Opiates: Use, Abuse, and Detection

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Palo Alto, California

Abused Prescription Drugs

<table>
<thead>
<tr>
<th>Opioids</th>
<th>CNS Depressants</th>
<th>Stimulants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine, codeine, etc.</td>
<td>Benzos</td>
<td>Cocaine</td>
</tr>
<tr>
<td>Oxycodone (OxyContin)</td>
<td>Benzodiazepines</td>
<td>Amphetamine</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Non-benzos</td>
<td>Methamphetamines</td>
</tr>
<tr>
<td>Methadone</td>
<td>Barbiturates</td>
<td>Methylphenidate</td>
</tr>
<tr>
<td>Fentanyl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meperidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propoxyphene</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OTC</td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>Ephedrine, etc.</td>
<td>Carisoprodol</td>
</tr>
<tr>
<td></td>
<td>Dextromethorphan</td>
<td>Ketamine</td>
</tr>
<tr>
<td></td>
<td>Antihistamines</td>
<td>Steroids</td>
</tr>
</tbody>
</table>

United States’ Drug Consumption

- 4.6% of world population
- Consumes 2/3 of illicit drug supply
- Consumes 80% of global opioid supply
- Consumes 99% of global hydrocodone supply

L. Manchikanti and A. Singh, 2008
**Prescription Opioids**

**Cocaine**

**Methamphetamine**

**Heroin**

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**Non-Medical Use of Drugs**

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**Oxycodone per Capita**

DEA 2013 Oxycodone Production Quota: 135,000 kg

2011 U.S. Population: 311,591,917

\[
\frac{135,000 \text{ kg}}{311,591,917 \text{ persons}} = 422 \text{ mg/person!}
\]

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**Retail Sales of Opioids (millions of grams)**

74 mg/person

329 mg/person +347%

Oxycodone +732%

Hydrocodone +244%

(#1 prescribed drug in U.S.)

Codeine -25%

Morphine +196%

Methadone +1177%

Mepertidine -28%

Hydromorphone +274%

Fentanyl +479%

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www.deadiversion.usdoj.gov
Increase in Abuse of Controlled Drugs

% increase
+ 542% – New teenager opioid abuse
+ 212% – 12 to 17 yr. olds abusing
+ 150% – Prescriptions
+ 81% – Adults abusing
+ 14% – U.S. Population

Past Year I illicit Drug Use

Thousands
Marijuana
Psychotherapeutic
Cocaine

Admitted Drug Abuse

Millions
Prescription
Cocaine
Hallucinogens
Inhalants
Heroin

CASA, "Under the Counter: …", 2005
Non-Medical Use of Prescription Drugs

Past Year Initiates in Illicit Drug Use

ED Visits

Drug Abuse Warning Network, 2005

NSDUH, 2007

L. Manchikanti, 2006
### Opiates: History

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>6000 BC</td>
<td>Sumerians “Plant of joy”</td>
</tr>
<tr>
<td>400 BC</td>
<td>Pain reliever (Hippocrates, Galen, Dioscorides)</td>
</tr>
<tr>
<td>1530</td>
<td>Paracelsus mixes opium with alcohol (“laudanum”)</td>
</tr>
<tr>
<td>1600s</td>
<td>1st modern anti-drug laws, China, against opium</td>
</tr>
<tr>
<td>1803</td>
<td>Morphine isolated (“Morpheus”)</td>
</tr>
<tr>
<td>1822</td>
<td>De Quincey <em>Confessions of an English Opium Eater</em></td>
</tr>
<tr>
<td>1832</td>
<td>Codeine isolated</td>
</tr>
<tr>
<td>1839, 56</td>
<td>Opium Wars (Hong Kong ceded to British)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
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</tr>
</thead>
<tbody>
<tr>
<td>1839</td>
<td>Opium Wars (Hong Kong ceded to British)</td>
</tr>
<tr>
<td>1853</td>
<td>Hypodermic syringe invented</td>
</tr>
<tr>
<td>1861-5</td>
<td>Civil War, 400,000 addicts (“soldier’s disease”)</td>
</tr>
<tr>
<td>1874</td>
<td>Diacetylmorphine synthesized</td>
</tr>
<tr>
<td>1875</td>
<td>S.F. ban on “opium houses” (1st US drug law)</td>
</tr>
</tbody>
</table>
| 1898 | Bayer markets Heroin (from “heroisch”), as non-addictive alternative to morphine
| same year as aspirin |
| 1906 | U.S. Pure Food and Drug Act, labelling requirements |
| 1909 | Opium Exclusion Act, no importation |
| 1923 | International Opium Commission, Shanghai |

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1914</td>
<td>Harrison Narcotic Act, heroin controlled (&lt;10 mg/g)</td>
</tr>
<tr>
<td>1923</td>
<td>Morphine structure</td>
</tr>
<tr>
<td>1924</td>
<td>Heroin Act, heroin illegal</td>
</tr>
<tr>
<td>1937</td>
<td>Methadone synthesized</td>
</tr>
<tr>
<td>1938</td>
<td>Meperidine (Demerol) introduced</td>
</tr>
<tr>
<td>1950s</td>
<td>Morphine total synthesis</td>
</tr>
<tr>
<td>1970s</td>
<td>Opiate receptors discovered</td>
</tr>
<tr>
<td></td>
<td>Enkephalins, endorphins, discovered</td>
</tr>
</tbody>
</table>
**Opiates: History**

