NEW MEDICATION DELIVERY SYSTEMS FOR OPIOID USE DISORDER

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Braeburn Pharmaceuticals – Research funding
Overview

- The Opioid Epidemic and Opioid Use Disorder (OUD)
- The big three: methadone, buprenorphine and naltrexone
- The rationale for long-acting medications in OUD
- Buprenorphine implants
  - The evidence base
  - Most recent data
  - FDA approval - May 2016
  - What’s a clinician to do?
  - What’s in the Pipeline?
Opioid Abuse is Epidemic in the United States

In 2014:
- ~2 million Americans abused/dependent on prescription opioids
- >70% of abused opioids obtained from friends or family
- ~772,000 sought treatment for prescription pain meds
- Greatest increases in heroin use in groups with historically low rates:
  - Women, the privately insured, and people with higher incomes.
- Heroin increased >2X among 18 to 25 year olds in last 10 years
- In 2014, >14,000 people died from overdoses involving prescription opioids, and >10,500 from heroin overdoses.

Increasing Prevalence of Heroin Use & Dependence: 2002-2011

+ Difference between this estimate and the 2014 estimate is statistically significant at the .05 level.

Results from the 2011 National Survey on Drug Use and Health

Most Recent Treatment Received in Past Year for Pain Relievers, Aged 12 or Older, by Age Group: 2002-2014

+ Difference between this estimate and the 2014 estimate is statistically significant at the .05 level.

Han B, Hedden SL, and Lipari R; RTI International: Copello EAP and Kroutil LA. Receipt of Services for Behavioral Health Problems: Results from the 2014 National Survey on Drug Use and Health
Most Recent Treatment in the Past Year for Heroin, Aged 12 or Older, by Age Group: 2002-2014

+ Difference between this estimate and the 2014 estimate is statistically significant at the .05 level.

Han B, Hedden SL, and Lipari R; RTI International: Copello EAP and Kroutil LA. Receipt of Services for Behavioral Health Problems: Results from the 2014 National Survey on Drug Use and Health

Nonmedical Pain Reliever Use among Nonmedical Psychotherapeutic Drug Users Aged ≥12 - 2014

- 6.5 Million Current Nonmedical Users of Psychotherapeutic Drugs
- 4.3 Million Current Nonmedical Users of Pain Relievers (66.2%)

Drug Overdose Deaths Involving Opioids By Type Of Opioid — United States, 2000–2014

Rudd et al., Increases in Drug and Opioid Overdose Deaths — United States, 2000–2014

*MMWR*
Jan 1, 2016 / 64(50);1378-82
Necessity of Medical Treatment for OUD

- Detoxification from opioids alone is typically insufficient
- High relapse rates after standard detoxification\(^1\)
- Relapse rates >50% 1 month after discontinuation of Bup maintenance\(^2\)
- Higher Bup doses associated with pre-induction 30-day heroin, IV use frequency, craving and withdrawal\(^3\)
- Lower Bup maintenance doses associated with lower relapse risk 1 month post taper \((p=0.04)\)^2
Buprenorphine: Limitations of Sublingual/ Buccal Transmucosal Formulations

- Missed doses, low adherence to treatment
- Variable exposure with risk of withdrawal
- Abuse, theft, and intentional diversion
- Accidental exposure: especially increased child ED visits
  - \( \approx 1,499 \) children <6 years evaluated in U.S. emergency departments for buprenorphine-product ingestions in 2010-11 (0 reported in 2004)
  - 9.5% of emergent hospitalizations for drug ingestion by children <6, greater proportion than any other medication

Emergency Department Visits and Hospitalizations for Buprenorphine Ingestion by Children — United States, 2010–2011. MMWR, Jan 25, 2013 / 62(03);56-56
Rationale for Sustained Release Implant Formulation

- Maintain efficacy, but minimize misuse/diversion
- Reduce dosing frequency
- Increase adherence
- Stabilize blood levels over 6 months
Plasma Pharmacokinetics

Probuphine Implant Description

- Sustained-release polymeric matrix of buprenorphine in ethyl vinyl acetate (EVA)
- Matchstick size: 26mm long
- 80mg of buprenorphine
- Continuous buprenorphine levels for 6 months
Implantation Procedure

- Under local anesthesia implants are inserted subdermally into the inner side of the upper arm in a 10-15 minute in-office procedure.
- Single 2.5- to 3-mm incision in the inner upper arm.
- Implants inserted one at a time 2-3 mm below the skin using a custom-designed applicator.
- 24 hour pressure dressing greatly reduces post-op adverse events.
- Sustained release of buprenorphine for 6 months.
- At the end of each 6-month period, implants are removed in a brief, in-office procedure using a custom-designed clamp.
Insertion Applicator
Insertion Location
Placement of Implants
24-week Placebo Controlled Trials of BUP Implants

Summary of Significant Findings of Implant Against Placebo (2 trials):

- Higher mean % urines negative for illicit opioids, weeks 1-24
- Higher retention rate: 64-66 % vs. 26-31 %
- Lower incidence of clinician-rated and patient-rated opioid withdrawal symptoms
- Lower patient-rated opioid craving
- Greater change on the clinician global ratings of improvement
- Decreased Supplemental Buprenorphine Use
Percentage of Urine Samples Opioid Negative Weeks 1–24 in 2 Placebo Controlled Trials

