Prescription Opioid Addiction Treatment Study
Findings and Strategies from a NIDA Clinical Trials Network Study
2013 Midwest Conference on Problem Gambling and Substance Abuse
Alex Barajas-Muñoz
Roadmap of the Training

• The goal of the training is to present the results of a new study on using buprenorphine to treat prescription opioid addiction

• To get there, we present information on
  – The scope of the prescription opioid problem
  – How opioids and the study medications work in the body
  – And finally, the results of the study.
The Headline

Treatment with buprenorphine works....

...but not necessarily in exactly the way you might expect.
Objectives for the Training

• Define the **prevalence** and **treatment admission** rates of prescription opioid dependence in the United States

• Describe the **mechanism of action** of buprenorphine-naloxone

• Review the **results** of a clinical trial that examined the use of buprenorphine-naloxone to treat prescription opioid dependent adults

• Describe the **implications** of these findings for the treatment of prescription opioid dependence
NIDA/SAMHSA Blending Initiative

• The goal is to move important scientific findings into mainstream addiction treatment

• NIDA and SAMHSA’s Center for Substance Abuse Treatment began the Blending Initiative in 2001 to work on a common vision:
  – To improve substance use disorder treatment and accelerate the dissemination of research-based findings into practice.
Blending Team Members

- **Thomas Freese, PhD** – Co-Chair – Pacific Southwest ATTC
- **Beth Rutkowski, MPH** – Co-Chair – Pacific Southwest ATTC
- **Leslie Cohen** – ATTC of New England
- **Joshua D. Lee, MD, MSc** – New York University, Longone Medical Center
- **Traci Rieckmann, PhD** – Northwest Frontier ATTC
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- **Hilary Smith Connery, MD, PhD** – Harvard Medical School, McLean Hospital
- **Roger Weiss, MD** – Harvard Medical School, McLean Hospital

| ATTC representative | NIDA/CTN representative |
Special Acknowledgements

- **Ron Dobbins, MBA** – NIDA, Center for Clinical Trials Network
- **Donna Doolin, LSCSW** – SAMHSA-CSAT
- **Katia Delrahim Howlett, PhD** – Synergy Enterprises, Inc.
- **Petra Jacobs, MD** – NIDA, Center for Clinical Trials Network
- **Mary Ellen Michel, PhD** – NIDA, Center for Clinical Trials Network
- **Harold Perl, PhD** – NIDA, Center for Clinical Trials Network
- **Michele Straus, RPh, MS** – NIDA, Center for Clinical Trials Network
National Focus Area ATTCs

These National Focus Area Centers will work with Regional Centers to serve as subject matter experts, provide information on the latest research-based best practices, and coordinate efforts on four topics of national focus.

WHO ARE WE?

National Frontier and Rural ATTC, Rono, NV
- Nancy Roget, MS, MFT, LADC - Project Director/Principal Investigator
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- Joyce Hartje, PhD - Evaluator
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Mid-America ATTC’s “Home”

- The COLLABORATIVE for Excellence in Behavioral Health Research and Practice

- University of Missouri-Kansas City, School of Nursing and Health Studies
How we work … core funding

• Substance Abuse & Mental Health Services Administration (SAMHSA)

• National Institute on Drug Abuse (NIDA)
What we do … our focus
What we do…

To improve treatment outcomes through the use of research-based practices by:

• raising awareness of those practices
• building the skills capacity of the workforce
• cultivating the systemic changes necessary for successful implementation
What we do…our focus is shifting

Separate specialty care system

Integrated behavioral health and primary care
• FREE Self-Paced Courses

• CEUs Available ($5/hour)
  - NASW
  - NBCC
  - NAADAC
  - CME/CNE

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FREE COURSES!

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ENROLL TODAY!

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Psychotherapeutic Medications Online & Mobile View

www.findrxinformation.org

Compatible across systems (i.e., device-agnostic)
Prescription Opioid Addiction Treatment Study

Background, Rationale, and Introduction of Key Terms and Issues
Opiate vs. Opioid – Is there a Difference?

• The short answer is YES!

• **Opiates** are derived directly from the opium poppy by purifying the various chemicals in the poppy.

• **Opioids** include all opiates but also include chemicals that have been synthesized in some way.
  
