Opioid Use Disorder and Its Management

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Objectives

• Outline trends in US drug overdose deaths, and understand the role prescription and non-prescription opioids play in overdose death risk
• Appreciate that detoxification alone is not an optimal treatment strategy
• Become familiar with current FDA approved treatments for opioid use disorders
• Identify at least three strategies that individual users, practitioners, family members and communities can implement to lower overdose risks
NATIONAL OVERDOSE TRENDS

National Overdose Deaths
Number of Deaths from Opioid Drugs

Source: National Center for Health Statistics, CDC Wonder
National Overdose Deaths
Number of Deaths from Prescription Opioid Pain Relievers (excluding non-methadone synthetics)

Source: National Center for Health Statistics, CDC Wonder

National Overdose Deaths
Number of Deaths from Heroin

Source: National Center for Health Statistics, CDC Wonder
ADVERSE OUTCOMES ASSOCIATED WITH OPIOID DEPENDENCE

Natural Course:

• Medical risks:
  — HCV
    • 70% IV users
    • 65% after 1 yr needle use; ~85% at 5 yrs
  — HIV
    • IV users ~25% of new HIV infections
    • HIV ~20%
Natural Course:

- **Death**
  - Overdose 1.5%/yr
  - 24 yr study – 28% sample deceased
  - 30 yr. study in California: 49% sample deceased
  - Annual risk of dying for a heroin addicted person is increased up to 20x compared to someone who does not use
  - Not in tx; 63x expected mortality rate

- **Major causes of death**
  - Drug overdose, suicide, violence, accidents, infection, chronic diseases

Natural Course:

- **Low employment:**
  - 36.4% active users employed
  - Heroin dosed Q 6 hours
  - Need time to recover
  - But need money to buy the drug

- **Crime:**
  - Most commit crimes
  - F/u 10 years ~18% incarcerated
  - One study n=573 12 month period:
    - >80,000 crimes reported

- **Costs:**
  - Medical costs: $1.2 billion per yr
  - Total cost estimate: $20 billion per yr
Natural Course: Summary

- Medical risks
- High mortality
- Low employment
- Crime
- High cost to society

DETOX ALONE DOES NOT WORK!
“Detoxification from heroin is good for many things – but staying off heroin is not one of them”

Walter Ling

Buprenorphine Maintenance vs Detox. RCT of cumulative retention in treatment

Similarities with Other Chronic Diseases
(Type II Diabetes, HTN, Asthma)

- Genetic impact is similar
- The contributions of environment and personal choice are comparable
- Medication adherence and relapse rates are similar.
- Long term maintenance treatments proven most effective. (McLellan, JAMA 2000)

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**Successful Outcomes at 3 Time Points**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Time Point</th>
<th>Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>4-week taper + 8 weeks follow-up</td>
<td>7%</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Week 12 (end of stabilization)</td>
<td>49%</td>
</tr>
<tr>
<td></td>
<td>Week 24 (8 weeks post-taper)</td>
<td>9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time Points</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Phase 2 week 12 vs phase 2 week 24</td>
<td>&lt;.001</td>
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</tbody>
</table>

Redefining Success

Appropriate comparisons

– Treat SUDs as _chronic_ diseases
– Comparable to other chronic diseases

• Reasonable expectations
  – Complete abstinence is not the only successful outcome

METHADONE- AGONIST THERAPY
Methadone

- Schedule II medication
- Highly regulated
- Narcotic program treatment settings
- Full Mu agonist
- Who is appropriate:
  - At least 1 year of documented opioid dependence
  - Parental consent needed if 16-17 years of age; also need to show at least 3 failed prior detoxification attempts
  - Infectious disease
  - Pregnant women

Methadone outcomes

- ↓ Heroin use by 50%
- ↓ HIV 4 fold
- ↑ Employment 24%
- ↓ 60% criminal activity
- Less incarceration
- More child support payments
- 3x as likely to remain in treatment
- Improved Hepatitis C treatment adherence
- Mortality reduced
- Cost effective
- Drug users out of methadone treatment 6x more likely to become HIV positive than those in methadone treatment [Metzger et al., 1993]
More benefits of maintenance treatment

- Decreased IV drug use
- Decreased needle sharing
- Decreased cocaine use
- Decreased unprotected sex
- Decrease in multiple sex partners
- Decrease in commercial sex work

What is an optimal dose?