*Wilcoxon rank sum (van Elteren) with gender and site as blocking variables*
Open Label SL Buprenorphine

- In second trial, the implants were non-inferior to open label group continued at 12-16 mg SL Bup
- However:
  - increased subjective and objective withdrawal symptoms
  - Increased use of 2mg SL Bup rescue doses
- Unclear how transition to implants from SL Bup would affect clinical stability in patients who are already clinically stable

Double **Blind** Double Dummy Study of Buprenorphine Implants and SL Buprenorphine Study:

- Head-to-head safety/efficacy trial of Bup implants and daily SL Bup on long-term remission in (N=177) patients stabilized on ≤8mg of SL Bup
- Responder rate defined as at least four of six study months with no evidence of illicit opioid use by urine test or self-report

Double Blind Double Dummy Study of Buprenorphine Implants and SL Buprenorphine

Summary:
♦ Transitioning to implants was not clinically destabilizing (e.g., increased craving or withdrawal symptoms).
♦ 96.4 vs 87.6% had no opioid-positive urine tests for at least four of the six study months ($P < .001$ non-inferiority; $P = .03$ superiority)
♦ Higher 6-month abstinence rate in the implant group 85.7% vs. 71.9% in the SL Bup group ($P < .03$; NNT=7.25 )

Double **Blind** Double Dummy Study of Buprenorphine Implants and SL Buprenorphine

**Implications:**

- Bup implants effective for maintenance of abstinence in opioid-dependent adults clinically stable on ≤ 8mg/d SL Bup.
- Boost maintenance of abstinence in appropriate patients while reducing the risk of diversion and adverse events.
- Patients doing well at moderate SL doses in OTPs that could transition to office-based care.
- Proposed new targets: criminal justice, other hard-to-reach populations.\(^2\)
- Issues with generalizability: most participants were white, domiciled, employed, ≥ HS education, and primarily prescription OUD.

Risk Evaluation and Mitigation Strategy

- Required REMS for Providers: probuphinerems.com
- DEA Waiver to prescribe or dispense BUP Implant.
- Must have performed at least one qualifying surgical procedure in the last 3 months under local anesthesia using aseptic technique, including, at a minimum, making skin incisions, or placing sutures.
- Prior to performing insertions or prescribing BUP implants Providers must successfully complete a live training program on the insertion and removal procedures and become certified in the PROBUPHINE REMS program.
Risk Evaluation and Mitigation Strategy

Acceptable transmucosal BUP doses for conversion:

- Buprenorphine sublingual tablet (Subutex or generic) 8 mg or less
- Buprenorphine/naloxone (Suboxone or generic) SL tablet 8 mg/2 mg or less
- Buprenorphine/naloxone buccal film (Bunavail) 4.2 mg/0.7 mg or less
- Buprenorphine/naloxone (Zubsolv) SL tablets 5.7 mg/1.4 mg or less
Pipeline

- At least 2 different companies testing subcutaneous liquid depot injections of buprenorphine that transform in contact with bodily fluids.
  - Biodegradable polylactide-co-glycolide polymer and biocompatible solvent (N-methyl-pyrrolidone) (RBP-6000)
  - Reversed-phase “water-in-oil” liquid crystal nanoparticle gel (CAM 2038)
- Ongoing randomized trials testing efficacy of weekly and monthly injections.
- Potential opportunity to vary dose clinically by changing the volume of depot injected.

Developing Pharmacological Treatments for Treating Alcohol Use Disorder

Lorenzo Leggio, M.D., Ph.D., M.Sc.
Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology (CPN)
Joint NIAAA – NIDA Lab
Brown University Center for Alcohol and Addiction Studies
FDA-approved Medications:
Disulfiram
Naltrexone
Acamprosate
<table>
<thead>
<tr>
<th>Medication</th>
<th>Activity</th>
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</table>
Baclofen in Alcoholism: Summary of Preclinical Studies

In animal models, baclofen reduces:

- Extra amount of alcohol consumes after a period of abstinence (Colombo et al. Drug Dep 2003)
- Motivational properties of alcohol (Colombo et al. Psychopharmacology 2003)
Baclofen in a Double-blind Controlled Randomized Study

\[ F_{\text{treat}}(1,78)=5.65 \quad p<0.05 \]

\[ F_{\text{treat}}(1,78)=4.60 \quad p<0.05 \]

\[ F_{\text{treat}}(1,78)=5.06 \quad p<0.05 \]

\[ F_{\text{treat}}(1,78)=10.71; \quad p<0.005 \]

Addolorato et al. Alcohol Alcohol 2002
Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study

Giovanni Addolorato, Lorenzo Leggio, Anna Ferrulli, Silvia Cardone, Luisa Vonghia, Antonio Mirijello, Ludovico Abenavoli, Cristina D’Angelo, Fabio Caputo, Antonella Zambon, Paul S Haber, Giovanni Gasbarrini
Trial Flow-chart & Results

148 consecutively screened for the study
84 randomised

- 42 placebo
  - 29 completed
    - 12 abstinents
    - 9 lapses
    - 21 relapses
- 13 dropouts
  - 8 lost to follow-up
  - 3 non-compliance
  - 2 condition worsened

- 42 badofen
  - 36 completed
    - 30 abstinents
    - 3 lapses
    - 9 relapses
  - 6 dropouts
    - 4 lost to follow-up
    - 1 non-compliance
    - 1 condition worsened