  • Morphine is an opioid and also an opiate
  
  • Methadone is an opioid but not an opiate
Partial vs. Full Opioid Agonist and Antagonist

**Opioid Effect**

- **Full Agonist** (e.g., methadone)
- **Partial Agonist** (e.g., buprenorphine)
- **Antagonist** (e.g., naloxone)

**Dose of Opioid**
The Prescription Drug Epidemic is Unique in Some Ways

• Prescription drugs are not inherently bad
• When used appropriately, they are safe and necessary
• Threat comes from abuse and diversion
• Just because prescription drugs are legal and are prescribed by an MD, they are not necessarily safer than illicit substances.

Prescription Drugs are Easy to Obtain

- Easily obtainable from family, friends, and health care professionals (doctors, dentists, pharmacists)
- Medicine cabinets are likely source
- “Pill mills” and storefront pain clinics
- Internet – online pharmacies
  - Credit card number + access to computer
  - No prescription necessary
  - No/incomplete identity verification

Sources Where Pain Relievers were Obtained: Past Year Non-Medical Users Aged 12 or Older: 2010

- Friend/Relative for Free: 0.4%
- Bought from Friend/Relative: 4.8%
- Took from Friend/Relative: 11.4%
- Prescription from One Doctor: 17.3%
- From Drug Dealer or Stranger: 6.7%
- From Internet: 4.4%
- Other/unknown: 55.0%

SOURCE: SAMHSA, NSDUH, 2010 results.
Safe Disposal of Prescription Drugs, Part 1

• Check with a medical professional about return options through medical clinic and/or pharmacy.

• Return pharmaceutical take-back locations that allow the public to bring unused drugs to a central location for safe disposal or by mail.

• Never flush prescription drugs down the toilet unless specifically instructs it is safe to do so.

Safe Disposal of Prescription Drugs, Part 2

• Take unused, unneeded, or expired prescription drugs out of their original containers.

• Mix the prescription drugs with an undesirable substance (e.g., coffee grounds, kitty litter)

• Put them in impermeable, nondescript containers, such as empty cans or sealable bags.

• Throw these containers in the trash.

The Role of a Prescription Drug Monitoring Program

- Reduce prescription drug abuse and diversion
- Collect, monitor, and analyze electronically transmitted prescribing and dispensing data
- Support states’ efforts in education, research, enforcement, and prevention
- Operational in 37 states

Epidemiology of Prescription Opioid Dependence
Past Month Illicit Drug Use among Persons Aged 12 or Older: U.S., 2010

- **Illicit Drugs:** 22.6
- **Marijuana:** 17.4
- **Psychotherapeutics:** 7.0
- **Cocaine:** 1.5
- **Hallucinogens:** 1.2
- **Inhalants:** 0.7
- **Heroin:** 0.2

**Numbers in Millions**

**SOURCE:** SAMHSA, OAS, NSDUH, 2010 results.
Percentage of U.S. Population with Past Month Non-Medical Use of Prescription Medications, by Type

SOURCE: SAMHSA, OAS, NSDUH, 2010 results.
### Lifetime Non-Medical Use of Prescription Pain Relievers among Individuals Aged 12 or Older

<table>
<thead>
<tr>
<th>Drug</th>
<th>2005</th>
<th>2010</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darvocet/Darvon</td>
<td>7.9%</td>
<td>7.0%</td>
<td>-0.9%</td>
</tr>
<tr>
<td>Percocet/Percodan</td>
<td>4.5%</td>
<td>5.4%</td>
<td>+0.9%</td>
</tr>
<tr>
<td>Vicodin/Lortab</td>
<td>7.2%</td>
<td>8.9%</td>
<td>+1.7%</td>
</tr>
<tr>
<td>Codeine</td>
<td>2.6%</td>
<td>2.7%</td>
<td>+0.1%</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>2.9%</td>
<td>4.0%</td>
<td>+1.1%</td>
</tr>
<tr>
<td>OxyContin</td>
<td>1.4%</td>
<td>2.4%</td>
<td>+1.0%</td>
</tr>
<tr>
<td>Morphine</td>
<td>1.0%</td>
<td>1.2%</td>
<td>+0.2%</td>
</tr>
</tbody>
</table>

*Prevalence and Patterns of Nonmedical Use of OxyContin and Other Pain Relievers, ages 12 or older.*

SOURCE: SAMHSA, OAS, NSDUH, 2010 results.
New Non-Medical Users of Prescription Pain Relievers

- In 2010 – 2.0 million new non-medical users
- Approximately 5,500 new users per day
- Among persons aged 12 to 49, average age at first use was 21.0 years for pain relievers
- 17.6% of new illicit drug initiates reported pain relievers as first drug used

SOURCE: SAMHSA, OAS, NSDUH, 2010 results.

