Opioid Dependence and Its Treatment

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- University of Pennsylvania, Dept of Psychiatry
Figure 2.1 Past Month Illicit Drug Use among Persons Aged 12 or Older: 2013

- Illicit Drugs: 24.6 million
- Marijuana: 19.8 million
- Psychotherapeutics: 6.5 million
- Cocaine: 1.5 million
- Hallucinogens: 1.3 million
- Inhalants: 0.5 million
- Heroin: 0.3 million

1 Illicit Drugs include marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically.

NSDUH 2013
Figure 2.3 Past Month Nonmedical Use of Types of Psychotherapeutic Drugs among Persons Aged 12 or Older: 2002-2013

*Difference between this estimate and the 2013 estimate is statistically significant at the .05 level.

NSDUH 2013
Figure 2.4 Past Month and Past Year Heroin Use among Persons Aged 12 or Older: 2002-2013

* Difference between this estimate and the 2013 estimate is statistically significant at the .05 level.

NSDUH 2013
Figure 2.16 Source Where Pain Relievers Were Obtained for Most Recent Nonmedical Use among Past Year Users Aged 12 or Older: 2012-2013

Source Where User Obtained

- More than One Doctor (2.6%)
- Free from Friend/Relative (53.0%)
- One Doctor (21.2%)
- Other\(^1\) (4.3%)
- Bought on Internet (0.1%)
- Drug Dealer/Stranger (4.3%)
- Bought/Took from Friend/Relative (14.6%)

Source Where Friend/Relative Obtained

- One Doctor (83.8%)
- More than One Doctor (3.3%)
- Free from Friend/Relative (5.1%)
- Bought/Took from Friend/Relative (4.9%)
- Drug Dealer/Stranger (1.4%)
- Bought on Internet (0.3%)

\(^1\)The Other category includes the sources "Wrote Fake Prescription," "Stole from Doctor's Office/Clinic/Hospital/Pharmacy," and "Some Other Way."

Note: The percentages do not add to 100 percent due to rounding.

NSDUH 2013
Source of Prescription Pain Relievers

How different misusers of pain relievers get their drugs

<table>
<thead>
<tr>
<th>Methods and sources for obtaining pain relievers</th>
<th>Recent Initiates</th>
<th>Occasional Users</th>
<th>Frequent or Chronic Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bought from friend/relative, dealer, or internet</td>
<td>9%</td>
<td>13%</td>
<td>28%</td>
</tr>
<tr>
<td>Prescribed from 1 or more doctors</td>
<td>17%</td>
<td>17%</td>
<td>26%</td>
</tr>
<tr>
<td>Obtained from friend/relative for free or w/o asking</td>
<td>68%</td>
<td>66%</td>
<td>41%</td>
</tr>
</tbody>
</table>

Commonly Abused Opioids

Diacetylmorphine (Heroin)
Hydromorphone (Dilaudid)
Oxycodone (OxyContin, Percodan, Percocet, Tylox)
Meperidine (Demerol)
Hydrocodone (Lortab, Vicodin) – recently moved from C-III to C-II
Commonly Abused Opioids (continued)

Morphine (MS Contin, Oramorph)
Fentanyl (Sublimaze)
Propoxyphene (Darvon)
Methadone (Dolophine)
Codeine
Opium
Commonly Abused Opioids

Opioids are abused by all routes of administration including oral, inhalation, smoking, and injection.

Heroin is most commonly used intranasally or intravenously, but can be inhaled, smoked, or injected intramuscularly or subcutaneously.

Opium is usually smoked.

The pharmaceutical opioids are usually taken orally (but may also be injected).
Opioid intoxication and withdrawal

It is important to recognize and distinguish symptoms of opioid intoxication and withdrawal, since their symptomatic presentations can overlap with the signs and symptoms of other psychiatric disorders.
Psychiatric Assessment – Features of Disorders

**Opioid intoxication**

Signs and symptoms:

- Feeling of “high” or euphoria
- Pupillary constriction
- Drowsiness or coma
- Slurred speech
- Impaired attention or memory
Psychiatric Assessment – Features of Disorders

Opioid withdrawal

Occurs after stopping or decreasing use that has been occurring regularly (e.g., daily for weeks) – this is spontaneous withdrawal.