$30.8 \pm 5.5 \quad p = 0.0002 \quad CAD: 30.8 \pm 5.5$

$62.8 \pm 5.4 \quad p = 0.001 \quad CAD: 62.8 \pm 5.4$
Baclofen & Liver Tests

- **Alanine aminotransferase**
  - Placebo vs Baclofen
  - Mean (U/L)
  - **p = 0.0195**

- **Bilirubin**
  - Placebo vs Baclofen
  - Mean (g/L)
  - **p = 0.0318**

- **International normalised ratio**
  - Placebo vs Baclofen
  - Mean
  - **p = 0.0140**

- **Albumin**
  - Placebo vs Baclofen
  - Mean (g/L)
  - **p < 0.0001**
Efficacy and Safety of Baclofen for Alcohol Dependence: A Randomized, Double-Blind, Placebo-Controlled Trial

James C. Garbutt, Alexei B. Kampov-Polevoy, Robert Gallop, Linda Kaika-Juhl, and Barbara A. Flannery

The graphs show the percentage of abstinent days and percent of heavy drinking days over time for placebo and baclofen groups. The x-axis represents time points from baseline to 12 months, and the y-axis shows the percentage values.
Differences Between European & US Baclofen-Treated Alcoholic Patients

Table 2. Drinking and Psychometric Characteristics of US and European Trials

<table>
<thead>
<tr>
<th>Trial Design</th>
<th>US Trial [49]</th>
<th>European Trial [47]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIWA-Ar Score</td>
<td>2.36 (±2.4)</td>
<td>12.3 (±9.1)</td>
</tr>
<tr>
<td>Years of Alcohol Dependence</td>
<td>14.5 (±11.4)</td>
<td>12.6 (±4.8)</td>
</tr>
<tr>
<td>Drinks/Day</td>
<td>7.0 (±3.5)</td>
<td>14.2 (±6.8)</td>
</tr>
<tr>
<td>Craving</td>
<td>15.7 (±5.6) (PACS; max = 30)</td>
<td>23.8 (±6.9) (OCDS; max = 47)</td>
</tr>
<tr>
<td>Zung Depression Inventory (Range= 20-80)</td>
<td>36.2 (±9.4)</td>
<td>40.7 (±10.3)</td>
</tr>
<tr>
<td>Spielberg State Anxiety (Range= 20-80)</td>
<td>38.0 (±11.4)</td>
<td>47.5 (±12.2)</td>
</tr>
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Leggio et al. CNS & Neurological Disorders - Drug Targets 2010
Baclofen and Alcoholism:

<table>
<thead>
<tr>
<th>Total alcohol abstinence (n [%])</th>
<th>Odds ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Baclofen</td>
</tr>
<tr>
<td>Child-Pugh A*</td>
<td>1/6 (17)</td>
<td>3/4 (75)</td>
</tr>
<tr>
<td>Child-Pugh B</td>
<td>5/20 (25)</td>
<td>12/20 (60)</td>
</tr>
<tr>
<td>Child-Pugh C</td>
<td>6/16 (38)</td>
<td>15/18 (83)</td>
</tr>
<tr>
<td>Total</td>
<td>12/42 (29)</td>
<td>30/42 (71)</td>
</tr>
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*Point and interval odds ratio estimates and relative p values were calculated using exact logistic regression.

Table 4: Total alcohol abstinence by Child-Pugh classification

Short Communication

Baclofen promotes alcohol abstinence in alcohol dependent cirrhotic patients with hepatitis C virus (HCV) infection

L. Leggio a,b,*, A. Ferrulli b, A. Zambon c, F. Caputo d, G.A. Kenna a, R.M. Swift a, G. Addolorato b

a Center for Alcohol and Addiction Studies, Brown University, Providence, RI, USA
b Institute of Internal Medicine, Catholic University of Rome, Italy
c Unit of Biostatistics and Epidemiology, Department of Statistics, University of Milan-Bicocca, Milan, Italy
d Department of Internal Medicine, SS Annunziata Hospital, Centro (Ferrara), Italy

Fig. 1. Fig. 1 shows that, with respect to the placebo group (3 out of 12, 25.0%), a significantly higher number of alcohol-dependent HCV-infected cirrhotic patients achieved and maintained total alcohol abstinence in the baclofen group (10 out of 12, 83.3%; p = 0.0123, Fisher’s exact test).
The GABA B agonist baclofen reduces cigarette consumption in a preliminary double-blind placebo-controlled smoking reduction study

Teresa R. Franklin *, Derek Harper, Kyle Kampman, Susan Kildea-McCrea, Will Jens, Kevin G. Lynch, Charles P. O’Brien, Anna Rose Childress

Baclofen (80mg/day) vs. Placebo: Cigarettes per day (CPD) p<0.05
A preliminary double-blind, placebo-controlled randomized study of baclofen effects in alcoholic smokers

Lorenzo Leggio • William H. Zywiak • Steven M. Edwards • Jennifer W. Tidey • Robert M. Swift • George A. Kenna
Baclofen in Alcoholic Smokers: A Randomized Controlled Study

Baclofen increases alcohol-tobacco co-abstinence days in alcoholic smokers.
Severity of Alcohol Dependence Moderated Baclofen Effect