SOURCE: SAMHSA, Treatment Episode Data Set, 2009 results.
Gender Differences in Prescription Opioid Abuse

- Study included 610 non-cancer patients with chronic pain who took opioid painkillers
- Men and women had similar rates of opioid abuse
- Drug abuse by women is motivated more by emotional issues and psychological distress
- Women who abuse prescription opioids are more likely to admit to being sexually or physically abused or have a history of psychiatric or psychological problems
- In men, this behavior usually stems from problematic social and behavioral problems that lead to substance abuse

SOURCE: Jamison et al. (2010).
Dependence on Heroin vs. Prescription Opioids

• We can’t assume that patients with prescription opioid dependence (POD) will have the same course of illness and/or response to treatment as those dependent on heroin

• Moore et al. (2007): POD patients more likely to:
  – Earn more income
  – Be hepatitis C-negative
  – Complete treatment
  – Have a higher % of opioid-negative urines

SOURCE: Moore et al. (2007).
Previous Research on Treatment of Opioid Dependence

• Most studies examine heroin addicts receiving methadone maintenance treatment; favor maintenance pharmacotherapy and more counseling

• Findings from **counseling research** in methadone treatment programs may not generalize to office-based buprenorphine treatment

• Findings regarding **length of pharmacotherapy** for heroin addiction may not generalize to prescription opioid addiction

**SOURCES:** Amato et al. (2008); McLellan et al. (1993); Sigmon (2006); Mendelson et al. (2008).
Previous Research on Counseling with Buprenorphine Treatment

• Most studies have focused on primarily heroin-dependent populations
• Fiellin et al. (2006): Examined optimal intensity of counseling for patients receiving office-based buprenorphine maintenance treatment.
  – Only 17% of study participants dependent on prescription opioids
  – 20-minute vs. 45-minute weekly counseling session
  – No difference in outcomes between counseling groups
Prevalence of Lifetime Opioid Use Disorder

Not all substance use leads to abuse or dependence

- Legitimate medical uses exist
- Occasional use may not lead to an SUD diagnosis

The question among many providers is, “What proportion of users do not have abuse or dependence?”

SOURCE: Wu et al. (2011).
Prevalence of Lifetime Opioid Use Disorder

- **Abuse w/o Dep**: 42%
- **Dep**: 7%

**Categories**:
- **PO Only**: 22%
- **PO+Heroin (PO)**: 14%
- **Heroin Only**: 29%
- **PO+Heroin (Heroin)**: 38%

**SOURCE**: Wu et al. (2011).

*Dep = Dependence  PO = Prescription Opioid*
The Medication

Buprenorphine/Naloxone
Buprenorphine

- Partial Opioid Agonist
  - Has effects of typical opioid agonists at lower doses
  - Produces a ceiling effect at higher doses
  - Binds to opioid receptors and is long-acting
- Safe and effective therapy for opioid maintenance and detoxification in adults
- Slow to dissociate from receptors so effects last even if one daily dose is missed.
- FDA approved for use with opioid dependent persons aged 16 and older
Formulations of Buprenorphine

• Buprenorphine is currently marketed for opioid treatment under the trade names:

  - Subutex® (buprenorphine)
  - Suboxone® (buprenorphine/naloxone)
  - Suboxone® Sublingual Film (buprenorphine/naloxone)

• Over 25 years of research
• Over 5,000 individuals received medication during clinical trials
• Proven safe and effective for the treatment of opioid addiction
Clinical trials with opioid dependent adults have established the effectiveness of buprenorphine for the treatment of heroin addiction. Effectiveness of buprenorphine has been compared to:

- **Placebo** (Johnson et al., 1995; Kakko et al., 2003; Ling et al., 1998)
- **Methadone** (Fischer et al., 1999; Johnson, Jaffee, & Fudula, 1992; Ling et al., 1996; Schottenfield et al., 1997; Strain et al., 1994)
- **Methadone and LAAM** (levo-alpha-acetyl-methadol) (Johnson et al., 2000)
Buprenorphine Research Outcomes

• Buprenorphine is as effective as moderate doses of methadone (Fischer et al., 1999; Johnson, Jaffee, & Fudula, 1992; Ling et al., 1996; Schottenfield et al., 1997; Strain et al., 1994).

• Buprenorphine is as effective as moderate doses of LAAM (Johnson et al., 2000).

