Opioid Abuse: A Dark Tunnel

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Disclosures

- Within the last 3 years, consulted for AstraZeneca, Camarus, Clinilabs, Guidepoint Global, Janssen, Mallinckrodt, Pfizer, Salix, Shire
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The Problem

• Opioid prescribing, abuse, and overdose have increased substantially in the past decade
The Problem

Kolodny et al. 2015 (figure from MMWR 60: 1487-92, 2011)
ADF: Abuse Deterrent Formulations
Addressing The Problem

Figure 1. Respondents Who Endorsed Past-Month Use of OxyContin or Heroin Before and After the Introduction of an Abuse-Deterrent Formulation (ADF)

Cicero and Ellis, 2015 JAMA Psychiatry 72(5): 424-429
Addressing The Problem

Figure 1. Respondents Who Endorsed Past-Month Use of OxyContin or Heroin Before and After the Introduction of an Abuse-Deterrent Formulation (ADF)

Cicero and Ellis, 2015 JAMA Psychiatry 72(5): 424-429
The Problem

![Graph showing trends in sales, deaths, and treatment admissions from 1999 to 2010.]

**Figure 1**

*Kolodny et al. 2015 (figure from MMWR 60: 1487-92, 2011)*
Outline of this Presentation

• Describe the methodology that we use to examine medications for treating opioid abuse

• Discuss what’s on the horizon
Methodology
Setting

- Controlled clinical pharmacology laboratory
  - Inpatient
  - Secure research unit
  - Clinical staff 24 hr/day
Research Participants

- Physically dependent on opioids (heroin)
- Paid for participating in the study
- Not seeking treatment for their drug use
Outcome Measures

- Multiple subjective responses used to reflect likelihood of abuse (e.g., “I feel high”)
- Drug self administration
- Physiological effects (respiration, etc.)
I like the drug

Not at All | Extremely

Next
I feel high

Not at All | Extremely

Next
Rate the degree to which you would be willing to take today’s drug again

- [ ] Very Much
- [x] Quite a Bit
- [ ] Moderately
- [ ] A Little
- [ ] Not at All
Drug self administration

- Behavioral measures of drug taking behavior (the reinforcing effects of drugs)
  - Progressive ratio schedule
Drug versus Money Choice

SAMPLE SESSION + CHOICE SESSION

Objective: Measure the amount of responding elicited by the drug and preference for drug over money.
Drug vs Money Choice Procedure
Drug vs Money Choice Procedure

Total clicks = 50
Drug vs Money Choice Procedure
Drug vs Money Choice Procedure

Total clicks = 100
Drug vs Money Choice Procedure
Drug vs Money Choice
Procedure

After 7 trials
(Total clicks on 7th trial = 1600)
Drug vs Money Choice Procedure
Drug vs Money Choice Procedure

Total clicks = 50
Drug vs Money Choice Procedure

7 units of drug (35 mg)  
Breakpoint = 1600

3 units money ($6)  
Breakpoint = 200
Drug vs Money Choice Procedure

Ahhhhh!
Potential Treatments

Buprenorphine

Methadone

Naltrexone
Buprenorphine

Mechanism of action:

- Partial mu opioid agonist
- Cross-tolerance and/or antagonism
15-20 mg = typical street dose

Comer, Walker, & Collins (2005)
Comer, Walker, & Collins (2005)

High

Buprenorphine/Naloxone Dose (mg, SL)

- 0
- 2/0.5
- 8/2
- 32/8

Rating (mm, range: 0-100)

Heroin Sample Dose (mg, IN)
Buprenorphine

- **Advantages**
  - Long duration of action (once or twice daily dosing)
  - Good medication compliance
  - Can be prescribed in private doctor’s office
  - Good physiological safety profile

- **Disadvantages**
  - Diversion (most diverters buy it to alleviate withdrawal)
  - Can be difficult to withdraw from buprenorphine
Methadone

Mechanism of action:

- **Full mu opioid agonist**
- **Cross-tolerance**
**Methadone**

**Methadone (mg/day)**

- 50
- 100
- 150

**Total Number of Injections**

**Heroin Choices**

Donny, Brasser, Bigelow, Stitzer & Walsh (2005)
Methadone

How High Are You?

Donny, Walsh, Bigelow, Eissenberg & Stitzer (2002)
Methadone

**Advantages**
- Long duration of action (once daily dosing)
- Good medication compliance

**Disadvantages**
- High doses are needed (80-120 mg)
- Sedation
- Difficult to withdraw from methadone
- Initially must go to clinic daily for supervised dosing
- Diversion
- Stigma
Naltrexone

Mechanism of action:

- Opioid antagonist
- Directly competes with agonists at opioid receptors and prevents them from binding and producing their effects
Naltrexone

- Naltrexone, an opioid antagonist, was FDA-approved in 1984 in oral form for treating opioid dependence.

- Although naltrexone is effective in antagonizing heroin, compliance with oral naltrexone is a major obstacle to treatment.

- Sustained-release naltrexone may circumvent the problems with medication compliance.
Depot Naltrexone Maintenance

Heroin Dose (mg, i.v.)

Progressive Ratio Break Point

Baseline

Week 1

384 mg Depot Naltrexone

Depot Naltrexone Maintenance


Heroin Dose (mg, i.v.)

Progressive Ratio Break Point

384 mg Depot Naltrexone
Depot Naltrexone Maintenance

Depot Naltrexone Maintenance


Heroin Dose (mg, i.v.)

Progressive Ratio Break Point

384 mg Depot Naltrexone
Depot Naltrexone Maintenance

Depot Naltrexone Maintenance

384 mg Depot Naltrexone

“Good Drug Effect”

Heroin Dose (mg)

Mean Peak Rating (mm)

Depot Naltrexone Dose

- 192 mg
- 384 mg

* P < 0.05, N=6 per group

Heroin Dose (mg)

Comer, Collins, Kleber, Nuwayser, Kerrigan, & Fischman (2006)
Naltrexone

**Advantages**
- Completely blocks the effects of opioid agonists
- Good side-effects profile
- No abuse liability

**Disadvantages**
- Need to detoxify patients from opioids prior to beginning treatment
- Medication compliance (oral)
Treatment Outcomes

**Krupitsky et al. (2011)**
Lancet 377: 1506-1513

**Soyka et al. (2008)**
Int J Neuropsychopharmacol 11: 641-653
## PRO’s and CON’s

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<th>Methadone</th>
<th>Buprenorphine</th>
<th>Oral Naltrexone</th>
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On the Horizon

- Sustained-release formulations of buprenorphine
- Opioid vaccines
- Non-opioid maintenance medications
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