% days abstinence from alcohol-tobacco co-use

Low ADS (< 14.5)  High ADS (> 14.5)

p < .001

- Placebo
- Baclofen
Baclofen in Alcoholic Smokers: A Randomized Controlled Study cont’d

\[ p < .001 \]
Baclofen in Alcohol Use Disorder: Summary

- Baclofen is safe and effective to treat alcoholic patients, especially those with liver disease (Addolorato, Leggio et al. Lancet 2007, Leggio et al. Addict Behav 2012)
- Baclofen in Internal Medicine/Liver clinical settings:
  - Baclofen is used off-label to treat some alcoholic patients
  - Both EASL and AASLD have included baclofen in their recent guidelines
    - (EASL. J Hepatol 2012, Runyon, AASLD. Hepatology, 2013)
- While some patients benefit from baclofen (e.g. alcoholic smokers? Alcoholic patients with high severity?), others do not
- Large RCT are needed to confirm these findings
Beyond Baclofen: Addiction Medicine in Clinical Practice

- Beyond baclofen, this may serve as an example of integration among Psychiatry, Addiction & medicine fields & expertise toward a multidisciplinary approach
  (Lee and Leggio, Am J Psychiatry, 2015)

- This integration becomes more and more important, especially in a new area where effective treatments for HCV are available.

- If the use of these new treatments for HCV will be accessible to all patients, it is likely that AUD (and obesity) will represent the main etiologies of advanced liver disease in Medicine
  (Leggio and Lee, AM J Med in Press)
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α₁-noradrenergic receptor antagonism blocks dependence-induced increases in responding for ethanol

Brendan M. Walker, Dennis D. Rasmussen, Murray A. Raskind, George F. Koob

1Molecular and Integrative Neurosciences Department
2Committee on the Neurobiology of Addictive Disorders, The Scripps Research Institute, La Jolla, CA, USA
3VA Puget Sound Health Care System and Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, USA

Fig. 2. Mean (+ S.E.M.) responses for ethanol during 30-min sessions that occurred twice weekly following prazosin (0.0–2.0 mg/kg) administration in nondependent and ethanol-dependent animals during acute withdrawal. At higher doses, prazosin decreased ethanol self-administration in both nondependent and ethanol-dependent animals (*P < .05 compared to air-exposed vehicle dose; **P < .01, and ***P < .001 compared to vapor-exposed vehicle dose).

Fig. 3. Mean (+ S.E.M.) responses for ethanol during 30-min sessions in nondependent and ethanol-dependent animals following 0.0 and 1.5 mg/kg prazosin. Prazosin (1.5 mg/kg) attenuated ethanol self-administration in ethanol-dependent animals (***P < .001), leaving nondependent self-administration intact.
The $\alpha_1$-Adrenergic Receptor Antagonist, Prazosin, Reduces Alcohol Drinking in Alcohol-Preferring (P) Rats

Dennis D. Rasmussen, Laura L. Alexander, Murray A. Raskind, and Janice C. Froehlich

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**Fig. 1.** Initial 2-day treatment: Effects of IP prazosin administration on 2-hour alcohol (15% v/v) intake by adult male alcohol-preferring P rats. Prazosin was injected on each of 2 consecutive days, identified as drug days 1 and 2, at 15 minutes prior to onset of a 2-hours, 2 bottle free-choice between alcohol and water. "p < 0.05 and "p < 0.01 versus saline control treatment within individual days. "p < 0.05 versus Praz 0.5 and Praz 1.5, p < 0.05 versus Praz 1.0 treatment. Each bar represents the mean ± SE of 11 rats.
A Pilot Trial of the Alpha-1 Adrenergic Antagonist, Prazosin, for Alcohol Dependence

Tracy L. Simpson, Andrew J. Saxon, Charles W. Meredith, Carol A. Malte, Brittney McBride, Laura C. Ferguson, Christopher A. Gross, Kim L. Hart, and Murray Raskind

Fig. 1. Mean days drinking per week and standard drinks among male study completers by study condition.
# A1-Blockade To Treat Alcoholism: Prazosin & Doxazosin

<table>
<thead>
<tr>
<th></th>
<th>Prazosin</th>
<th>Doxazosin</th>
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<tbody>
<tr>
<td>Most common commercial name</td>
<td>Minipress®</td>
<td>Cardura®</td>
</tr>
<tr>
<td>FDA approval</td>
<td>HTN, BPH</td>
<td>HTN, BPH</td>
</tr>
<tr>
<td>α₁ subtypes targeted</td>
<td>α₁A, α₁B, α₁D</td>
<td>α₁A, α₁B, α₁D</td>
</tr>
<tr>
<td>t₁/₂</td>
<td>2.5 hours</td>
<td>~22 hours</td>
</tr>
<tr>
<td>Maximum daily dose</td>
<td>16mg</td>
<td>16mg</td>
</tr>
<tr>
<td>Daily titration</td>
<td>3 times</td>
<td>once</td>
</tr>
<tr>
<td>Fasting requirement</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Side-effects</td>
<td>First-dose phenomenon, hypotension, syncope, drowsiness, tiredness, headache</td>
<td>Similar to prazosin, but less frequent, especially BP-related side-effects</td>
</tr>
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Role of the $\alpha_1$ blocker doxazosin in alcoholism: a proof-of-concept randomized controlled trial

George A. Kenna¹, Carolina L. Haass-Koffler²,³, William H. Zywiak¹,⁴, Steven M. Edwards⁵, Michael B. Brickley², Robert M. Swift¹,⁶ & Lorenzo Leggio²,³