Note it can also occur if person receives a dose of an opioid antagonist or partial agonist – this is precipitated withdrawal.
Psychiatric Assessment – Features of Disorders

Opioid withdrawal

Signs and symptoms:
- Dysphoric mood
- Nausea or vomiting
- Muscle aches/cramps
- Lacrimation
- Rhinorrhea
Psychiatric Assessment – Features of Disorders

Opioid withdrawal (continued)

- Pupillary dilation
- Sweating, piloerection
- Diarrhea
- Yawning
- Fever
- Insomnia
Endogenous Opioid System

• Unknown early 70’s, remained unproven
  - Recognized, opiate receptor binding sites in the brain discovered

• Three distinct families of opioid peptides
  - Enkephalins
  - Endorphins
  - Dynorphins

Reference: Opioid Analgesics, Chapter 21, Goodman and Gilman’s The Pharmacological Basis of Therapeutics, 11th edition.
Opioid Receptors

- **Mu – (MOR) Subtypes:** $\mu_1, \mu_2$

- **Kappa – (KOR) Subtypes:** $\kappa_1, \kappa_2, \kappa_3$

- **Delta – (DOR) Subtypes:** $\delta_1, \delta_2$

Reference: Opioid Analgesics, Chapter 21, Goodman and Gilman’s The Pharmacological Basis of Therapeutics, 11th edition.

http://www.opioids.com/receptors/index.html
Opioid Effects upon Physiological Systems

- Produce analgesia
- Affect mood
- Affect rewarding behavior
- Alter respiratory function
- Alter cardiac function
- Alter gastrointestinal function
- Alter neuroendocrine function

References:
- Opioid Analgesics, Chapter 21, Goodman and Gilman's The Pharmacological Basis of Therapeutics, 11th edition.
Respiratory

• Direct effect on brainstem respiratory centers
  - Reduction in responsiveness to carbon dioxide

• Depress all phases of respiratory activity (rate, minute volume, tidal exchange)

• Rate may fall to 3 - 4 breaths/min

• Underlying pulmonary dysfunction

References:
Opioid Analgesics, Chapter 21, Goodman and Gilman’s The Pharmacological Basis of Therapeutics, 11th edition.
Opioid Physiological Effects

• **Cough**
  - Depress cough center in the medulla

• **Anti-Nausea/Emetic**
  - Stimulation of chemoreceptor trigger zone in the medulla

• **Skin**
  - Dilatation of cutaneous blood vessels
  - Sweating, pruritus

• **Cardiovascular**
  - ↑Peripheral vasodilation
  - ↓Peripheral resistance

• **Gastrointestinal**
  - ↓Decrease gastric motility, prolongs gastric emptying
  - Bilary tract, constricts Sphincter of Odi, epigastric distress to typical biliary colic

References: Opioid Analgesics, Chapter 21, Goodman and Gilman’s The Pharmacological Basis of Therapeutics, 11th edition.
**Opioid Physiological Effects**

- **Ureter / Urinary Bladder**
  - ↑Smooth muscle tone, combined with antidiuretic → decrease urine flow

- **Immune System**
  - Complex, acute and chronic
  - Overall suppression
  - Different opioid agonist have unique immunomodulatory properties

- **Hypothalamus**
  - Morphine inhibits GnRH, CRH → ↓LH, FSH, ACTH and β-endorphins
    - Pituitary concentrations of testosterone and cortisol decline
  - **Women (Methadone)**
    - Chronic administration, tolerance develops, menstrual cycles normalize after disruption due to heroin
  - **Men (Methadone)**
    - Chronic administration, tolerance to hypothalamic releasing factors develops, circulation concentrations of LH and testosterone are wnl
    - **Antidiuretic effect** → urinary retention

References: Opioid Analgesics, Chapter 21, Goodman and Gilman’s The Pharmacological Basis of Therapeutics, 11th edition.
Heroin Simulated 24 Hr. Dose/Response
With established heroin tolerance/dependence

