Best Practice Treatment for Opioid Use Disorders

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Opioid Use Disorder Treatment

• History of Opioid Use
• Why do we have this epidemic?
• What are opioid use disorders?
• Evidence based treatments: Adults and Adolescents
What is the best that we can do to promote recovery?

Since 1990, the number of Americans who have died every year from drug overdoses...
Opium History

- First cultivation of opium poppies was in Mesopotamia, approximately 3400 B.C., plant called Hul Gil, the "joy plant”

- The Greek gods Hypnos (Sleep), Nyx (Night), and Thanatos (Death) were depicted wreathed in poppies

- The Persian physician, al-Razi (845-930 A.D.) made use of opium in anesthesia and recommended its use for the treatment of melancholy.

Opium History

- Between 400 and 1200 AD, Arab traders introduced opium to China.
- 14th century Ottoman Empire-opium used to treat headache and back pain.
- 15th century China- first officially recorded use of opium as a recreational drug.
- 1874- heroin developed
- 1898- heroin marketed by Bayer as safe pediatric cough suppressant
Opiates & Opioids

*Opiates* = naturally present in opium
- e.g. morphine, codeine, thebaine

*Opioids* = manufactured
- Semisynthetics are derived from an opiate
  - heroin from morphine
  - buprenorphine from thebaine
- Synthetics are completely man-made to work like opiates
  - methadone

Opioid Use Disorders: DSM-5
“Opioid Addiction”

- Take more than intended
- Desire/unsuccessful efforts to cut back or quit
- Time spent using, obtaining or recovering
- Craving
- Failure to fulfill work, school, home obligations
- Continued use despite problems (social, psychological, physical)
- Activities given up
- Use in hazardous situations
- Tolerance
- Withdrawal
THE PROBLEM:
Emergency room mentions of opioid use

- Analgesia
- Euphoria
- Miosis (‘pinned’ pupils)
- Constipation
- Sedation
- Itching, red eyes (histamine release)
- Respiratory depression and reduced cough reflex
- Decreased level of consciousness (‘on the nod’)
- Hypotension/bradycardia

DAWN, 2002
Why Heroin? Why so many deaths?

- More access to opioids
- Shutting down "pill mills"/Loss of Oxycontin
- Increased regulation of prescribing (Inspect)
- Increasing supply of synthetic heroin
- Decreasing cost of heroin
- Increasing purity of heroin
- Black Tar Fentanyl/carfentanil

Why do people die from opioids?

- Overdose = RESPIRATORY DEPRESSION
- Other complications = HEART INFECTIONS, HEART FAILURE, HIV
What increases risk for death in opioid users?

• Tainted supply: Fentanyl and Carfentanil
• Co-administration with benzodiazepines and alcohol
• Intermittent use decreasing tolerance

Lethal Dose
What the heroin user feels...

Diagrammatic summary of functional state of typical "insulin" heroin user. Arrows show the repetitive injection of heroin in uncertain dose, usually 10 to 30 mg but sometimes much more. Note that addict is hardly ever in a state of normal function ("straight").

From "Narcotic Blockade" by V. P. Dole, M. E. Niewandt and M. J. Koek, 1968, Archives of Internal Medicine, 121, pp. 343

Dole, Arch Int Med, 1966

Behavioral Interventions
Psychotherapies for Adults

- CBT
- Contingency Management
- Motivational Enhancement Therapy
- 12 step models
- Can be co-located (ideal) in methadone/bup program or separate (more common)

(SAMHSA)

Cognitive Behavior Therapy (CBT)

- Individual
- Group Based
- Recognize and stop negative patterns of behavior
- Become aware of how stressors, feelings, situations lead to substance use
- Learn to avoid situations
- Reframe thoughts
- Cope with cravings
- Inpatient or outpatient
- Requires some degree of cognitive abilities
Contingency Management

- Provides incentives to reinforce positive behaviors (e.g., abstinence, compliance with treatment)
- Very effective intervention
- Not therapy in a traditional sense
- Rewards can be provided by the clinic or family or patient
- Can be stand alone or in combination with CBT/12 step

Motivational Interviewing Techniques

- Be supportive of their need for autonomy
- Collaborative: confidential sessions
- Avoid righting reflex: correction/advice giving/data
- Express empathy
- Develop discrepancy: “change talk”
- Roll with resistance
- Support self-efficacy: goal setting, positive focus
12-step

- Most widely used treatment model
- Provides long term support
- My personal bias: I prefer it in addition to other treatment (particularly in the recovery support phase)

Recovery Supports

- Augment treatment both during, but particularly after a treatment episode
- Transportation
- Employment support
- Specialized living
- Peer-to-peer supports (12 step or other)
- Support groups
- Drop in centers
- Respite
- Wellness coaching
Peer Supports

- Peers = individuals in recovery who can use their own experiences to help others work toward recovery
- “lived experience”
- Majority are 12 step
- Other curricula exist (NAMI)
- Can be a paid job!