Departments of Psychiatry and Human Behavior¹ and Behavioral and Social Sciences², Center for Alcohol and Addiction Studies, Brown University, Providence, RI, USA, Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology, National Institute on Alcohol Abuse and Alcoholism, National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD, USA², Decision Sciences Institute, PIRE, Pawtucket, RI, USA³, Department of Psychology, University of Nebraska-Lincoln, Lincoln, NE, USA⁴ and Veterans Affairs Medical Center, Providence, RI, USA⁵
The $\alpha_1$-Adrenergic Receptor Antagonist, Doxazosin, Reduces Alcohol Drinking in Alcohol-Preferring (P) Rats

Meghan L. O’Neil, Lauren E. Beckwith, Carrie L. Kincaid, and Dennis D. Rasmussen

Fig. 1. Trial 1, 3-day treatment: effects of doxazosin (1.25 to 5 mg/kg, IP) on alcohol intake (mean ± SEM). Doxazosin dose-dependently decreased alcohol intake, independent of day. Each bar represents data from 11 to 12 rats. ***$p < 0.001$ versus vehicle control treatment for 1.25, 2.5, and 5 mg/kg; $p < 0.01$, 5 mg/kg versus 1.25 and 2.5 mg/kg. For significant differences between days, see text. Pretreatment values reflect the averages from 5 daily sessions.
Doxazosin Study Design

- A 10-week between-subject double-blind placebo-controlled preliminary RCT
- Outpatient setting with treatment-seeking AD patients
Doxazosin Study: Study Outcomes

- No significant differences between groups in Drinks Per Week (DPW) and Heavy Drinking Days (HDD) per week ($p's > 0.05$; low effect sizes $d = .23$ and $.35$, respectively)
Doxazosin Study: Effect On Obsessive Craving

p = .034
## Doxazosin Study: Family History of Alcoholism

**Table 2.** Family History Density of Alcoholism (FHDA) as moderator of the primary alcohol-related aims \([M \pm (SE)]\)

<table>
<thead>
<tr>
<th>FHDA X Medication</th>
<th>Drinks Per Week (DPW)</th>
<th>Heavy Drinking Days (HDD)</th>
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<tr>
<td></td>
<td><strong>Doxazosin</strong></td>
<td><strong>Placebo</strong></td>
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<tr>
<td>High FHDA</td>
<td>2.3 (0.7)</td>
<td>6.1 (0.8)</td>
</tr>
<tr>
<td>Low FHDA</td>
<td>3.3 (0.7)</td>
<td>0.2 (0.9)</td>
</tr>
<tr>
<td>(p)</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>High FHDA X Medication effect size ((d))</td>
<td>1.18</td>
<td>1.30</td>
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</table>
Doxazosin Study: Family History of Alcoholism
Archival Report

Higher Pretreatment Blood Pressure Is Associated With Greater Posttraumatic Stress Disorder Symptom Reduction in Soldiers Treated With Prazosin

Murray A. Raskind, Steven P. Milard, Eric C. Petrie, Kris Peterson, Tammy Williams, David J. Hoff, Kimberly Hart, Hollie Holmes, Jeffrey Hill, Colin Daniels, Rebecca Hendrickson, and Elaine R. Peskind
Doxazosin Study: Standing Blood Pressure

Haass-Koffler et al. in preparation
Prazosin & Doxazosin in Alcohol Use Disorder: Summary

- Alpha-1 blockade seems another effective approach to treat alcoholic patients
- Patients with AUD and PTDS comorbidity might be a sub-group who respond best to these treatments
- Family history of alcoholism and standing blood pressure might represent moderators of doxazosin response
- Large RCT are needed to confirm these findings
## Collaborators

### NIAAA
- Veronica Alvarez, PhD
- Mark Egli, PhD
- Daniel Falk, PhD
- Joanne Fertig, PhD
- David Goldman, MD
- Colin Hodgkinson, PhD
- Andrew Holmes, PhD
- Raye Litten, PhD
- Reza Momenan, PhD
- Vijay Ramchandani, PhD
- Melanie Schwandt, PhD
- Dardo Tomasi, PhD
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- Andras Hajnald, MD, PhD

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CPN Lab

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  - BBRF (formerly NARSAD): Baclofen Project
  - Peter G. Dodge Foundation (PGDF): Gut Microbiome Project
  - NIH B2B: Oxytocin Project (PI: Mary Lee, MD)
Novel Pharmacological Targets for Treating Alcohol Use Disorder

Barbara J. Mason, Ph.D

Pearson Family Professor, Committee on the Neurobiology of Addictive Disorders
Director, Laboratory of Clinical Psychopharmacology
ASAM State of the Art Course
October 8, 2016
Disclosure Information

Barbara J. Mason, Ph.D
Depomed, Inc. – Consulting Fee - Consultant
Medication Targets in the Cycle of Alcohol Dependence

- Acute Withdrawal
- Binge/Intoxication
- Protracted Abstinence
Neuropeptides Associated with the Withdrawal N-Affect Stage and the Extended Amygdala

- Corticotropin-releasing factor
- Dynorphin
- Vasopressin
- Orexin (hypocretin)
- Substance P
- Glucocorticoids

- Neuropeptide Y
- Nociceptin (orphanin FQ)
- Endocannabinoids
Human Lab Model of Protracted Abstinence

Method: Affective priming and *in vivo* beverage cues

Subjects: Non treatment-seeking males and females with alcohol dependence, abstinent 3 days prior to testing

Design: Double-blind, placebo-controlled, random assignment, dosing based on PK, typically 1-week

Primary outcome: Visual Analogue Scale - craving
  - Confirmatory outcomes: EMG, heart rate, GSR
  - Exploratory outcome: sleep, mood, cognition

Safety: Physical exam, labs, vital signs, SAFTEE, ARCI
Beverage Cue Exposure Procedures

- The subject’s preferred alcoholic beverage or bottled water are presented in random order for 90 seconds following each mood condition.

