Opioid Dependence

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Average Purity of Retail Heroin
Street Samples in U.S

Source: DEA, 2002
Trends In Emergency Department Mentions 1992-2002

Opioid Emergency Department Mentions 2004

Opioid Dependence
- Pharmacology
- Neurobiology
- Intoxication & Withdrawal
- Treatment
  - Behavioral
  - Naltrexone
  - Methadone
  - Buprenorphine
- Pregnancy and Neonatal issues
Types of Opioid Receptors

- Endomorphins
- Dynorphins
- β-endorphin
- Enkephalins

Opioid Receptors

Drugs and medications that activate mu receptors:
- morphine
- methadone
- hydromorphone
- codeine
- fentanyl
- heroin
- LAAM
- buprenorphine
- oxycodone
- hydrocodone
**Function at Receptors: Full Opioid Agonists**

- activates the mu receptor
- is highly reinforcing
- is the most abused opioid type
- includes heroin, codeine, & others

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**Full Opioid Agonist Activity Levels**

Increasing full agonist dose produces increasing mu opioid receptor specific activity. Until maximum opioid agonist effects are achieved and no further effects can be produced, even by giving more drug.

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**Function at Receptors: Opioid Antagonists**

- occupies without activating
- is not reinforcing
- blocks abused agonist opioid types
- includes naloxone and naltrexone
Antagonist Activity Levels

Opioid antagonists bind and occupy mu opioid receptors but result in no specific intrinsic activity regardless of dose (e.g., naloxone).

Function at Receptors: Partial Agonists

- activates the receptor at lower levels
- is relatively less reinforcing
- is a less abused opioid type
- includes buprenorphine

Partial Agonist Activity Levels

At higher doses, even when partial agonist drug completely binds all mu receptors, maximum opioid agonist effect is never achieved. Like full agonists, partial agonist drugs produce increasing mu opioid receptor specific activity at lower doses.
Anatomic sites of opioid action

Acting through mu receptors opioids modulate function in brain areas related to:

- nociception
- arousal
- reward/reinforcement
- memory
- emotional regulation
OPIOID GASTROINTESTINAL EFFECTS

**EFFECTS**
- Decreased Acid Secretion
- Decreased Motility

**WITHDRAWAL**
- Nausea
- Emesis
- GI Cramping
- Diarrhea

OPIOID CARDIOVASCULAR EFFECTS

**EFFECTS**
- Peripheral Vasodilation
- Reduced Peripheral Resistance
- Inhibition of Baroreceptor Reflexes

**WITHDRAWAL**
- Hypertension
- Tachycardia
**Opioid CNS Effects**

### Effects
- Analgesia
- Sedation
- Euphoria
- Body Temperature Changes
- Miosis
- Respiratory Depression

### Withdrawal
- Muscle Pain
- Cramping
- Insomnia
- Dysphoria
- Chills, Piloerection
- Mydriasis
- Yawning, Sneezing, Rhinorrhea

**Management of Opioid Intoxication**

- Ventilatory support if needed
- Parenteral Naloxone
  - If IV access, bolus 0.1mg/min titrated to RR>10/min
  - Improved level of consciousness
  - No withdrawal
  - If needed ongoing IV infusion 2/3 of initial bolus dose/hr.
  - If no IV access, 0.4-0.8mg sub q or IM and observe

**Clonidine for Opioid Withdrawal**

- α2 adrenergic agonist binds to pre-synaptic autoreceptors on adrenergic neurons
  - In Locus Coeruleus
  - Possibly in A1 and A2 cell groups of the caudal medulla that project to BNST (extended amygdala)
- FDA approved for hypertension
  - Limiting side effect: hypotension
- Reduces W/D signs and sx:
  - Significantly better than placebo
  - Nearly comparable to slow methadone taper
- Most commonly used approach over past 20 years
Clonidine for Methadone W/D