What about adolescents?
Existing Models

- Separate treatment programs for psychiatric disorders and addictions
- Group Treatments: 12 step, CBT
- Inpatient
- Residential “Rehab”
- ENCOMPASS: outpatient co-occurring model
- Family Therapy: Multidimensional Family Therapy, Functional Family Therapy, SOFT, Adolescent Community Reinforcement Approach (A-CRA)
- Non evidence based practices

Goals of family/parenting interventions

- Parent training
- Improve Family Functioning
- Reduce/Eliminate Substance Use
- Increase Problem Solving Skills
- Develop (Nurture Existing) Future Orientation
- Address Ecology of the Problem
Adolescent Treatment

- **Medication Management**
  - Comorbidities
    - Depression and Anxiety have clear pharmacologic targets
    - ADHD: Stimulants (controversial), Bupropion
  - SUDs
    - Small literature for use in adolescents but wealth of adult research in treatment for SUDs
Medication Assisted Treatments for Opioid Use Disorders

Medication Assisted Treatment (MAT) actually means medication + other psychosocial treatments together
Phases of Substance Use that are Targets for Pharmacotherapy

- intoxication/overdose: Narcan (naloxone)
- withdrawal/detoxification (clonidine, bup, methadone)
- abstinence initiation/use reduction (methadone, bup)
- relapse prevention (methadone, bup, naltrexone)
- sequelae (psychosis, agitation, etc.): antipsychotics? Antidepressants?
OUD Maintenance Treatment Options

Pharmacology Terminology

- agonist (replacement/substitution)
- antagonist (blockade)
- aversive (negative reinforcement)
- correction of underlying/associated disorders (such as depression, etc.)
Rationale for Opioid Replacement/Agonist Therapy

- Traditional treatment has been to provide opioid agonist therapy
  - Methadone (Dolophine®)
  - Levo-Alpha Acetyl Methadol (LAAM) – not available
  - Buprenorphine
- Stabilize neuronal circuitry
  - Mu occupation/blockade
  - Cross-tolerant, long-acting, oral
- Prevent withdrawal and craving
- Extinguish compulsive behavior
- Prevent spread of HIV and HCV
- Prevent criminal activity

<table>
<thead>
<tr>
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<tr>
<td>Duration</td>
<td>24-36 hours</td>
<td>3-6 hours</td>
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<tr>
<td>Euphoria</td>
<td>Absent</td>
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Stabilization by Agonist Treatment

Methadone
History of Methadone

- Synthesized in Germany: Less addictive than morphine 1930s
- Used in US for pain 1947
- Research demonstrated efficacy for heroin addiction 1964
- Federal regulations developed for methadone maintenance treatment 1971
- Federal regulations updated to allow more effective and consistent use 2001

http://www.cesar.umd.edu/cesar/drugs/methadone.asp

Methadone Maintenance

- Maintenance=help avoid negative consequences of illicit opiate misuse
- Dosed once daily
- <80-100 mg daily
- When properly managed, reduce narcotics related deaths, users' involvement in crime, the spread of AIDS, and helps users gain control of their lives
- If used correctly, few side effects, no high
Methadone: Does it work?

• 11 clinical trials
• More effective than non-methadone treatments at keeping people in treatment, staying off of opiates
(Cochrane Review, 2009)

Methadone Effectiveness
Gunne & Gronbladh, 1984

Baseline

Methadone

Regular Outpatient
Methadone Effectiveness
Gunne & Gronbladh, 1984

After 2 Years

Methadone

No Methadone

1- Sepsis & endocarditis
2- Leg amputation
3- Sepsis
Purple=expelled from tx
P=prison
H=heroin

After 5 Years

Methadone

No Methadone
Myth: There Isn’t Any Proof That MAT Is Better Than Abstinence

FACT: MAT is evidence-based (many, many clinical trials in 1970s-2000s) and is the recommended course of treatment for OUDs. The National Institute on Drug Abuse, Substance Abuse and Mental Health Services Administration, National Institute on Alcohol Abuse and Alcoholism, Centers for Disease Control and Prevention, and other agencies emphasize MAT as first line treatment.
Myth: MAT Is Only For The Short Term

• **FACT:** Research shows that patients on MAT for at least 1-2 years have the greatest rates of long-term success. There is currently no evidence to support benefits from cessation.

• **FACT:** Patients with long-term abstinence can follow a slow taper schedule under a physician’s direction, when free of stressors, to attempt dose reduction or total cessation.