“Loaded”
“High”
“Abnormal Normality”
Normal Range
“Comfort Zone”
Subjective w/d
“Sick”
Objective w/d
Methadone Simulated 24 Hr. Dose/Response
At steady-state in tolerant patient

"Load"d
"High"

"Abnormal Normality"

Normal Range
"Comfort Zone"

Subjective w/d

"Sick"

Objective w/d
Medication Options

• Agonists:
  - Methadone
  - Buprenorphine

• Antagonists:
  - Naltrexone, p.o.
  - Naltrexone depot
Rationale for opioid agonist medications

Advantages of opioid agonist medication over heroin

Non-parenteral administration
Known composition
Gradual onset and offset
Long-acting
Mildly reinforcing
Medically supervised
Rationale for opioid agonist medications

Opioid agonist treatment

Most effective treatment for opioid dependence

Controlled studies have shown significant:

- Decreases in illicit opioid use
- Decreases in other drug use
- Decreases in criminal activity
- Decreases in needle sharing
- Improvements in prosocial activities
- Improvements in mental health
Methadone
OUTCOMES

Effectiveness of Treatment:
Early Efficacy & Outcome Studies

• Retention - VS. TC and Drug Free
  - NYC, DARP, & TOPS (>40K patients)

• Retention relative to dose/placebo
  - Newman, Strain, & Caplehorn

• Reincarceration and heroin use
  - Dole, Newman & Whitehill (‘69 & ‘76)
## Efficacy: Retention Studies

### Methadone Modality

<table>
<thead>
<tr>
<th>Study</th>
<th>Size</th>
<th>Treatment</th>
<th>Dropout %/wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYC</td>
<td>20,603</td>
<td>MMT</td>
<td>0.76</td>
</tr>
<tr>
<td>Newman</td>
<td>100</td>
<td>MMT</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>7.1</td>
</tr>
</tbody>
</table>
# Efficacy: Retention Studies

## Methadone Modality by Dose

<table>
<thead>
<tr>
<th>Study</th>
<th>Size</th>
<th>Treatment</th>
<th>Dropout %/wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strain</td>
<td>212</td>
<td>50 mg/d</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 mg/d</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>7.1</td>
</tr>
<tr>
<td>Caplehorn</td>
<td>238</td>
<td>&gt;80 mg/d</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60-80 mg/d</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;60 mg/d</td>
<td>2.1</td>
</tr>
</tbody>
</table>
Evidence-Based Practices:

Elements to Maximize OAT Outcomes

- **Adequate** Methadone Dose
- Availability of counseling
- Maintenance versus abstinence/detoxification program orientation
- Contingency management with focus on positive and immediate reinforcement/rewards

Source: Opioid Agonist Therapy Monitoring System (OMS) Willenbring et al. 2003
What Does OMT DO?

Impact of Treatment!
Impact of Maintenance Treatment

- Reduction death rates (Grondblah, ‘90)
- Reduction IVDU (Ball & Ross, ‘91)
- Reduction crime days (Ball & Ross)
- Reduction rate of HIV seroconversion (Bourne, ‘88; Novick ‘90,; Metzger ‘93)
- Reduction relapse to IVDU (Ball & Ross)
- Improved employment, health, & social function
DEATH RATES IN TREATED AND UNTREATED HEROIN ADDICTS

% Annual Death Rates

- MMT
- VOL DC TX
- INVOL DC TX
- UNTREATED

Impact of MMT on IV Drug Use for 388 Male MMT Patients in 6 Programs

Adapted from Ball & Ross - The Effectiveness of Methadone Maintenance Treatment, 1991
Crime among 491 patients before and during MMT at 6 programs

Adapted from Ball & Ross - The Effectiveness of Methadone Maintenance Treatment, 1991
HIV Infection Rates by Treatment Status at Time of Enrollment