Gold et al., 1978

Subjective Rating

Nervousness Irritability

Baseline Clonidine (5 mcg/kg)

Clonidine for Opioid Withdrawal

- Doses: 0.1 mg tid to 0.4 mg tid
- Push dose until withdrawal sx abate or diastolic BP <60
- Use adjunctive benzodiazepines, anti-emetics, anti-diarrheals

Rapid Opioid Withdrawal

- Administer opioid antagonists to provoke W/D
- Manage emergent sx with:
  - Clonidine
  - Benzodiazepines
  - Antiemetics
  - Antidiarrheals
- W/D essentially resolved in 2-3 days with patient on full dose of antagonist (naloxone)
Ultra Rapid Opioid Withdrawal

- Patient placed under general anesthesia or very heavy sedation
  - General Anesthesia requires intubation
- Administer opioid antagonists to provoke W/D
- Manage emergent sx with:
  - Clonidine
  - Benzodiazepines
  - Antiemetics
  - Antidiarrheals
- W/D essentially resolved in 12-24 hours with patient ± on full dose of antagonist (naltrexone)

RCT of Ultra Rapid Withdrawal

(Croen et al., 2003)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthesia Assisted W/D</td>
<td>3/27 mostly abstinent during 12 week F/U</td>
</tr>
<tr>
<td>Naltrexone day 1 (27/28)</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine Assisted W/D</td>
<td>5/32 mostly abstinent during 12 week F/U</td>
</tr>
<tr>
<td>Naltrexone day 2 (31/32)</td>
<td></td>
</tr>
<tr>
<td>Clonidine Assisted W/D</td>
<td>2/28 mostly abstinent during 12 week F/U</td>
</tr>
<tr>
<td>Naltrexone day 7 (8/28)</td>
<td></td>
</tr>
</tbody>
</table>

*2 SAEs in Anesthesia group

TREATMENT FOR OPIOID DEPENDENCE

- Therapeutic Communities (Condelli & Hubbard, 1994)
  - 40% of heroin users reported daily or weekly use in year after discharge.
  - Each month in tx led to 6% reduction in odds of using heroin in follow-up year.

- Medical
  - Medically Supervised Withdrawal (Detox)
  - Naltrexone
  - Methadone Maintenance
  - Buprenorphine
Naltrexone for Opioid Dependence

- Most ideal pharmacologic treatment
- Requires detoxification before initiation or severe withdrawal will be precipitated
- Requires Naloxone challenge test
- Risk of OD if medication stopped
- In general poor patient compliance but superb treatment for selected patients

Depot Naltrexone to Block Heroin Effect

Opioid Agonist Treatment CSAT Regulations

- 1 Year History of Opioid Addiction
- Physical Exam on Entry
- Observed Ingestion of Methadone or buprenorphine
- Counseling as Clinically Necessary
- Urine Toxicology Screening
Methadone Pharmacology

- Rapidly absorbed orally
- Peak Levels in 4 hours
- Half-life=24 hours
- Metabolized in liver
- Doses should be individualized but higher doses generally more effective

Kyle et al., 1999

Swedish Methadone Study

Experimental Group (Methadone)  |  Control Group (No Methadone)

Gunne & Gronbladh, 1981
Swedish Methadone Study

After 2 Years

Experimental Group (Methadone)

Control Group (No Methadone)

Gunne & Gronbladh, 1981

- Sepsis
- Sepsis and Endocarditis
- Leg Amputation
- In Prison

Strain et al., 1999
Moderate vs. High Dose Methadone

Strain et al., 1999
Moderate vs. High Dose Methadone
### Methadone Side Effects

- Minimal sedation once tolerance achieved
- Constipation
- Increased Appetite/Weight Gain
- Lowered Libido; May decrease gonadal hormone levels
- Exhaustively studied in all other organ systems with no evidence of chronic harm