• Buprenorphine's partial agonist effects make it mildly reinforcing, encouraging medication compliance (Ling et al., 1998).

• After a year of buprenorphine plus counseling, 75% of patients retained in treatment compared to 0% in a placebo-plus-counseling condition (Kakko et al., 2003).
Why did they make two formulations?

Buprenorphine/
Naloxone

Buprenorphine
Advantages of Buprenorphine/Naloxone

• Discourages IV use

• Diminishes diversion
What is the Ratio of Buprenorphine to Naloxone in the Combination Tablet?

- Each tablet contains buprenorphine and naloxone in a **4:1 ratio**
  - Each 8 mg tablet contains 2 mg of naloxone
  - Each 2 mg tablet contains 0.5 mg of naloxone
- Ratio was deemed optimal in clinical studies
  - Preserves buprenorphine’s therapeutic effects when taken as intended sublingually
  - Sufficient dysphoric effects occur if injected by physically dependent persons to discourage abuse
Why Combining Buprenorphine and Naloxone Sublingually Works

• Buprenorphine and naloxone have different sublingual (SL) to injection potency profiles that are optimal for use in a combination product.

<table>
<thead>
<tr>
<th><strong>Sublingual Bioavailability</strong></th>
<th><strong>Injection Potency</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine 40-60%</td>
<td>Buprenorphine ≈ 2:1</td>
</tr>
<tr>
<td>Naloxone 10% or less</td>
<td>Naloxone ≈ 15:1</td>
</tr>
</tbody>
</table>

Areas of Potential Concern about Using Buprenorphine

• General *philosophical opposition* to medication-assisted substance abuse treatment

• *Denial of severity* of addiction by patient and family

• *Diversion potential*

• *Compliance, side effects, drug interactions, storage, and other safety issues*

• *Cost*

• *Appropriate dosing, duration, and taper*
Use of Buprenorphine: Studies on Cost-Effectiveness

• Medication costs are only one factor. Costs of providing treatment also include costs associated with clinic visits, staff time, etc. These costs are greater for methadone.

• A cost-effective comparison of buprenorphine versus methadone for opioid dependence both demonstrated increases in heroin-free days.

• There is no statistically significant difference between the cost-effectiveness for buprenorphine and methadone due to difference in the way that the treatment is provided.

SOURCE: Doran et al. (2003).
Use of Buprenorphine: Studies on Cost-Effectiveness

• Treatment with buprenorphine-naloxone was associated with a reduction in opioid utilization and cost in the first year of follow-up (Kaur & McQueen, 2008).

• Systematic review found good studies supporting buprenorphine as a cost-effective approach to opioid treatment (Doran, 2008).
Use of Buprenorphine: Studies on Cost-Effectiveness

• Another study in Australia found buprenorphine demonstrated lower crime costs and higher quality adjusted life years (QALY), concluding the likelihood of net benefits from substituting buprenorphine for methadone (Harris, Gospodarevshaya, & Ritter, 2005).
Prescription Opioid Addiction Treatment Study

The NIDA CTN Clinical Trial

R. Weiss, MD
Principal Investigator
Harvard Medical School, McLean Hospital

REFERENCES:


The Context of the Study

• While opioids have been used for decades to treat chronic pain, serious concerns about prescription opioid abuse have increased in recent years.

• Most treatment studies of opioid dependent populations have heretofore focused either exclusively or predominantly on heroin users.

• Clinical research over the last 10 years has established sublingual buprenorphine/naloxone as a safe and effective pharmacotherapy for opioid dependence.
The Prescription Opioid Addiction Treatment Study (POATS)

• Largest study ever conducted for prescription opioid dependence – 653 participants enrolled

• Compared treatments for prescription opioid dependence, using buprenorphine-naloxone and counseling

• Conducted as part of NIDA Clinical Trials Network (CTN) at 10 participating sites across U.S.