1993: Morphine µ-receptor sequenced, cloned

1990s: Heroin trials: Switzerland, several other countries

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**Urine Morphine after Poppy Seed Consumption**

$n=9$

poppy seeds: morphine content: 152 µg/g

morphine intake: 1.6–6.8 mg

codeine levels: 60–820 ng/mL

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**Opiate Testing Cut-offs (ng/mL)**

<table>
<thead>
<tr>
<th></th>
<th>SAMHSA Previous</th>
<th>12/98</th>
<th>DoD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>300</td>
<td>2000</td>
<td>2000</td>
</tr>
<tr>
<td>Confirmation</td>
<td>Morphine</td>
<td>300</td>
<td>2000</td>
</tr>
<tr>
<td>Codeine</td>
<td>300</td>
<td>2000</td>
<td>2000</td>
</tr>
<tr>
<td>6-MAM</td>
<td>___</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>
Resolution of Opiate Positives: Poppy Seeds or Not?

- Examine claimed consumption (positives unlikely for >1 day)
- Eliminate seeds from diet, collect another specimen after 3 days
- Test for 6-monoacetylmorphine (presence proves heroin use)
- Measure total morphine levels (>5000 ng/mL unlikely for seeds)
- Measure morphine/codeine ratio (morphine > codeine for seeds)
- Look for evidence of opiate use (needle tracks, needles, behavior)

![Chemical structures of Heroin, Morphine, and 6-Monoacetylmorphine]

Heroin, 12 mg i.v.

![Graph showing the concentration of 6-AM (ng/mL) over time (Hr.) after Heroin administration]

M. Smith et al., 2001
**Total Morphine, 6-AM after Heroin Dosing**

Lower dosing (3–7 mg)
- Total morphine: 1,392–9,250 ng/mL (median 3,620)
- 6-AM: 6.1–298 ng/mL (median 106)
  - Detection time @ 10 ng/mL: 0–5.1 hr (median 2.3)

Higher dosing (10.5–13.9 mg)
- Total morphine: 2,065–29,030 ng/mL (median 16,470)
- 6-AM: 13–568 ng/mL (median 242)
  - Detection time @ 10 ng/mL: 2.3–11.2 hr (median 4.5)

*M. Smith et al., 2001*

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**6-AM After Heroin Dosing (3, 6 mg)**

- 6-AM (ng/mL)
  - n = 6
  - t = 2–8 hr

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**6-AM in Morphine Specimens >5000 ng/mL**

- 6-AM (ng/mL)
  - n = 73

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*Cone et al., 1991*  
*O’Neal and Poklis, 1998*
<table>
<thead>
<tr>
<th>Cross-Reactivity</th>
<th>Opiate assay</th>
<th>6-AM assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Acetylmorphine</td>
<td>435</td>
<td>300 ng/mL</td>
</tr>
<tr>
<td>Morphine</td>
<td>360</td>
<td>2,000 ng/mL</td>
</tr>
<tr>
<td>Morphine-3-glucuronide</td>
<td>626</td>
<td>10 ng/mL</td>
</tr>
<tr>
<td>Morphine-6-glucuronide</td>
<td>600,000</td>
<td>10,000,000</td>
</tr>
<tr>
<td>Codeine</td>
<td>102–306</td>
<td>600–1,980</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>291</td>
<td>500,000</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>498</td>
<td>5,349</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>247</td>
<td>100,000</td>
</tr>
<tr>
<td>Oxymorphine</td>
<td>9,300</td>
<td>&gt;100,000</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>1,500</td>
<td>23,000</td>
</tr>
</tbody>
</table>

**Oxycodone**

► Effects: analgesia, euphoria, sedation, miosis (pupil constriction)

► Adverse effects: nausea, constipation, respiratory depression, hypotension, tolerance, withdrawal

► High oral bioavailability: 60% (vs. 20–30% for morphine)

► $t_{1/2}$ = 5 hr (vs. 1.5–2 hr for morphine)

► Metabolism/Elimination: Oxycodone, oxymorphone, and noroxycodone conjugates

**OxyContin**

► 1996 Slow-release form of oxycodone (1915)

► Schedule II controlled substance

► 10–160 mg tablets (Purdue Pharma)

► Street price: $1/mg = 10x prescription cost

► Dosing: initial 10 mg/12 hr (vs. 10–30 mg/4 hr for oxycodone)

► Potency: 6x more potent than codeine

► equipotent to morphine and hydrocodone (Vicodin)

► 1/4 potency of hydromorphone (Dilaudid)

► 10x more potent than meperidine (Demerol)

► DAWN: 3–4K mentions for oxycodone (3–5x morphine)
**Oxycodone Metabolism and Elimination**

Oxycodone

\[
\text{H}_2\text{CO} \quad \text{Oxymorphone}
\]

