory Depression
- Sedation
Treatment

- Supportive care: respiratory support
- Naloxone
  - Synthetic $\mu$ antagonist

No one should die from an opioid overdose
Unique Toxicities of Opioids

- **Meperidine** – MAOI, Serotonin Syndrome
  - Libby Zion, 1974
- **Methadone** – QT prolongation, long half-life
- **Propoxyphene** – Na⁺ blockade
- **Tramadol** – NE/5HT reuptake inhibition
- **Fentanyl** – Rigid Chest Syndrome, Serotonin Syndrome
OTC Opioids

- Dextromethorphan
  - Weak mu agonist
  - NMDA antagonist
  - Serotonin syndrome

- Loperamide
  - Cardiac conduction abnormalities

- Diphenoxylate with atropine
  - Atropinization with IV administration
Epidemiology of Current Abuse

- 27 million aged >12 used an illicit drug within the last 30 days
- 4.3 million abused a Rx opioid
- 1.9 million w/ substance abuse disorder
Figure 5. Nonmedical Use of Pain Relievers and Other Psychotherapeutic Drugs among Current Nonmedical Users of Any Psychotherapeutic Drug Aged 12 or Older: 2014

- 4.3 Million Current Nonmedical Users of Pain Relievers (66.2%)
- 2.2 Million Current Nonmedical Users of Psychotherapeutics Other Than Pain Relievers (33.8%)

6.5 Million Current Nonmedical Users of Psychotherapeutic Drugs

Behavioral Health Trends in the United States:
Results from the 2014 National Survey on Drug Use and Health; SAMHSA
Behavioral Health Trends in the United States: Results from the 2014 National Survey on Drug Use and Health; SAMHSA

Source: National Drug Threat Survey
CHART 6. SOURCE WHERE PAIN RELIEVERS WERE OBTAINED FOR MOST RECENT NONMEDICAL USE AMONG PAST YEAR USERS AGED 12 OR OLDER: 2012 - 2013

Source Where User Obtained

- One Doctor: 21.2%
- More than One Doctor: 3.6%
- Other: 4.3%
- Bought on the Internet: 0.1%
- Drug Dealer/Stranger: 4.3%
- Bought/Took from Friend or Relative: 14.6%

Source Where Friend/Relative Obtained

- Free from Friend or Relative: 53.0%
- One Doctor: 83.8%
- More than One Doctor: 3.3%
- Other: 5.1%
- Drug Dealer/Stranger: 4.9%
- Bought on the Internet: 0.3%

Source: NSDUH
Chart 7. How Different Misusers of Pain Relievers Obtain Their Drugs (Percentage)

<table>
<thead>
<tr>
<th>Methods and sources for obtaining pain relievers</th>
<th>Recent Initiates</th>
<th>Occasional Users</th>
<th>Frequent or Chronic Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bought from friend, relative, dealer, or Internet</td>
<td>9.9%</td>
<td>11.6%</td>
<td>24.5%</td>
</tr>
<tr>
<td>Prescribed from one or more doctors</td>
<td>19.3%</td>
<td>21.3%</td>
<td>30.8%</td>
</tr>
<tr>
<td>Bought from pharmacist without asking</td>
<td>66.2%</td>
<td>63.3%</td>
<td>39.9%</td>
</tr>
</tbody>
</table>

Source: NSDUH
(U) **Chart 8. All Opioid CPDs Compared to the Number of Hydrocodone and Oxycodone CPDs Available on the Legitimate Market, 2006 - 2013**

Source: DEA
How Increasing Medical Access to Opioids Contributes to the Opioid Epidemic: Evidence from Medicare Part D

David Powell‡
Rosalie Liccardo Pacula†
Erin Taylor††

September 2016

States with High Elderly Shares Versus States with Low Elderly Shares

Mortality, Ages 0-64

Substance Abuse Treatments, Ages 12-54

Sources: National Vital Statistics System and Treatment Episode Data Set
Notes: “Above Median” and “Below Median” refer to the elderly share of the population in 2003.
Figure 4: Opioid Abuse: Mortality per 100,000 (Ages 0-64)

Figure 6: Heroin Mortality per 100,000 (Ages 0-64)

Notes: We estimate equation (1) but allow the effect of Elderly Share in 2003 to vary by year, normalizing the coefficient for 2003 to zero.
Powell et al. concluded the following:

- Part D = increased opioid utilization for 65+
- Medicare-ineligible population
  - Increased mortality
  - Increased substance abuse treatment
- Estimated 10% increase in medical opioid supply
  - 7.4% increase in opioid-related deaths
  - 14.1% increase in substance abuse treatment admission rates
Potential for Addiction?