- **Baseline through 36 Months**

**Percent Testing Positive**

- **In Treatment**
- **Out of Treatment**

<table>
<thead>
<tr>
<th>Time</th>
<th>% Testing Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>13%</td>
</tr>
<tr>
<td>6</td>
<td>21%</td>
</tr>
<tr>
<td>12</td>
<td>21%</td>
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<td>18</td>
<td>18%</td>
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<td>24</td>
<td>18%</td>
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<td>30</td>
<td>39%</td>
</tr>
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<td>36</td>
<td>39%</td>
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<tr>
<td>42</td>
<td>48%</td>
</tr>
<tr>
<td>48</td>
<td>51%</td>
</tr>
<tr>
<td>60</td>
<td>51%</td>
</tr>
<tr>
<td>72</td>
<td>51%</td>
</tr>
</tbody>
</table>

**Treatment Research Institute**
Relapse to IV drug use after MMT
105 male patients who left treatment

Adapted from Ball & Ross - The Effectiveness of Methadone Maintenance Treatment, 1991
McLellan, et al, 1993
Other Pharmacotherapies for Maintenance Treatment of Opioid Dependence:
Buprenorphine, Buprenorphine/Naloxone and Naltrexone
Buprenorphine and Buprenorphine/Naloxone
Intrinsic Activity: Full Agonist (Methadone), Partial Agonist (Buprenorphine), Antagonist (Naloxone)
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
Potential for Physical Dependence

Repeated administration of buprenorphine produces or maintains physical dependence.

However, degree of physical dependence is less than that produced by full agonist opioids.

This means withdrawal syndrome should be less severe for buprenorphine.
Rationale for Buprenorphine/naloxone

• When taken sublingually
  - Buprenorphine will be well absorbed
  - Naloxone absorption will be minimal

• If taken intravenously
  - Naloxone 100% bioavailable
  - Precipitated withdrawal occurs in opioid maintained patients
Buprenorphine/naloxone infusion

• Study on methadone maintained patients (Mendelson)
• Looked at 6 patients on stable methadone doses of 45 to 60 mg/day
• Challenged IV with
  - Buprenorphine 0.2 mg
  - Naloxone 0.1 mg
  - Buprenorphine 0.2 and Naloxone 0.1 mg
  - Placebo
PEAK EFFECTS – MEAN (±SD)

**Bad Drug**
- A: Buprenorphine placebo, Naloxone placebo
- B: Buprenorphine 0.2 mg, Naloxone placebo
- C: Buprenorphine placebo, Naloxone 0.1 mg
- D: Buprenorphine 0.2 mg, Naloxone 0.1 mg

**Sickness**
- C: Buprenorphine placebo, Naloxone 0.1 mg
- D: Buprenorphine 0.2 mg, Naloxone 0.1 mg
### Mean Peak Amount Would Pay for Drug

- **Bup/Nal**: $1.90 ± 3.70
- **Naloxone**: 0.00 ± 0.00
- **Buprenorphine**: 11.90 ± 7.00
- **Placebo**: 0.00 ± 0.00
Benzodiazepines and Other Sedating Drugs

Reports of deaths when buprenorphine injected along with benzodiazepines

Reported from France, where tablets available – appears patients dissolve and inject tablets

Probably possible for this to occur with other sedatives as well
Numerous outpatient clinical trials comparing efficacy of daily buprenorphine to placebo, and to methadone.
Maintenance Treatment Using Buprenorphine

These studies conclude:

- Buprenorphine more effective than placebo
- Buprenorphine equally effective as moderate doses of methadone (e.g., 60 mg per day)
Different Doses of Buprenorphine: Opiate Use

(Ling et al., 1998)
**Buprenorphine, Methadone, LAAM: Treatment Retention**

Adapted from Johnson, et al., 2000
Buprenorphine, Methadone, LAAM: Opioid Urine Results

Mean % Negative

Study Week

All Subjects

19%
40%
49%
39%
19%

LAAM
Bup
Hi Meth
Lo Meth

Adapted from Johnson, et al., 2000
Buprenorphine – methadone: treatment retention

(Strain et al., 1994)
Buprenorphine – methadone: opioid urine results

(Strain et al., 1994)
PATIENT SELECTION

Issues related to recommending buprenorphine over methadone:

- Psychiatric co-morbidities
- Substance abuse co-morbidity
  - BZD’s and alcohol
- Policy regarding take-home doses
- Finances
POLICY ISSUES

Other policy issues:

Whether to offer buprenorphine at all

Patient selection
POLICY ISSUES
What to do if patient refuses physician recommendation of medication?