• Examined detoxification as initial treatment strategy, and for those who were unsuccessful, how well buprenorphine stabilization worked
Key Features of POATS Design

• Adaptive treatment research design approximates clinical practice

• All subjects receive buprenorphine-naloxone

• Start with a less-intensive treatment to see if it works

• Try a more intensive treatment when needed
The Prescription Opioid Addiction Treatment Study (POATS): Design

• Subjects who succeed in **Phase 1** (1-month taper plus 2-month follow-up) are successfully finished with the study

• Subjects who relapse may go into **Phase 2**:  
  — Re-randomized to SMM or SMM + ODC in Phase 2  
  — 3 months of BUP-NX stabilization,  
  — 1-month taper off BUP-NX,  
  — 2 months of follow-up
Study Design - Phase 1

Randomization

SMM

SMM + ODC

Week

1-2 Bup/nx

3-4 Taper

5-12 FU

Successful

Unsuccessful

Phase 2
Study Design - Phase 2

Randomization

SMM

SMM + ODC

Week 1-12 Bup/nx

Successful

Unsuccessful

Week 13-16 Taper

Week 17-24 FU

Successful

Unsuccessful
Study Design – Both Phases

**Phase 1**

Randomization

- SMM
- SMM + IDC

Week
- 1-2 Bup/Inx
- 3-4 Taper
- 5-12 FU

Successful

Unsuccessful

**Phase 2**

Randomization

- SMM
- SMM + ODC

Week
- 1-12 Bup/Inx
- 13-16 Taper
- 17-24 FU

Successful

Unsuccessful
Study Locations

WA: Providence Behavioral Health Svc
OR: ADAPT, Inc.
CA: SF General Hospital
CA: UCLA ISAP
SC: Behavioral Health Services of Pickens Co
IN: East Indiana Treatment Center
WV: Chestnut Ridge Hospital
NY: Bellevue Hospital Center
NY: St. Luke's Roosevelt Hospital Center
MA: McLean Hospital
Key Eligibility Criteria

• DSM-IV opioid dependence
• ≥ 20 days opioid use in past 30
• Additional SUDs eligible if not requiring immediate medical treatment
• Non-psychotic, psychiatrically stable
### Inclusion/Exclusion Study Criteria

**Inclusion**
- Informed Consent
- Age $\geq 18$
- Birth control
- Able to meet study requirements
- Opioid Dependence
- Medical help for withdrawal
- Stable physical health
- Psychiatrically stable
- Locator Information
- Prior to inductions, COWS $>8$
- For pain, clearance to withdraw
- Methadone for pain $<40\text{mg/day}$

**Exclusion**
- Medical condition
- Allergy/sensitivity to meds
- Severe psychiatric condition
- Suicide risk in past 30 days
- ETOH/Sed/Stim dependence
- Clinical trial participant (30 d)
- Opioid maintenance tx (30 d)
- Pending legal issues
- Preg/lactating/no birth control
- Leaving local area during study
- LFT $>5\times$ upper normal limit
- Surgery scheduled (6 m)
- Current SUD treatment

---

**Current participation in formal substance abuse treatment**
(only if not self-help groups)
Factors in Defining a Study Population of Subjects with Prescription Opioid Dependence

• Heroin use

• Chronic pain
Heroin Use

• Previous studies of opioid dependence included mostly subjects with heroin dependence.

• The POATS sample needed to broadly represent people dependent upon prescription opioids. Some of these people would use heroin to varying extents.
Heroin-Related Exclusion Criteria

• >4 days of heroin use in past 30 days
• Ever met criteria for opioid dependence as a result of heroin use alone
• Ever injected heroin

SOURCE: Potter et al. (2010).
Chronic Pain

- Many, but not all, subjects with POD have been prescribed opioids for pain

- “Prescription” use ≠ pain

- Some people with pain obtain opioids illicitly
Pain-Related
Inclusion/Exclusion Criteria

• Subjects prescribed opioids for pain were included only if approved by prescribing physician
• Cancer pain excluded
• No traumatic or major pain event within past 6 months
• Subjects expressed interest in stopping opioids
Heroin and Chronic Pain
Design Decisions

Subjects were stratified on the basis of

• Presence/absence of current chronic pain

• Lifetime history of heroin use
POATS Study Questions

• Does adding individual drug counseling to buprenorphine-naloxone (BUP-NX) + standard medical management (SMM) improve outcome?
  – May be a proxy for drug abuse treatment program vs. office-based opioid treatment

• Is initial detox strategy successful for subjects?
POATS Study Questions (cont.)

• For those who fail the initial phase, does adding individual drug counseling to buprenorphine-naloxone (BUP-NX) + standard medical management (SMM) improve outcome when administered over a longer stabilization period?