- Hoppe et al. 2015
  - Opioid-naïve patients prescribed opioids for acute pain are at increased risk for additional opioid use at 1 year.
  - Adjusted odds ratio = 1.8 (95% CI, 1.3-2.3)
Excluded:
- Repeat visit: 715
- Exclusion criteria: 75
- Incomplete data: 6

Total eligible patients: 5,597

Patients for analysis: 4,801

Opioid-naive: 2,499 (52%)
Non-naive: 2,302 (48%)

No opioid prescription: 1,420 (57%)
Opioid prescription on discharge: 1,079 (43%)

Filled prescription: 775
Did not fill prescription: 304

Recurrent use:
- Filled prescription: 146 (10%)
- Did not fill prescription: 130 (17%)
- Recurrent use: 23 (8%)

(Hoppe, Kim et al. 2015)
<table>
<thead>
<tr>
<th>Variable</th>
<th>No Rx</th>
<th>Not Filled</th>
<th>Filled</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1,420</td>
<td>304</td>
<td>775</td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>35 (26–48)</td>
<td>42 (31–53)</td>
<td>39 (28–51)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>538 (38)</td>
<td>133 (44)</td>
<td>359 (46)</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>410 (29)</td>
<td>78 (26)</td>
<td>182 (24)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>378 (27)</td>
<td>89 (29)</td>
<td>181 (24)</td>
</tr>
<tr>
<td>White</td>
<td>501 (35)</td>
<td>103 (34)</td>
<td>358 (46)</td>
</tr>
<tr>
<td>Other</td>
<td>104 (7)</td>
<td>32 (11)</td>
<td>46 (6)</td>
</tr>
<tr>
<td>Missing</td>
<td>27 (2)</td>
<td>2 (0)</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Insurance (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Federal</td>
<td>369 (26)</td>
<td>57 (19)</td>
<td>154 (20)</td>
</tr>
<tr>
<td>Medically indigent</td>
<td>428 (30)</td>
<td>83 (27)</td>
<td>304 (39)</td>
</tr>
<tr>
<td>Private</td>
<td>318 (22)</td>
<td>76 (25)</td>
<td>170 (22)</td>
</tr>
<tr>
<td>Self-pay</td>
<td>278 (19)</td>
<td>77 (25)</td>
<td>128 (17)</td>
</tr>
<tr>
<td>Worker’s compensation, VA, CHP</td>
<td>27 (2)</td>
<td>11 (4)</td>
<td>19 (2)</td>
</tr>
<tr>
<td>Chief complaint (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdomen/pelvic (n=705)</td>
<td>500 (71)</td>
<td>70 (10)</td>
<td>135 (19)</td>
</tr>
<tr>
<td>Extremity (n=514)</td>
<td>196 (38)</td>
<td>92 (18)</td>
<td>226 (44)</td>
</tr>
<tr>
<td>Back (n=324)</td>
<td>123 (38)</td>
<td>39 (12)</td>
<td>162 (50)</td>
</tr>
<tr>
<td>Injury (n=286)</td>
<td>138 (48)</td>
<td>50 (18)</td>
<td>98 (34)</td>
</tr>
<tr>
<td>Head (n=269)</td>
<td>226 (84)</td>
<td>14 (5)</td>
<td>29 (11)</td>
</tr>
<tr>
<td>Other (n=152)</td>
<td>113 (74)</td>
<td>11 (7)</td>
<td>28 (19)</td>
</tr>
<tr>
<td>ENT/dental (n=89)</td>
<td>36 (40)</td>
<td>13 (15)</td>
<td>40 (45)</td>
</tr>
<tr>
<td>Chest (n=75)</td>
<td>49 (65)</td>
<td>4 (5)</td>
<td>22 (29)</td>
</tr>
<tr>
<td>Neck (n=51)</td>
<td>23 (45)</td>
<td>6 (12)</td>
<td>22 (43)</td>
</tr>
<tr>
<td>Missing (n=34)</td>
<td>16 (47)</td>
<td>5 (15)</td>
<td>13 (38)</td>
</tr>
<tr>
<td>Recurrent use (%)</td>
<td>146 (10)</td>
<td>23 (8)</td>
<td>130 (17)</td>
</tr>
</tbody>
</table>

No Rx, Patients who did not receive a prescription; not filled, patients who received but did not fill a prescription; filled, patients who filled an opioid prescription.