- The subject is told to view and sniff the beverage for 90 seconds and to not drink it.
Gabapentin
Rationale for Gabapentin (Neurontin) as a Treatment for Alcohol Dependence

- Available as a FDA-approved drug for epilepsy and pain
- Associated with modulation of GABAergic activity via action on voltage-gated calcium channels
- Hypothesized to functionally restore homeostasis in brain stress systems dysregulated in dependence and withdrawal
- Used off-label to treat symptoms associated with protracted withdrawal and risk of relapse
  - Depression
  - Anxiety
  - Insomnia
- Acceptable safety and tolerability
  - Not metabolized in the liver
Cellular Neuroadaptive Mechanisms in the Central Nucleus of the Amygdala in Ethanol Dependence

(CRF antagonists and gabapentin both decrease GABA release in dependent rats)

Roberto M, Gilpin NW, O’Dell LE, Cruz MT, Morse AC, Siggins GR, Koob GF. *J Neurosci*, 2008, 28:5762-71
POC Human Laboratory Cue Reactivity Study: Gabapentin in Alcohol Dependence

Week 0: Randomization
n= 33

Days 0-7
Gabapentin
1200mg

Days 0-7
Placebo

Week 1: Laboratory Cue Session
VAS Craving Scores: Alcohol Minus Water

Effect of Gabapentin vs. Placebo on Pittsburgh Sleep Quality Index

1 Higher values indicate greater disturbance; subscale range 0-2

(Figure displayed on next slide)
Summary of POC Human Lab Study of Gabapentin

- Gabapentin 1200mg/d vs placebo was associated with
  - Decreased craving (p < .05)
  - Improved sleep (p < .05)
  - Good safety and tolerability
  - No evidence of abuse potential
- A randomized controlled trial (rct) to evaluate the efficacy of gabapentin for relapse prevention in alcohol dependence is warranted.

Hypothesis

- Gabapentin will have efficacy for the treatment of alcohol dependence by
  - acting directly on drinking behavior
    - rates of abstinence and no heavy drinking
    - drinking quantity and frequency
  - acting on symptoms of protracted withdrawal that may modulate drinking behavior,
    e.g., craving and disturbances in mood and sleep
Disposition of Patients

Randomization
n=150

Excluded n=35
19 not eligible
16 declined

Weeks 0-12 Abstinence-Oriented Counseling

900mg
Gabapentin
n=54

59.4 Days on Study
30 Completed

68.2 Days on Study
29 Completed

Rates of Complete Abstinence and No Heavy Drinking on Study

Over the 12-week Study in the ITT Population (n=150)

Graph A: Linear dose effect
- Placebo
- 900 mg
- 1800 mg
- NNT = 8 for 1800 mg

Graph B: Linear dose effect
- Placebo
- 900 mg
- 1800 mg
- NNT = 5 for 1800 mg

Gabapentin Effects on Dysphoria, Craving and Insomnia

Clinical Implications for Gabapentin

- **Generic gabapentin may be a cost-effective treatment for alcohol dependence**
  - Effect sizes for rates of abstinence and no heavy drinking were equivalent or superior to approved drugs, with unique benefits re: mood and sleep
  - Effects on craving, abstinence and no heavy drinking were found in a RCT of 60 detoxed alcoholics in Brazil (*)
- **A pivotal multi-center RCT of gabapentin enacarbil (HORIZANT®) extended release tablets is being conducted by NIAAA and the manufacturer, XenoPort, Inc., in support of FDA-approval**
  - a prodrug of gabapentin with more uniform bioavailability, faster time to full therapeutic dose, and less fluctuating gabapentin blood levels with twice daily dosing
  - FDA-approved for pain and restless leg syndrome

Mifepristone
Rationale for Glucocorticoid Antagonism as a Treatment for Alcohol Dependence

- Heavy alcohol use and withdrawal is associated with abnormal HPA axis activity and glucocorticoid receptor feedback, and sensitization of CRF in the amygdala

- Mifepristone, a Type II glucocorticoid receptor antagonist, is available for re-purposing: FDA-approved to control hyperglycemia secondary to hypercortisolism in adults with endogenous Cushing’s syndrome who have type 2 diabetes mellitus or glucose intolerance (Korlym, Corcept Therapeutics)

- Clinically, administering mifepristone in alcoholics following acute withdrawal may normalize HPA axis dysregulation and thereby protect against relapse during protracted withdrawal
Increased Glucocorticoid Receptor Function Mediates Compulsive-like Alcohol Self-administration in Alcohol-dependent rats

J Clin Invest, 2015, 125:3193-7
Glucocorticoid receptor antagonism decreases alcohol seeking in alcohol-dependent individuals.