• Do answers vary according to (1) presence of current chronic pain, or (2) a lifetime history of any heroin use?
Study Treatments
Buprenorphine-Naloxone

• Subjects received 8-12 mg on Day 1
• Allowable dose was 8-32 mg/day
• Target dose was 16 mg/day, but flexible dosing allowed
• Once-daily dosing recommended
• Lost prescriptions were not refilled
Standard Medical Management

• Manualized treatment*
• Weekly visits with buprenorphine-certified physician
• Initial visit: 45-60 min; f/u visits 15-20 min
• Assess substance use, craving, medication response
• Recommend abstinence, self-help

*SOURCE: Fiellin et al. (1999).
Individual Opioid Drug Counseling

- Manualized drug counseling*, based on previous successful counseling manuals
- 45-60 min visits
- Phase 1: 2x/week
- Phase 2: 2x/wk for 6 weeks, 1x/wk for 6 weeks

*SOURCE: Pantalon et al. (1999).
Individual Opioid Drug Counseling (cont.)

- Provide education about addiction and recovery
- Recommend abstinence
- Recommend self-help
- Provide skills-based interactive exercises and take-home assignments
- Address relapse prevention issues including: high-risk situations, managing emotions, and dealing with relationships

Description of the Study Population

N=653 in Phase 1
Baseline Stratification Factors and Sociodemographic Characteristics

Mean Age = 32.7 years
Mean Years Education = 13 years

- Lifetime Heroin Use: 23%
- Chronic Pain: 42%
- Female: 40%
- Caucasian: 91.4%
- Hispanic: 4.7%
Participant Demographics

### Employment Status

- **Full Time**: 62.9%
- **Part Time**: 10%
- **Unemployed**: 12.6%

### Marital Status

- **Never**: 50.1%
- **Married**: 27.6%
- **Divorced**: 15.5%
No significant differences between subjects assigned to SMM vs. SMM + ODC
# Prevalence of Other Substance Use Disorders

<table>
<thead>
<tr>
<th>Substance</th>
<th>Past Year</th>
<th>Lifetime</th>
<th>Ab = Abuse</th>
<th>Dep = Dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>10%</td>
<td>60%</td>
<td>60%</td>
<td>10%</td>
</tr>
<tr>
<td>Cannabis</td>
<td>4%</td>
<td>47%</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Cocaine</td>
<td>5%</td>
<td>32%</td>
<td>15%</td>
<td>5%</td>
</tr>
<tr>
<td>Sed/Hyp</td>
<td>6%</td>
<td>25%</td>
<td>3%</td>
<td>18%</td>
</tr>
<tr>
<td>Stimulant</td>
<td>3%</td>
<td>22%</td>
<td>11%</td>
<td>11%</td>
</tr>
</tbody>
</table>

(Ab = Abuse, Dep = Dependence)
# Days of Use - Past 30 Days

<table>
<thead>
<tr>
<th>Substance</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opioid analgesics</strong></td>
<td></td>
</tr>
<tr>
<td>Cannabis</td>
<td>4.9 (9.4)</td>
</tr>
<tr>
<td><strong>Sedatives/hypnotics (not barbiturates)</strong></td>
<td>3.8 (7.9)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>3.0 (6.0)</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>0.5 (3.3)</td>
</tr>
<tr>
<td>Cocaine</td>
<td>0.5 (2.0)</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>0.2 (2.0)</td>
</tr>
<tr>
<td>Heroin</td>
<td>0.1 (0.6)</td>
</tr>
</tbody>
</table>
## Other Baseline Substance Use Characteristics

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Mean years of opioid use</td>
<td>4.5</td>
</tr>
<tr>
<td>Current cigarette smoker</td>
<td>70.6%</td>
</tr>
</tbody>
</table>
**Most Frequently Used Opioids in Past 30 Days**

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone (sustained)</td>
<td>35%</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>32%</td>
</tr>
<tr>
<td>Oxycodone (immediate)</td>
<td>19%</td>
</tr>
<tr>
<td>Methadone</td>
<td>6%</td>
</tr>
<tr>
<td>Other</td>
<td>8%</td>
</tr>
</tbody>
</table>
Of those who received any treatment (N=210)*:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-help</td>
<td>124 (59%)</td>
</tr>
<tr>
<td>Inpatient/residential</td>
<td>88 (42%)</td>
</tr>
<tr>
<td>Outpatient counseling</td>
<td>84 (40%)</td>
</tr>
<tr>
<td>Methadone maintenance</td>
<td>64 (31%)</td>
</tr>
<tr>
<td>Buprenorphine maintenance</td>
<td>46 (22%)</td>
</tr>
<tr>
<td>Intensive outpatient</td>
<td>33 (16%)</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Other medications</td>
<td>11 (5%)</td>
</tr>
</tbody>
</table>