1. Engage the patient in motivational therapy
2. Educate the patient on the reasons for the decision
3. Offer higher level of care
4. Ensure that patient knows the clinic is available if/when s/he decides to engage at an appropriate level of care
Buprenorphine Maintenance

Once patient has achieved stable dose, determine office schedule.

Normal daily dose is ~14mg/day; little evidence of need for dose greater than 24mg/day.

NO evidence of need for more than once daily dose; patients may prefer more than once daily dose.
Withdrawal Using Buprenorphine

Studies have primarily looked at buprenorphine maintenance, not withdrawal.

In general, withdrawal using opioids (e.g., methadone) has had poor outcomes.

Results with buprenorphine may be better (may have a milder withdrawal syndrome).
Buprenorphine Maintenance/Withdrawal

- Buprenorphine maintenance vs. withdrawal:
  - Double-blind, random assignment to:
    - 16 mg/day SL buprenorphine tablets, or
    - 6 day buprenorphine withdrawal followed by placebo
  - 20 patients per group
  - Used tablets of buprenorphine, placebo

Kakko et al. 2003
Buprenorphine Maintenance-Withdrawal

• **Comparison of buprenorphine maintenance vs. withdrawal:**
  - First week of study was inpatient; study lasted one year; take home doses allowed after 6 months of treatment
  - Outcome measures included
    - treatment retention
    - urine samples that were collected under supervision and tested three times per week
    - ASI scores
Comparison of buprenorphine maintenance vs. withdrawal:

- All participants also received a relatively rich set of psychosocial treatments:
  - group and individual counseling
  - assistance with various social service agencies (for example, for housing and employment)
Buprenorphine Maintenance/Withdrawal: Retention

(Kakko et al., 2003)
### Buprenorphine Maintenance/Withdrawal: Mortality

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Buprenorphine</th>
<th>Cox Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead</td>
<td>4/20 (20%)</td>
<td>0/20 (0%)</td>
<td>$X^2 = 5.9; p = 0.015$</td>
</tr>
</tbody>
</table>

(Kakko et al, 2003)
Summary

Buprenorphine/naloxone and buprenorphine are safe and highly effective in treating opioid dependence.

Buprenorphine can be effectively utilized in OTPs and in office-based practice to assist opioid-dependent patients.

Physicians and allied health personnel need to understand the complex pharmacology of buprenorphine in order to use it effectively for their patient’s good.
Naltrexone
2 Groups of patients are appropriate for use of naltrexone injectable:

- Patients entering treatment in active addiction OR after short-term detoxification/rehabilitation

- Patients who have succeeded on methadone or buprenorphine and successfully tapered off agonist medication
Naltrexone Injectable Use for Opioid Dependence

Unintended precipitation of opioid withdrawal
To prevent occurrence of an acute abstinence syndrome (withdrawal) in patients dependent on opioids, or exacerbation of a preexisting subclinical abstinence syndrome:
• Patients must be opioid free for a minimum of 7-10 days before starting VIVITROL treatment
• Patients must be free of all opioid-containing medications, including medications used to treat opioid dependence (e.g., methadone, buprenorphine and buprenorphine/naloxone)
The absence of an opioid drug in the urine is often not sufficient proof that a patient is opioid free:

A naloxone challenge test should be given if the prescribing physician feels there is risk of precipitating a withdrawal reaction following administration of VIVITROL
The efficacy of naltrexone injectable in the treatment of opioid dependence was evaluated in a 24 week, placebo-controlled, multi-center, double-blind, randomized trial of opioid-dependent (DSM-IV) outpatients, who were completing or had recently completed detoxification. Subjects were treated with an injection every 4 weeks of naltrexone injectable 380 mg or placebo. Oral naltrexone was not administered prior to the initial or subsequent injections of study medication. Standardized, manual-based psychosocial support was provided on a biweekly basis to all subjects in addition to medication.
Naltrexone Injectable Efficacy for Opioid Dependence

Patients Sustaining Varying Percentages of Opioid-Free Weeks

- VIVITROL With Psychosocial Support (n=126)
- Placebo With Psychosocial Support (n=124)

5/24 Weeks
Percent of Opioid-Free Weeks
24/24 Weeks

Data on file, Alkermes, Inc.