### Overview of Buprenorphine

- Buprenorphine, a thebaine derivative (classified in the law as a narcotic)
- High potency \( \mu \)-opioid partial agonist
- Produces sufficient agonist effects to be detected by the patient
- Available as a parenteral analgesic (typically 0.3-0.6 mg im or iv every 6 or more hours)
- Long duration of action when used for the treatment of opioid dependence contrasts with its relatively short analgesic effects

### Buprenorphine Affinity and Dissociation

- Buprenorphine has:
  - high affinity for \( \mu \) opioid receptor – competes with other opioids and blocks their effects
  - slow dissociation from \( \mu \) opioid receptor – prolonged therapeutic effect for opioid dependence treatment (contrasts to its relatively short analgesic effects)
Properties of a Partial $\mu$-Opioid Agonist

- Ceiling effect on respiratory depression
- Less physical dependence capacity
- Ameliorates sx of mild to moderate withdrawal
- Can precipitate withdrawal in physiologically dependent individuals not already in early withdrawal

Intrinsic Activity: Full Agonist (Methadone), Partial Agonist (Buprenorphine), Antagonist (Naloxone)

Buprenorphine Pharmacology

- Extensive 1st pass metabolism; given Sub-Lingually
- Slow onset, long duration (24 - 48 hours)
- Slow offset
- Half life > 24 hours
- Once a day or every other day dosing
  - Range=2 – 32 mg/d
Greenwald et al., 2003

Zubieta et al., 2000

Buprenorphine vs. Placebo for Heroin Dependence

Kakko, Lancet 2003

Treatment duration (days)

Remaining in treatment (nr)

0 5 10 15 20

Detoxification

Maintenance

4 Subjects in Control Group Died

Buprenorphine vs. Placebo for Heroin Dependence

Kakko, Lancet 2003
Combination of Buprenorphine plus Naloxone

- Sublingual buprenorphine has good bioavailability
- Addition of naloxone to buprenorphine to decrease abuse potential of tablets
- Combination ratio is 4 to 1 (buprenorphine to naloxone)
- Buprenorphine tablet with naloxone marketed as Suboxone
- Buprenorphine tablet without naloxone marketed as Subutex

Combination of Buprenorphine plus Naloxone

- Combination tablet containing buprenorphine with naloxone – if taken under tongue, predominant buprenorphine effect

- If opioid dependent person dissolves and injects buprenorphine/naloxone tablet – predominant naloxone effect (and precipitated withdrawal)
Opioid Dependence and Pregnancy

- Opioid dependent women and their neonates have poor outcomes without treatment
- Methadone treatment of opioid dependent pregnant women
  - has a 30 year track record of success
  - has become the standard of care
  - Requires adequate methadone doses
  - Usually higher and/or split doses needed in 3rd trimester
  - Neonatal abstinence syndrome common

Neonatal Abstinence Syndrome

- Onset typically within 72 hrs. May occur later
  - Hyperirritability
  - GI dysfunction
  - Respiratory distress
  - Yawning
  - Sneezing
  - Fever
  - Uncoordinated suck reflex
- Generally treated with oral morphine or methadone

Buprenorphine vs. Methadone in Pregnancy

- N=18 opioid dependent women randomly assigned during weeks 24-29 of pregnancy to receive either
  - Buprenorphine (mean titration dose=13.5 mg/d)
  - Methadone (mean titration dose=47.5 mg/d)
- Double-blind, Double dummy
- n=14 completers
  - Statistically less opioid use among methadone group
  - No differences in birth outcomes
  - No statistical differences in NAS
  
Fischer et al., 2006
Buprenorphine vs. Methadone: Effects on NAS

Mean Bup dose=18.7mg/d
Mean Methadone dose=79.1mg/d

Opioid Dependence

Conclusions

- Much of the pathophysiology of opioid dependence can be understood based upon function of μ-opioid receptor
- Intoxication and Withdrawal can be managed, but these interventions do not constitute treatment
- Effective long term interventions require opioid agonist or intensive residential treatment