*Subjects could endorse >1 type of treatment.
## Buprenorphine Doses Prescribed

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 mg 8%</td>
<td>8 mg -</td>
</tr>
<tr>
<td>12 mg 18%</td>
<td>12 mg 14%</td>
</tr>
<tr>
<td><strong>16 mg 38%</strong></td>
<td><strong>16 mg 27%</strong></td>
</tr>
<tr>
<td>20 mg 10%</td>
<td>20 mg 14%</td>
</tr>
<tr>
<td>24 mg 13%</td>
<td>24 mg 16%</td>
</tr>
<tr>
<td>32 mg -</td>
<td>32 mg 11%</td>
</tr>
<tr>
<td>Other 13%</td>
<td>Other 18%</td>
</tr>
</tbody>
</table>
Counseling Attendance*

*Not significantly different
Results
Study Question #1: Does adding individual opioid drug counseling (ODC) to buprenorphine-naloxone + Standard Medical Management (SMM) improve outcome?
### Phase 1 Successful Outcome
**(N=653)**

<table>
<thead>
<tr>
<th>SMM+</th>
<th>SMM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6%</td>
<td>7%</td>
<td>0.45</td>
</tr>
</tbody>
</table>

**Phase 1 Successful Outcome Criteria**
- ≤ 4 days opioid use per month
- Absence of 2 consecutive opioid-positive urine tests results
- No more than 1 missing urine sample during the 12 weeks
- No other formal substance abuse treatment
- No injection of opioids
Phase 2 Successful Outcome
(n=360)

<table>
<thead>
<tr>
<th>SMM+ ODC</th>
<th>SMM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 12</td>
<td>52%</td>
<td>47%</td>
</tr>
</tbody>
</table>

(end of stabilization)

**Phase 2 Successful outcome criteria**
- Abstinent for ≥ 3 of final 4 weeks (including final week) of bup-nx stabilization (urine-confirmed self-report)
### Phase 2: Successful Outcome at End of Taper & at Follow-up

<table>
<thead>
<tr>
<th></th>
<th>SMM+ ODC</th>
<th>SMM</th>
<th>Overall</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 16 (end of taper)</strong></td>
<td>28%</td>
<td>24%</td>
<td>26%</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Week 24 (8 wks post-taper)</strong></td>
<td>10%</td>
<td>7%</td>
<td>9%</td>
<td>0.2</td>
</tr>
</tbody>
</table>
Study Question #2:
How does length of buprenorphine-naloxone treatment affect outcomes in subjects with prescription opioid dependence?
## Successful Outcomes at 3 Time Points

<table>
<thead>
<tr>
<th>Phase</th>
<th>Event Description</th>
<th>Success</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 1</strong></td>
<td>4-week taper + 8 weeks f/u</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Phase 2</strong></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>
Percent Opioid Positive Urine over Time

(EMM = SMM+ODC)
Percent Opioid Positive Urine over Time

Phase 2

(EMM = SMM+ODC)
Percent Opioid Positive Urine over Time

Phase 1

Phase 2

(EMM = SMM+ODC)
Predictors of Outcome
## Variables: Phase 2, Week 12

<table>
<thead>
<tr>
<th></th>
<th>Success</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>47%</td>
<td>0.48</td>
</tr>
<tr>
<td>Female</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>49%</td>
<td>0.56</td>
</tr>
<tr>
<td>Not White</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>72%</td>
<td>*</td>
</tr>
<tr>
<td>Not Hispanic</td>
<td>48%</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>47%</td>
<td>0.23</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>56%</td>
<td></td>
</tr>
</tbody>
</table>

*Not tested because of small sample with Spanish origin (5%).
## Phase 2 Outcome Predictors: Lifetime Heroin Use

<table>
<thead>
<tr>
<th>Heroin use</th>
<th>Success</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 12 end of stabilization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>37%</td>
<td>0.002</td>
</tr>
<tr>
<td>No</td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td><strong>Week 24 8 weeks post-taper</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5%</td>
<td>0.13</td>
</tr>
<tr>
<td>No</td>
<td>10%</td>
<td></td>
</tr>
</tbody>
</table>
Chronic Pain Subject Outcomes
Chronic Pain Subjects (n=274)