P=0.0002
Pharmacokinetics

Mean steady-state naltrexone concentration following monthly XR-NTX 380 mg compared to daily oral dosing

Dean RL. *Front Biosci*. 2005 Jan 1;10:643-655.
Data on File, Alkermes, Inc.
Naltrexone Injectable

- Steady state by 2\textsuperscript{nd} dose
- Minimal accumulation 6\beta-\textit{naltrexol}
- Limited 1\textsuperscript{st} pass metabolism by liver
- Monthly naltrexone (380 mg vs 1,500 mg)
Response Profile
Cumulative % of Participants at Each Rate of Weekly Confirmed Abstinence: XR-NTX 380 mg vs. Placebo

Total abstinence (100% opioid-free weeks) during Weeks 5-24 was reported in 45 (35.7%) of subjects in the XR-NTX group versus 28 (22.6%) subjects in placebo group (P=0.0224).
Mean Change From Baseline in VAS-Opioid Craving Score

Baseline craving scores: XR-NTX = 18; Placebo = 22

XR-NTX patients showed a 50% reduction-from-baseline in VAS-craving vs. no change for placebo
XR naltrexone is effective for heroin users

Extended Release Naltrexone Improves Abstinence

Opiate-Negative Urines

Arch Gen Psychiatry 2006; 63: 210-218
Mean Neonatal Morphine Dose, Length of Neonatal Hospital Stay, and Duration of Treatment for Neonatal Abstinence Syndrome

Issues Related to Pregnancy
Figure 3. Racial Distribution of Respondents Expressed as Percentage of the Total Sample of Heroin Users

Data are plotted as a function of decade in which respondents initiated their opioid abuse.

Cicero, et al  Archives Psychiatry 2014
Figure 2. Sex Distribution of Respondents Expressed as Percentage of the Total Sample

Data are plotted as a function of decade in which respondents initiated their opioid abuse.

Cicero, et al  Archives Psychiatry 2014
Methadone as Gold Standard for Pregnant Opiate Addict

- NIH Consensus Panel 1998
- WHO Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence 2009
- CSAT Tip 43
- ASAM/ACOG Opinion of the Committee on Health Care for Underserved Women 2012
Methadone as “Gold Standard” for the Pregnant Opiate Addict

- As evidenced by jails, which do not provide MAT to addicts, do provide methadone for pregnant addicts
- Steady levels of opiates normalize neuroendocrine functioning and prevent fetal distress
- Decreases rates of pregnancy complications, e.g. miscarriage, stillbirth, IUGR, abruptio placenta, hemorrhage, infection
- Improves prenatal care
- Allows for psychosocial interventions to improve level of functioning
Risk-Benefit Comparison of Methadone during Pregnancy

Risks
- Opiate abstinence syndrome in newborn

Benefits
- Protects fetus from repeated withdrawal episodes in utero
- Decreases risk of obstetric and fetal complications
- Decreases IUGR
- Decreases neonatal morbidity and mortality
Risk-Benefit Comparison of Methadone during Pregnancy

• **Benefits**
  - Decreases infections which could be vertically transmitted
  - Decreases opiate and other illicit drug use
  - Decreases criminal activity
  - Improves overall health and well-being
Figure 1. Annualized NICU Admission Rates for the Neonatal Abstinence Syndrome and Median Length of Stay, According to Year.