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**Signs of Recovery Over Time**

1-12 Months
- More abstinent friends
- Less illegal activity and incarceration
- Less homelessness, violence, and victimization
- Less use by others at home, work, and by social peers

1-3 Years
- Virtual elimination of illegal activity and illegal income
- Better housing and living situations
- Increasing employment and income

4.7 Years
- More social and spiritual support
- Better mental health
- Housing and living situations continue to improve
- Dramatic rise in employment and income
- Dramatic drop in people living below the poverty line

Source: Dennis, Flann & Scott, 2007
Myth: Many Patients’ OUDs Are Not Severe Enough to Require MAT

**FACT:** MAT utilizes a multitude of different medication options (agonists, partial agonists and antagonists) that can be tailored to fit the unique needs of the patient.

Myth: It is best to take the lowest possible dose of methadone.

• Fact: The appropriate dose of methadone should be determined by cessation of cravings for each individual.
• Fact: Too low of a dose has been shown to result in cravings and relapse.
Why is methadone so tightly regulated?

- Complex pharmacokinetics: blood levels build quickly (non-linear) as dose increases, thus there is risk of overdose
- Very dangerous when combined with benzodiazepines, especially early in treatment
- Can interact with many commonly used medications
  - Decreased methadone concentrations:
    - Pentazocine
    - Phenytoin
    - Carbamazepine
    - Rifampin
    - Efavirenz
    - Nevirapine
    - Lopinavir (Kaletra)
      - Opiate withdrawal syndrome
  - Increased methadone concentrations:
    - Ciprofloxacin
    - Fluoxetine
    - Discontinuation of inducing drug
      - Cognitive impairment
      - Respiratory depression
      - QTc prolongation; Torsade de Pointes

McCance-Katz et al. 2009

Federal and State Rules for OTPs
Why use it?

**Methadone**

Benefits:
- Lifestyle stabilization
- Improved health and nutritional status
- Decrease in criminal behavior
- Employment
- Decrease in injection drug use/shared needles

CSAT, 2005

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**Methadone Treatment Decreases HIV Seroincidence**

Metzger et al. JAIDS 1993;6:1049.

![Graph showing percentage seropositive over time](chart.png)
Where do you get it?

OUDs -> Opioid Treatment Programs (OTPs)

Pain -> Any prescriber can write a script that can be filled at traditional pharmacies

Opioid Treatment Programs (OTPs)

• Only source of methadone for maintenance
• Provide a multi-modal approach including medication, counseling, and other supportive services, to treat opioid addiction
• Heavily regulated by state and federal agencies
• Historically 13 clinics (3 CMHCs) + 5 new (Plus VA)
• Serve approximately 15,000 people
• Can also administer buprenorphine
• Opioid use disorders are widespread and Indiana is still underserved
“Take Homes”

- Privilege earned through clean drug screens
- Incentive for “good behavior”
- Improves compliance, sobriety from other drugs
Methadone

PROS

- Close supervision: daily dosing
- Enforce therapy
- Incentivize “take homes”
- Most effective treatment

CONS

- Hassle: interfere with employment, parenting, etc.
- Expensive
- Societal consequences for take homes

Treatment Options

Opiate Addiction

- Buprenorphine Maintenance Program
- Naltrexone (Vivitrol) Program
- Methadone Maintenance Program
Buprenorphine
Suboxone, Subutex, etc

Buprenorphine/Naloxone

• Semi-synthetic partial agonist (limited effects) + antagonist
• Does not require daily dispensing
• Safer in overdose = much less regulation
• Easier to stop than methadone, milder withdrawal
Sublingual Film or Tab

Buprenorphine treatment is evidence based

- Many clinical trials have shown that it is superior to placebo.
- Outcomes are similar to methadone, if patients are able to comply with less structured buprenorphine in Office Based Outpatient Treatment (OBOT) settings.
Drug Abuse Treatment Act (DATA) of 2000

- Allowed “Qualified” physicians to treat opioid dependence outside methadone facilities
  1. Addiction certification from approved organization, or
  2. Physician in clinical trial of qualifying medication, or
  3. Complete 8-hour course from approved organization
- DEA issues (free) to qualifying physicians a new DEA number to use medication for opioid dependence
- As of today, only one medication formulation is approved for this use

Buprenorphine’s Properties

- Modest $\mu$ agonist activity with ceiling
- Long half life
- Precipitated withdrawal if taken after full agonist
- Decreased risk of respiratory, CNS depression
- Sublingual route of administration
- “Combo” tablet with naloxone limits abuse by injection
Buprenorphine Safety

- No alteration of cognitive functioning
  - feel “normal”
- No organ damage
  - Early concern of hepatic toxicity unconfirmed
  - No evidence of QT prolongation
- Ceiling prevents respiratory depression, OD
  (Overdose reports with combining use with benzodiazepines)
- No clinically significant interactions with other drugs