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain severity (0-10)</td>
<td>4.4 (2.17)</td>
</tr>
<tr>
<td>Pain interference (0-10)</td>
<td>4.2 (2.67)</td>
</tr>
<tr>
<td>Course</td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>43.1%</td>
</tr>
<tr>
<td>Intermittent</td>
<td>54.7%</td>
</tr>
<tr>
<td>Duration</td>
<td></td>
</tr>
<tr>
<td>&gt; 1 year</td>
<td>81.4%</td>
</tr>
<tr>
<td>&gt; four years</td>
<td>54.7%</td>
</tr>
</tbody>
</table>
# Chronic Pain Location

<table>
<thead>
<tr>
<th>Location</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head/face</td>
<td>16.1%</td>
</tr>
<tr>
<td>Chest/abdomen</td>
<td>5.5%</td>
</tr>
<tr>
<td>Upper extremities</td>
<td>29.6%</td>
</tr>
<tr>
<td>Cervical</td>
<td>27.0%</td>
</tr>
<tr>
<td>Thoracic</td>
<td>26.3%</td>
</tr>
<tr>
<td>Lumbar/sacral</td>
<td>65.0%</td>
</tr>
<tr>
<td>Lower extremities</td>
<td>52.9%</td>
</tr>
<tr>
<td>Multiple spinal areas</td>
<td>36.1%</td>
</tr>
</tbody>
</table>
### Chronic Pain (CP) vs. no CP: Sociodemographics

<table>
<thead>
<tr>
<th></th>
<th>CP (n=274)</th>
<th>No CP (n=379)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female</strong></td>
<td>42.3%</td>
<td>38.3%</td>
</tr>
<tr>
<td><strong>Age, in years</strong></td>
<td>35.4 (10.3)</td>
<td>30.8 (9.7)</td>
</tr>
<tr>
<td><strong>Caucasian</strong></td>
<td>91.2%</td>
<td>93.1%</td>
</tr>
<tr>
<td><strong>Years of education</strong></td>
<td>12.9 (2.3)</td>
<td>13.1 (2.1)</td>
</tr>
</tbody>
</table>

**statistically significant difference (p-value= 0.001)**
Chronic Pain Subjects were...

• No more likely to drop-out or terminate from Phase 1
• Equally likely to enter Phase 2
• No more likely to have an adverse event (AE) or serious adverse event (SAE)
## Chronic Pain and Outcome

<table>
<thead>
<tr>
<th>Phase 2 Week 12 (end of stabilization)</th>
<th>Success</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Pain</td>
<td>53.0%</td>
<td>0.22</td>
</tr>
<tr>
<td>No</td>
<td>46.5%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase 2 Week 24 (8 weeks post-taper)</th>
<th>Success</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Pain</td>
<td>9.4%</td>
<td>0.60</td>
</tr>
<tr>
<td>No</td>
<td>8.1%</td>
<td></td>
</tr>
</tbody>
</table>
Imaging Study
Highly Selected Cohort

Demographics not different from larger sample

SOURCE: Upadhyay et al. (2010).
Gray Matter Changes: Amygdala Volume Decrease

SOURCE: Upadhyay et al. (2010).
Imaging Study: Summary

- Prescription opioid dependence is associated with structural and functional changes in brain regions implicated in the regulation of affect and impulse control, reward and motivational functions.

- Might have clinical implications for understanding long-term effects of treatment strategies for prescription opioid use.

SOURCE: Upadhyay et al. (2010).
Implications of the POATS Study
Take Home Messages

• Tapering from buprenorphine-naloxone, whether initially or after a period of substantial improvement, led to nearly universal relapse

• SMM produced outcomes equal to SMM + individual opioid drug counseling

• Patients with chronic pain had outcomes equal to those without chronic pain
Questions for the Future

• What is the effect of a lower intensity medical management (MM)?
  • Weekly SMM is more intensive than is often provided in the community
  • There was no low-intensity MM condition

• What are the outcomes of using buprenorphine-naloxone with prescription opioid-dependent adolescents?

• What is the optimal rate and length of taper of buprenorphine-naloxone after prolonged treatment stabilization?
Interactive Activity #2: “Gallery Walk”

Questions for easel pad:

1. Before today, what were your thoughts about medication-assisted treatment?

2. What challenges do you see regarding the provision of medication-assisted treatment for those addicted to prescription opioids?

3. What are the advantages of medication-assisted treatment for prescription opioid addiction?
Interactive Activity #2: “Gallery Walk”

4. What further research do you think is needed regarding medication-assisted treatment?

5. As a result of this workshop how have your opinions changed regarding medication-assisted treatment for prescription opioid addiction?