(Hoppe, Kim et al. 2015)
Johnson et al. 2016
- 13% of 59,725 opioid-naïve patients continued to fill Rx between 90 and 180 days after surgery
- Elective surgery patients more likely than trauma (13.5% vs 10%)
- Prolonged opioid use was associated with the following:
  - Younger age
  - Female gender
  - Lower income
  - Comprehensive insurance
  - Higher Elixhauser comorbidity index
  - Mental health disorders
  - Tobacco dependence or abuse

<table>
<thead>
<tr>
<th>Elixhauser comorbidity index</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 or 1</td>
<td>1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2</td>
<td>1.4 (1.3–1.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>3</td>
<td>1.6 (1.4–1.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&gt;3</td>
<td>2.2 (2.0–2.3)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

(Johnson, Chung et al. 2016)
Chart 16. Percentage of the total heroin-dependent sample that used heroin or a prescription opioid as their first opioid of abuse

*Note: 2010s data includes only 2010 to 2013.*

Boscarino et al

- Interviewed 705 patients with 4+ physician orders for opioids in the past 12 months
- Non-malignant pain
- Assessed risk factors

(Boscarino, Rukstalis et al. 2010)
Applying the Opioid Epidemic to Oral Health Occupations

- Dentists follow PCPs as the second-leading prescriber of immediate-release opioids (15% and 12% respectively) (Katz, Bimbaum et al. 2010)
- Paucity of prescribing data
  - 85% of patients were prescribed an opioid after third-molar extraction by OMFS (Moore, Nahouraii et al. 2006)
2010 West Virginia state wide survey
- 52% of all dentists responded
  - 79% were general practitioners
  - 73% prescribed IR opioid
    - 10-20 doses was most common

{Tufts, 2010}

72% of respondents in a Utah survey had leftover medications
- 71% with leftover opioid medications kept them

{CDC, 2010}
(Hill, McMahon et al. 2016)
Prevention

- Identify risk factors
- SBIRT (SAMHSA initiative)
  - 33% of dentists responding to Tufts survey did not routinely ask patients about substance abuse {Tufts, 2010}
- Consider UDS
- Only prescribe what is needed
- Encourage patients to participate in prescription take-back programs
- Utilize Prescription Drug Monitoring Programs (PDMP)
PDMP

  - South Carolina PDMP searched over 2 year time frame (2012-2013)
  - On 324 occasions, dentist prescribed IR opioid to person who had filled >10 opioid rx within 30 days of visit
### Table 2

**Frequencies of preexisting multiple concurrent opioid prescription volumes at the time of dental opioid prescribing incidents.**