Appropriateness for Office-based Treatment

- Patient is less likely to be an appropriate candidate for office-based treatment:
  - Dependence on high doses of benzodiazepines, alcohol, or other CNS depressants
  - Significant psychiatric co-morbidity
  - Multiple previous treatments (methadone) and relapses
Most often heard quotes with Buprenorphine

“Doc, I feel normal”
“I wake up not sick”
“I have my life back”

• Treatment in normal medical settings:
  • Encourages continuity of medical/specialty care
  • Encourages relationship building with clinicians
  • Legitimize opioid dependence as a normal, treatable, chronic illness

Buprenorphine: Reduces Other Drug Use

Fudala, NEJM 2003
Buprenorphine Diversion

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**Figure 1. Average Number of Cases of Abuse of Buprenorphine Products, Methadone, Tramadol, and Oxycodone per Drug Abuse Report.**

The arrow indicates the launch date of buprenorphine for use in office-based treatment of opioid dependence. Q denotes quarter.

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**Buprenorphine**

**PROS**

- Convenient
- Safer to have at home
- Easier to stop

**CONS**

- Still on an opioid
- Hard to find qualified providers in some areas
- Less effective than methadone for people who need structured programming.
- Diversion is a possibility.
BIG NEWS: Long Acting Injectable Buprenorphine

- 2 Formulations: Sublocade (single dose available) and another formulation pending FDA approval
- Sublocade: subcutaneous, requires 7 days of oral bup, two monthly initial doses of 300 mg followed by 100 mg monthly maintenance doses
- NOW COVERED BY IN MEDICAID

Opiate Use Disorders and Pregnancy

- Detoxification is associated with high rates of spontaneous abortions in the first trimester and premature delivery in the third trimester
- Babies exposed to heroin have lower birth weights
- Babies exposed to heroin were more likely to require morphine than those with methadone treated mothers (40% vs. 19%)
- Current recommendations: Treat with Methadone or Buprenorphine
Neonatal Abstinence Syndrome

• “Neonatal abstinence syndrome is an expected and treatable condition that follows prenatal exposure to opioid agonists.”
  -American College of Obstetricians and Gynecologists

Naltrexone (Vivitrol)
Antagonist Treatment

Naltrexone

Why antagonist therapy?

• Block effects of a dose of opiate (Walsh et al. 1996)
• Prevent impulsive use of drug
• Dose (oral): 50 mg daily, 100 mg every 2 days, 150 mg every third day
• Blocks agonist effects
• Side effects: hepatotoxicity, monitor liver function tests every 3 months
• Biggest issue is lack of compliance; but those who “test” naltrexone by taking a dose of opioid and experiencing no effect do better with the medication (Cornish JW, et al. 1997)
Who is a Candidate for Naltrexone?

- The patient is opioid free for 7-10 days (DIFFICULT IN OUTPATIENT SETTINGS)
- The patient does not have severe or active liver or kidney problems (Typical guidelines suggest liver function tests no greater than 3 times the upper limits of normal, and bilirubin normal)

Risks: side effects, costs, take home doses

Benefits: Decrease drug use, improve health, reduce high risk behaviors, increase employment
MYTH: Providing MAT Will Only Disrupt and Hinder a Patient’s Recovery Process

• FACT: MAT has been shown to assist patients in recovery by improving quality of life, level of functioning and the ability to handle stress. Above all, MAT helps reduce mortality while patients begin recovery.

National Council for Behavioral Health

MAT Summary

• Studies have shown that MAT reduces illicit drug use, disease rates, and related harmful behaviors, including criminal activity.
• People in MAT are up to 75% less likely to die from a cause related to their addiction.
• Despite what the National Institute of Health says is “unequivocal” evidence of MAT’s effectiveness and safety, many myths persist about MAT. As a result, people are denied potentially life saving addiction treatment.
Economics of MAT

• Investment in MAT makes good economic sense.

• Every dollar spent on MAT yields $38 in related economic benefit - seven times more than previously thought. (2005 study)

MAT for other Substance Use Disorders

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<th>Nicotine</th>
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<td>Naltrexone</td>
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<td>Varenicline</td>
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<tr>
<td>Acamprosate (Campral)</td>
<td>Bupropion</td>
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We need to advocate for a full continuum of care

What to do if you are concerned about care being provided to people with OUDs?

- FSSA’s Division of Mental Health and Addiction licenses and certifies addiction providers.
- Please report concerns to DMHA’s consumer service line at: 1-800-901-1133
Summit Resources

- IN.gov/recovery
- IN OBOT Guidelines
- Benchcard

References

- Acamprosate Information: http://www.rxlist.com/revia-drug.htm
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