- One person’s optimal dose is not another person’s optimal dose
- Usually 80-120, but much variability
- Remember, patients on higher doses exhibit superior outcomes in terms of abstinence, treatment retention, and psychosocial rehabilitation [Payte et al., 2003]
- High dose maintenance=REDUCED risk of fatal heroin overdose during treatment [Caplehorn, 1996]
- Dole: “As with antibiotics, the prudent policy is to give enough medication to ensure success.” [1988]
Methadone side effects

- Minimal sedation at right dose
- Constipation
- Increased appetite-weight gain
- Lowered libido
- May decrease gonadal hormone levels
- Extensively studied in other organ systems with no evidence of harm in long term use
- QTc prolongation

Methadone drug interactions

- Decreased methadone concentrations- opioid withdrawals
  - Pentazocine
  - Phenytoin
  - Rifampin
  - Nevirapine
  - Risperidone
  - Carbamazapine
  - Efavirenz
  - Lopinavir

- Increased methadone concentrations- sedation, respiratory depression, QTc prolongation
  - Ciprofloxacin
  - Fluoxetine
  - [Drugs that inhibit CYP3A4, CYP2D6, CYP2B6]
Methadone: treatment barriers

• Out of medical mainstream
• Stigma of specialized clinics
• Location of clinics
• Daily dosing
• Federal regulations

BUPRENORPHINE- PARTIAL AGONIST TREATMENT
Buprenorphine

- 2002: FDA approves long acting sublingual buprenorphine as schedule III opioid
- Drs required to have 8 hour special training and an X number
- Upto 30 patients 1st year, then may apply to treat upto 100 patients
- CARA: limit increased to 275; PA/NPs can also obtain waiver
Buprenorphine

- High affinity partial mu agonist and kappa antagonist
- Available as sublingual strips and tablets; implant also available
- Combination product: naloxone added to reduce IV use
- Reduced opioid agonist effects, ceiling at 24-32 mg; less respiratory suppression
- Half life 37 hrs
- Dosing 8-32mg/d
- Can precipitate withdrawal
- Absorption (poor oral)
- Metabolized by CYP 3A4 system

Maintenance

- ONCE daily dose in most cases when using for addictions
- Doses greater than 16 mg rarely indicated
- 16 mg bup decreased mu opioid availability by 85-92%, and 32 mg decreased it by 94-98% [Greenwald et al., Neuropsychopharm 28: 2000-2009; 2003]
**Cochrane Review**

- Meta analysis of 8 studies through 2006
- N = 1068
- Methadone more likely than bup to retain patients [RR 0.85; 95% CI 0.73-0.98]
- No significant differences in opioid use by UA
- [Mattick et al., 2008]

**Benefits of Office-Based Treatment**

- Private, confidential, and safe treatment provided in a doctor’s office
- Allows for continuity of care with primary physician
- Does not require daily visits to a clinic or out-of-town, costly residential treatment
- May allow more patient time for work, family and other activities
- Improved access
In case of positive drug screens

- Do not D/c treatment in case of 1, or even several positive urine drug screens
- Increase intensity/frequency of counseling
- Reduction in take home doses
- **Raising** the dose if ongoing opioid use
- Consider switching to higher structure- OTP, methadone

Strategies to minimize diversion

- Is the person appropriate for office based treatment?
- Open discussion of diversion concerns
- Treatment agreement
- UDS randomly
- PMP monitoring
- Counseling weekly
- Initial weekly scripts-increase to monthly as patient does well
- Use a therapeutic dose
- Random pill counts
- Enlist aid of pharmacists!!
- Consider lock boxes
- Contingency management principles
Training Resources

• PCSS B: http://www.pcssb.org/ training and mentoring program focused on increasing access to treatment for opioid dependent patients.
• PCSS O: http://www.pcss-o.org/ mentoring, webinars
• PCSS-B has patient/family information, screening forms, tx agreements, 42 CFR compliant consent forms, COWS

NALTREXONE
Naltrexone: Potential Benefits

1. Orally Effective
2. Rapid onset of action
3. Long duration of action
4. Safe
5. Few side effects
6. Completely blocks effects of heroin
7. Non-addicting
8. No tolerance
9. No dependence
10. No withdrawal

FDA Approval

- 1984: FDA approves Naltrexone as a treatment for heroin addiction

- Marketing issues become problematic
  - Difficult to convince patients to use medication
  - Resistance on part of methadone clinics - cost
  - fails to impact treatment community in a significant way
Oral Naltrexone Retention Rates

Kranzler et al., Addiction 2008

XR-NTX Opioid Treatment, Comer 2006: better retention, less relapse to sustained opioid use

Retention in treatment
XR-NTX Opioid Treatment, Comer 2006: Less opioid and other drug use

Urine Toxicology Results

XR-NTX Opioid Treatment Pivotal Trial: Krupitsky 2010
(APA 2010, FDA 2010)

- 24 week double-blind, placebo-controlled, randomized trial following inpatient detox, N=250
- Russia, no agonist TAU alternative
- Clear superiority vs. placebo at preventing lapses and sustained relapse/dependence
- No ODs or deaths
- FDA approval of XR-NTX for opioid dependence 10/10
XR-NTX: The Russian study
Key Efficacy Outcomes

3A. % Opioid-Free Urines by Week
   (Kaplan-Meier)

3B. Mean Change From Baseline in Craving

3C. Time-to-Discontinuation

Key findings

• The median proportion of weeks of confirmed abstinence was 90.0% (95% CI 69.9–92.4) in the XR-NTX group compared with 35.0% (11.4–63.8) in the placebo group (p=0.0002).