*J Clin Invest*, 2015, 125:3193-7
Hypothesis

- Mifepristone, relative to placebo, will show POC efficacy in non treatment-seeking outpatient alcoholics by significantly decreasing:
  - Craving in response to *in vivo* alcohol cues in a human lab model of protracted abstinence
  - Alcohol consumption under naturalistic conditions during 1 week of treatment and 1 week of post-treatment follow-up
Participant Flow Chart

Randomized
n=56

Days 0-7
Mifepristone 600mg
n=28

Days 0-7
Placebo
n=28

Discontinued mifepristone: n=0

Discontinued placebo: n=2


J Clin Invest, 2015, 125:3193-7
Alcohol-cued Craving: Visual Analogue Scale (VAS) Scores

Number of Drinks Per Week


*J Clin Invest, 2015, 125:3193-7
Mifepristone Future Directions

A clinical trial is underway to extend our POC results using:

- A treatment-seeking sample of 150 outpatients with current alcohol dependence
- 1-week of drug followed by 8 weeks of counseling to consolidate and maintain drug effects
- 3-arm study of 1200, 600 or 0 mg/d, based on an association between drinking outcome and plasma concentration
- Polymorphisms in FKBP5 gene, a key regulator of GR complex, predict mifepristone effects on drinking

1-week of treatment with mifepristone to re-set the HPA-axis in protracted withdrawal, in conjunction with a course of psychosocial treatment, may offer a novel treatment paradigm that optimizes healthcare resources.
Acknowledgments

All studies were funded by:

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Gabapentin and matched placebo was provided by Pfizer Pharmaceuticals, Inc.

Mifepristone and matched placebo was provided by Corcept Therapeutics, Inc.
NEW MEDICATION DELIVERY SYSTEMS FOR OPIOID USE DISORDER

Richard N Rosenthal, MD
Professor of Psychiatry
Icahn School of Medicine at Mount Sinai
ASAM STATE OF THE ART
Course in Addiction Medicine
October 6-8, 2016
Disclosure Information

Richard N Rosenthal, MD, FASAM, DLFAPA, DFAAAP
Braeburn Pharmaceuticals – Research funding
Overview

- The Opioid Epidemic and Opioid Use Disorder (OUD)
- The rationale for long-acting medications in OUD
- Buprenorphine implants
  - The evidence base
  - Most recent data
  - FDA approval - May 2016
  - What’s a clinician to do?
  - What’s in the Pipeline?
Opioid Abuse is Epidemic in the United States

In 2014:
- ~2 million Americans abused/dependent on prescription opioids
- >70% of abused opioids obtained from friends or family
- ~772,000 sought treatment for prescription pain meds
- Greatest increases in heroin use in groups with historically low rates:
  - Women, the privately insured, and people with higher incomes.
- Heroin increased >2X among 18 to 25 year olds in last 10 years
- In 2014, >14,000 people died from overdoses involving prescription opioids, and >10,500 from heroin overdoses.

Increasing Prevalence of Heroin Use & Dependence: 2002-2011

+ Difference between this estimate and the 2014 estimate is statistically significant at the .05 level.

Results from the 2011 National Survey on Drug Use and Health

Most Recent Treatment Received in Past Year for Pain Relievers, Aged 12 or Older, by Age Group: 2002-2014

Difference between this estimate and the 2014 estimate is statistically significant at the .05 level.

Han B, Hedden SL, and Lipari R; RTI International: Copello EAP and Kroutil LA. Receipt of Services for Behavioral Health Problems: Results from the 2014 National Survey on Drug Use and Health
Most Recent Treatment in the Past Year for Heroin, Aged 12 or Older, by Age Group: 2002-2014

+ Difference between this estimate and the 2014 estimate is statistically significant at the .05 level.

Han B, Hedden SL, and Lipari R; RTI International: Copello EAP and Kroutil LA. Receipt of Services for Behavioral Health Problems: Results from the 2014 National Survey on Drug Use and Health
Nonmedical Pain Reliever Use among Nonmedical Psychotherapeutic Drug Users Aged ≥12 - 2014

- 6.5 Million Current Nonmedical Users of Psychotherapeutic Drugs
- 4.3 Million Current Nonmedical Users of Pain Relievers (66.2%)

Drug Overdose Deaths Involving Opioids By Type Of Opioid — United States, 2000–2014

Graph showing the number of deaths per 100,000 population from drug overdose involving opioids, natural and semisynthetic opioids, synthetic opioids excluding methadone, methadone, and heroin from 2000 to 2014.
Necessity of Medical Treatment for OUD

- Detoxification from opioids alone is typically insufficient
- High relapse rates after standard detoxification\(^1\)
- Relapse rates >50% 1 month after discontinuation of Bup maintenance\(^2\)
- Higher Bup doses associated with pre-induction 30-day heroin, IV use frequency, craving and withdrawal\(^3\)
- Lower Bup maintenance doses associated with lower relapse risk 1 month post taper (\(p=0.04\))\(^2\)
Buprenorphine: Limitations of Sublingual/ Buccal Transmucosal Formulations

◆ Missed doses, low adherence to treatment
◆ Abuse, theft, and intentional diversion
◆ Accidental exposure: especially increased child ED visits
  ◆ Estimated 1,499 children aged <6 years evaluated in U.S. emergency departments (EDs) for buprenorphine-product ingestions in 2010-11 (0 reported in 2004)
  ◆ 9.5% of emergent hospitalizations for drug ingestion by children <6, greater proportion than any other medication