<table>
<thead>
<tr>
<th>NO. OF PRIOR OPIOID PRESCRIPTIONS</th>
<th>NO. OF INCIDENTS</th>
<th>PERCENTAGE OF INCIDENTS INVOLVING FEMALE PATIENTS</th>
<th>PERCENTAGE OF INCIDENTS INVOLVING CHILDREN</th>
<th>NO. OF PATIENTS REPRESENTED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 d</td>
<td>90 d</td>
<td>180 d</td>
<td>30 d</td>
</tr>
<tr>
<td>0</td>
<td>491,636</td>
<td>439,922</td>
<td>401,519</td>
<td>54.5</td>
</tr>
<tr>
<td>1</td>
<td>94,414</td>
<td>105,634</td>
<td>113,934</td>
<td>56.9</td>
</tr>
<tr>
<td>2</td>
<td>36,067</td>
<td>42,918</td>
<td>59.4</td>
<td>58.8</td>
</tr>
<tr>
<td>3</td>
<td>8,861</td>
<td>17,793</td>
<td>20,477</td>
<td>61.7</td>
</tr>
<tr>
<td>4</td>
<td>3,636</td>
<td>9,873</td>
<td>12,209</td>
<td>62.5</td>
</tr>
<tr>
<td>5</td>
<td>1,565</td>
<td>5,746</td>
<td>8,343</td>
<td>67.2</td>
</tr>
<tr>
<td>6</td>
<td>784</td>
<td>4,134</td>
<td>6,620</td>
<td>69.5</td>
</tr>
<tr>
<td>7</td>
<td>373</td>
<td>2,594</td>
<td>4,740</td>
<td>69.0</td>
</tr>
<tr>
<td>8</td>
<td>183</td>
<td>1,681</td>
<td>3,556</td>
<td>67.7</td>
</tr>
<tr>
<td>9</td>
<td>126</td>
<td>1,179</td>
<td>2,567</td>
<td>67.9</td>
</tr>
<tr>
<td>10</td>
<td>112</td>
<td>770</td>
<td>2,045</td>
<td>60.4</td>
</tr>
<tr>
<td>11</td>
<td>51</td>
<td>551</td>
<td>1,578</td>
<td>47.6</td>
</tr>
<tr>
<td>12</td>
<td>34</td>
<td>418</td>
<td>1,443</td>
<td>33.3</td>
</tr>
<tr>
<td>13</td>
<td>19</td>
<td>307</td>
<td>1,118</td>
<td>29.4</td>
</tr>
<tr>
<td>14</td>
<td>16</td>
<td>221</td>
<td>907</td>
<td>50.0</td>
</tr>
<tr>
<td>15</td>
<td>10</td>
<td>170</td>
<td>685</td>
<td>50.0</td>
</tr>
<tr>
<td>Greater Than 15</td>
<td>82</td>
<td>717</td>
<td>3,118</td>
<td>66.2</td>
</tr>
<tr>
<td>Total Greater Than 0</td>
<td>156,141</td>
<td>187,855</td>
<td>226,258</td>
<td>NA</td>
</tr>
</tbody>
</table>

* Female patients accounted for 55.1% of total patients with known sex in the full sample.
† Children were defined as people younger than 21 years, and they accounted for 12.5% of total patients in the full sample.
‡ NA: Not applicable.

(McCauley, Hyer et al. 2016)
The Larger Picture

The resurgence of heroin and rise of fentanyl, its derivatives, and designer opioids
In 2014, there were approximately 435,000 active heroin users in the U.S.

- 0.2% increase from in 2014 from 2013 (2015 data pending)
- 2015 expected to be much higher
CHART 18. HEROIN SEIZURES AT THE SOUTHWEST BORDER, 2000 - 2014

Source: EPIC National Seizure System
Deaths

- Drug overdose deaths have become the leading cause of injury deaths in the U.S.
- 120 people die each day
(U) **Chart 17. Drug-poisoning Deaths Involving Heroin, 1999 - 2013**

- **Number of Deaths**
  - Scale: 1,000 to 9,000
  - Data points from 1999 to 2013

- **Note:** Heroin includes opium.

- **Source:** National Center for Health Statistics/Centers for Disease Control,
  Final death data for each calendar year

- **244% increase**
  - **2007 - 2013**
New Hampshire Overdose Deaths

2015 Current Drug Data as of 1-8-2016

- Other Drugs: 34 deaths
- Other Opiates/Opioids: 58 deaths
- Heroin & Fentanyl: 34 deaths
- Heroin and other drugs: 12 deaths
- Fentanyl and other drugs: 71 deaths
- Pure Fentanyl: 148 deaths
- Pure Heroin: 28 deaths

*There are currently 45 cases from 2015 that are “Pending Toxicology”*
OCTOBER 16, 2016

NEW DRUG PINK CAUSING DEATHS NATIONWIDE, OPIOID U-47700 EASILY PURCHASED ONLINE DESPITE FEDERAL BAN
Alternative Treatments

- Long-acting bupivacaine for prolonged analgesia after procedure
- Full therapy with *ibuprofen* or *naproxen*
  - Consider first line (Hersh, Cooper et al. 1993)
  - As effective as opioids (Desjardins et al. 2010)
Future Research

- Fixed interval vs “as needed”
- Polymorphisms that predict pain relief, AE, and abuse
- More evidence re: utility of NSAIDs/APAP in limiting need for opioids
- Utility of LA anesthetics alone or in combination with buprenorphine to manage pain
- Potential for limiting the dose of opioids with adjunctive therapy: NMDA antagonists, anticonvulsant agents