13–14% conjugated
86–100% cross-reactivity

13–19% free
7–29% conjugated

Noroxycodone

**Urine Concentrations of Oxycodone**

<table>
<thead>
<tr>
<th>n</th>
<th>Dose</th>
<th>Oxycodone, ng/mL</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>5 mg oral</td>
<td>640 and 400 (0–24 hr)</td>
<td>Baselt and Stewart, 1978</td>
</tr>
<tr>
<td>9</td>
<td>10 mg im</td>
<td>-500–1,000 (0–24 hr)</td>
<td>Pophia et al., 1992</td>
</tr>
<tr>
<td>9</td>
<td>20 mg oral</td>
<td>2,500 and 750 (5–9 hr)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10 mg im</td>
<td>2,500–10,000 (3–9 hr)</td>
<td>Smith et al., 1995</td>
</tr>
<tr>
<td>2</td>
<td>20 mg im</td>
<td>600–800 (2–9 hr)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>700 mg/day</td>
<td>12,900</td>
<td>Weinstein and Gaylord, 1979</td>
</tr>
</tbody>
</table>

**Buprenorphine**

\[
\text{HO}_2\text{CO} \quad \text{Naloxone}
\]

**Morphine**

\[
\text{HO}_2\text{CO} \quad \text{Naloxone}
\]
**Buprenorphine** *(Subutex, Suboxone)*

- Partial µ-opioid receptor agonist (strong binding, weak effects)
- κ-opioid receptor antagonist
- Combined with naloxone (Suboxone) to minimize abuse
- 25–40x more potent analgesic than morphine
- Reduced physical dependence, reduced respiratory depression
- FDA approval 10/8/02 (Schedule III)

**Buprenorphine (Subutex, Suboxone)**

- Dosing: Addiction treatment 12–16 mg/d (sublingual)
  - Pain: <1 mg
- Therapeutic urine concentrations:
  - Addiction treatment: few to several hundred ng/mL
  - Pain: 4–60 ng/mL Bup, 6–26 ng/mL Nor
- Abusers: few to several hundred ng/mL or more
- Fatal overdoses: 4–1,000 ng/mL
  - 3,400 ng/mL Bup, 600 Nor

- Assay cutoff: 5 ng/mL
  - Sensitivity: 0.7 ng/mL
  - Good recovery @ 30 ng/mL

**Buprenorphine Metabolism and Elimination**

- Glucuronidation
- Hydroxylation (minor)
- Dealkylation
- Hydroxylation (minor)
- Norbuprenorphine active

- 10%, mostly conjugated
- 2/3 in feces
- 1/3 in urine
- 14%, mostly conjugated
Urine Buprenorphine in Suboxone Patients

70 patients, 8–24 mg/d
n=216 specimens
for n=176 unadulterated
avg. 164 ng/mL.

M. Hull et al., 2008

Abuse
Supra-therapeutic use, misuse
Therapeutic use

Pharmacokinetics

Pharmacodynamics

Dose → Blood → Receptors → Effects

Absorption
Distribution
Metabolism
Elimination → Urine, sweat, oral fluid, hair, ...

Concentration
Urine Drug Concentrations (ng/mL): 10,922 Chronic Pain Patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>10,163</td>
<td>3,910</td>
<td>196-93,372</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>15,674</td>
<td>1,854</td>
<td>108-329,591</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>7,599</td>
<td>2,690</td>
<td>100-341,009</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>4,930</td>
<td>1,637</td>
<td>100-188,306</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>2,955</td>
<td>1,580</td>
<td>100-405,020</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1,062</td>
<td>476</td>
<td>100-64,526</td>
</tr>
<tr>
<td>Methadone</td>
<td>4,167</td>
<td>2,179</td>
<td>104-93,322</td>
</tr>
<tr>
<td>Meperidine</td>
<td>3,086</td>
<td>1,138</td>
<td>195-52,216</td>
</tr>
<tr>
<td>Normeperidine</td>
<td>3,490</td>
<td>1,375</td>
<td>124-19,908</td>
</tr>
</tbody>
</table>

*E. Cone et al., 2008*

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**Assay response**

Positive sample

Cut-off

“Negative” sample

Estimated concentration

Estimated concentration

**“Negative”**

*does NOT mean*

*“No drug”*
µ-Opioid Receptor Genotype and Naltrexone Response

<table>
<thead>
<tr>
<th>% With good clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Asn40</td>
</tr>
</tbody>
</table>

R. Anton et al., 2008

Resources on Prescription Drug Abuse

- National Institute on Drug Abuse (NIDA), www.drugabuse.gov/drugpages/prescription.html
- National Survey on Drug Use and Health (NSDUH), www.oas.samhsa.gov/nduh.htm
- Monitoring the Future, www.monitorthefuture.org
- Drug Abuse Warning Network (DAWN), www.dawninfo.samhsa.gov/default.asp
- Treatment Episode Data Set (TEDS), www.oas.samhsa.gov/dasis.htm#teds2
- Community Epidemiology Working Group (CEWG), www.drugabuse.gov/about/organization/CEWG/CEWGHome.html
- Medline (PubMed), www.pubmed.gov