• Patients in the XR-NTX group self reported a median of 99.2% (range 89.1–99.4) opioid-free days compared with 60.4% (46.2–94.0) for the placebo group (p=0.0004).

• Median retention was over 168 days in the XR-NTX group compared with 96 days (95% CI 63–165) in the placebo group (p=0.0042).
Hepatic Concerns

- a black box warning for hepatotoxicity (causes liver damage).
- does not appear to be a hepatotoxin at the recommended doses.
- In the XR-NTX Phase III clinical trial, mean AST and ALT levels did not change significantly over the course of treatment or with medication.
- AST elevation [reversible] in 1.5% vs 0.9% placebo

Emergency pain management

- Patients should be advised to carry a patient alert card that informs medical personnel they are taking XR-NTX.
- A suggested plan for pain management is:
  - Regional analgesia, Use of non-opioid analgesics
- In an emergency situation requiring opioid analgesia, the amount of opioid required may be greater than usual and the resulting respiratory depression may be deeper and more prolonged
  - Such patients should be continuously monitored in an anesthesia care setting by persons not involved in the conduct of the surgical or diagnostic procedure
  - The opioid therapy must be provided by individuals specifically trained in the use of anesthetic drugs and the management of the respiratory effects of potent opioids, specifically the establishment and maintenance of a patent airway and assisted ventilation
Emergency pain management

• A rapidly acting opioid analgesic that minimizes the duration of respiratory depression is preferred

• Patients should be closely monitored by trained personnel in a setting equipped for cardiopulmonary resuscitation.

ADDITIONAL TREATMENT COMPONENTS
Naloxone

• Studies show a reduction in overdose mortality
• Consider co‐prescription with any opioids
• First responders
• Can they lead to a person seeking treatment?

Psychosocial Interventions

• Combining psychosocial treatment with medication alone results in:
  – Better treatment retention
  – Less opiate + urines
  – Higher likelihood of abstinence at follow-up
  – Better clinic attendance
  – *Little data to support the use of psychosocial interventions alone in opioid dependence*
Psychosocial interventions

- Twelve step
- Individual and group therapy
- Family therapies
- Network therapy with naltrexone
- CBT
- Motivational interviewing
- Contingency management VERY useful [eg: take home doses]
- Random urine toxicology screening

Prevention: syringe exchange programs

- HIV testing/counseling, public funding, and expansion of needle exchange programs in NY city led to significant reductions in risk behaviors and HIV incidence among IVDU who participated [Des Jarlais et al., 2000]
- Syringe programs also provide other services- links to tx, counseling and health services
- Education about high risk behaviors is an essential component of these programs [NIDA, 2002]
- NOT associated with increase in initiation, duration, or frequency of IVDU
Possible role of integrated clinics

• Daily contact with patients in a methadone clinic
• On-site medical care at methadone clinics is associated with better rates of treatment seeking in:
  – Primary care [92% vs 35%]
  – Tuberculosis directly observed treatment completion
  – HIV treatment
  – 81% of IVDU patients voluntarily used on-site primary care services, with care being used more by HIV positive patients

SOME STRATEGIES TO ADDRESS THIS
Figure 1. Opportunities to reduce overdose risk through primary prevention. There are multiple access points for primary prevention initiatives on an individual, friends and family, community, prescriber, and government level. Abbreviations: Prescription Monitoring Program (PMP), Prescription (Rx), Center for Disease Control (CDC), National Institute of Health (NIH), Substance Abuse and Mental Health Services Administration (SAMHSA).

Figure 2. Opportunities to reduce overdose risk by increasing treatment engagement. There are multiple access points for initiatives on an individual, friends and family, community, prescriber, and government level. Medication-assisted treatment augments counseling and behavioral therapies with medications, such as methadone or buprenorphine. Abbreviations: Prescription (Rx), Treatment (Tx), National Institute of Health (NIH), National Institute of Drug Abuse (NIDA), Medication-Assisted Treatment (MAT).
New Mexico - A Case Study

- Historically one of the highest rates of drug overdose death rates in the nation.
- 2015 rates: 17.9/100K for opioids [9th in nation] and 25.3/100K for all drugs [8th in nation]
- 11% reduction in opioid death rates [4th in nation]
- 7% decrease in overall death rate [2nd in nation]
New Mexico- A Case Study

• Mandatory CME requirements on chronic pain management
• Mandatory PDMP monitoring requirements
• Naloxone distribution
• Good Samaritan Laws
• Educational campaigns for public and providers
• Improving access to MAT
• Engaging providers

Conclusions:

• Opioid dependence is destructive
• Treatment helps!
• Addiction is a chronic illness, and requires chronic treatment
• Treat the whole person!