Bars in Panel B represent interquartile ranges. NICU denotes neonatal intensive care unit.
Primary and Secondary Outcomes in the Methadone and Buprenorphine Groups

| Table 2. Primary and Secondary Outcomes in the Methadone and Buprenorphine Groups. * |
|---------------------------------|-----------------|------------------|-----------------|---------------|
| **Outcome**                      | Methadone (N=73) | Buprenorphine (N=58) | Odds Ratio (95% CI) | P Value       |
| **Primary outcomes**             |                 |                  |                 |               |
| Treated for NAS — no. (%)       | 41 (57)         | 27 (47)          | 0.7 (0.2–1.8)   | 0.26          |
| NAS peak score                   | 12.8±0.6        | 11.0±0.6         |                 | 0.04          |
| Total amount of morphine for NAS — mg | 10.4±2.6        | 1.1±0.7           | <0.0001†         |               |
| Duration of infant’s hospital stay — days | 17.5±1.5       | 10.0±1.2         | <0.0001†         |               |
| Infant’s head circumference — cm | 33.0±0.3        | 33.8±0.3         |                 | 0.03          |
| **Secondary neonatal outcomes**  |                 |                  |                 |               |
| Duration of treatment for NAS — days | 9.9±1.6        | 4.1±1.0           | <0.000125†       |               |
| Weight at birth — g             | 2875.5±663      | 3093.7±726       |                 | 0.03          |
| Length at birth — cm            | 47.8±0.5        | 49.8±0.5         | 0.0005           |               |
| Preterm, <37 wk — no. (%)       | 14 (19)         | 4 (7)            | 0.3 (0.1–2.0)   | 0.07          |
| Gestational age at delivery — wk| 37.9±0.3        | 39.1±0.3         | 0.007            |               |
| Apgar score                     |                 |                  |                 |               |
| 1 min                           | 8.0±0.2         | 8.1±0.2          | 0.87             |               |
| 5 min                           | 9.0±0.1         | 9.0±0.1          | 0.69             |               |
| **Secondary maternal outcomes** |                 |                  |                 |               |
| Cesarean section — no. (%)      | 27 (37)         | 17 (29)          | 0.6 (0.2–2.0)   | 0.23          |
| Maternal weight gain — kg       | 8.6±1.0         | 8.3±0.9          | 0.80             |               |
| Abnormal fetal presentation during delivery — no. (%) | 10 (14) | 3 (5) | 0.3 (0.0–2.4) | 0.09 |
| Analgesia during delivery — no. (%) | 60 (82)       | 49 (85)          | 1.1 (0.3–4.8)   | 0.85          |
| Positive drug screen at delivery — no. (%) | 11 (15)  | 5 (9)           | 0.5 (0.1–2.7)   | 0.27          |
| Medical complications at delivery — no. (%) | 37 (51) | 18 (31) | 0.5 (0.2–0.9) | 0.03 |
| Did not complete study — no. (%) | 16 (18)        | 28 (33)          | 2.0 (1.3–5.6)   | 0.02          |
| Amount of voucher money earned for drug-negative tests — U.S. $ | 1,570.00±121.72 | 1,391.39±123.59 | 0.31            |               |
| No. of prenatal obstetrical visits | 8.8±0.5       | 8.7±0.4          | 0.86             |               |

* Plus–minus values are means ±SE. In accordance with the alpha level chosen for the tests of significance, 99.09% confidence intervals (CIs) were used for the primary outcome measures, and 99.6825% CIs were used for the neonatal and maternal secondary outcome measures. The number of patients who underwent randomization was 175, the number who did not complete the study was 44, and the number who did complete the study was 131. A small percentage of data was missing. For four of the five primary outcomes, the number of patients with missing data was 1 in each medication group except for the outcome on length of hospital stay for neonates, for which no data were missing. For two of the seven secondary neonatal outcomes, the number of patients with missing data was 1 in each medication group for days treated for NAS and 1 in the methadone group for infant length at birth. For four of the nine secondary maternal outcomes, the number of patients with missing data in the methadone group was 2 for maternal weight gain, 2 for abnormal fetal presentation during delivery, 1 for positive drug screen at delivery, and 1 for amount of voucher money earned. The number of patients with missing data in the buprenorphine group was 4 for maternal weight gain, 1 for positive drug screen at delivery, and 1 for voucher money earned.

† These P values were calculated in accordance with prespecified thresholds for significance.

Summary

• Addiction is a common problem, across all sectors of society.

• It is frequently undiagnosed or, if recognized ignored.

• Opioid addiction is on the rise.
  - Appropriate therapies are available, but may be difficult to access.
  - Agonist therapy is the preferred modality for patients with long-standing opioid addiction.