Emergency Department Visits and Hospitalizations for Buprenorphine Ingestion by Children — United States, 2010–2011. MMWR, Jan 25, 2013 / 62(03);56-56
Rationale for Sustained Release Implant Formulation

- Minimize misuse and diversion
- Eliminate daily dosing
- Increase adherence
- Stabilize blood levels over 6 months
Plasma Pharmacokinetics

Probuphine Implant Description

- Sustained-release polymeric matrix of buprenorphine in ethyl vinyl acetate (EVA)
  - Matchstick size: 26mm long
  - 80mg of buprenorphine
- Continuous buprenorphine levels for 6 months
Implantation Procedure

- Under local anesthesia implants are inserted subdermally into the inner side of the upper arm in a 10-15 minute in-office procedure.
- Single 2.5- to 3-mm incision in the inner upper arm.
- Implants inserted one at a time 2-3 mm below the skin using a custom-designed applicator.
- 24 hour pressure dressing greatly reduces post-op adverse events.
- Sustained release of buprenorphine for 6 months.
- At the end of each 6-month period, implants are removed in a brief, in-office procedure using a custom-designed clamp.
Insertion Applicator
Insertion Location
Placement of Implants
24-week Placebo Controlled Trials of BUP Implants

Summary of Significant Findings of Implant Against Placebo (2 trials):

- Higher mean percentage of urines negative for illicit opioids, weeks 1-24:
- Higher retention rate: 64-66 % vs. 26-31 %
- Lower incidence of clinician-rated and patient-rated opioid withdrawal symptoms
- Lower patient-rated opioid craving
- Greater change on clinician global ratings of improvement
Percentage of Urine Samples Opioid Negative Weeks 1–24 in 2 Placebo Controlled Trials

PRO-805

![Graph showing percentage of urine samples opioid negative for PRO-805 placebo and BPN Implant groups with p<0.0142*.]

PRO-806

![Graph showing percentage of urine samples opioid negative for PRO-806 placebo and BPN Implant groups with p<0.0001*.]

*Wilcoxon rank sum (van Elteren) with gender and site as blocking variables.
Head-to-Head Comparison Rationale

- In second trial, the implants were non-inferior to open label group continued at 12-16 mg SL Bup
- However:
  - increased subjective and objective withdrawal symptoms
  - Increased use of 2mg SL Bup rescue doses
  - ≤8mg of SL Bup
Double Blind Double Dummy Study of Buprenorphine Implants and SL Buprenorphine

Study:
- Head-to-head safety/efficacy trial of Bup implants and daily SL Bup on long-term remission (≥ 6 months) in patients (N=177) clinically stable on ≤ 8mg of SL Bup for at least 90 days
- Responder rate defined as at least four of six study months with no evidence of illicit opioid use

Double **Blind** Double Dummy Study of Buprenorphine Implants and SL Buprenorphine

**Summary:**
- Transitioning to implants was not clinically destabilizing (e.g., increased craving or withdrawal symptoms).
- 96.4% vs 87.6% had no opioid-positive urine tests for at least four of the six study months ($P<.001$ non-inferiority; $P=.03$ superiority)
- Higher 6-month abstinence rate in the implant group 85.7% vs. 71.9% in the SL Bup group ($P<.03$; NNT=7.25)

Double **Blind** Double Dummy Study of Buprenorphine Implants and SL Buprenorphine

Implications:

- Bup implants effective for maintenance of abstinence in opioid-dependent adults clinically stable on ≤ 8mg/d SL Bup.
- Boost maintenance of abstinence in appropriate patients while reducing the risk of diversion and adverse events.
- Patients doing well at moderate SL doses in OTPs that could transition to office-based care.
- Proposed new targets: criminal justice, other hard-to-reach populations.²
- Issues with generalizability: most participants were white, domiciled, employed, ≥ HS education, and primarily prescription OUD.

2 Compton & Volkow JAMA. 2016;316(3):277-79
Risk Evaluation and Mitigation Strategy

- Required REMS for Providers: probuphinerems.com
- DEA Waiver to prescribe or dispense BUP Implant.
- Must have performed at least one qualifying surgical procedure in the last 3 months under local anesthesia using aseptic technique, including, at a minimum, making skin incisions, or placing sutures.
- Prior to performing insertions or prescribing BUP implants Providers must successfully complete a live training program on the insertion and removal procedures and become certified in the PROBUPHINE REMS program.
Risk Evaluation and Mitigation Strategy

Acceptable transmucosal BUP doses for conversion:

- Buprenorphine sublingual tablet (Subutex or generic) 8 mg or less
- Buprenorphine/naloxone (Suboxone or generic) SL tablet 8 mg/2 mg or less
- Buprenorphine/naloxone buccal film (Bunavail) 4.2 mg/0.7 mg or less
- Buprenorphine/naloxone (Zubsolv) SL tablets 5.7 mg/1.4 mg or less
### Table 3: Adverse Events, Implant-site related

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Sublingual BPN (n=89)</th>
<th>Probuphine (n=87)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT LEAST ONE AE PER SYSTEM ORGAN CLASS</td>
<td>TOTAL</td>
<td>12 (13.5%)</td>
<td>20 (23.0%)</td>
<td>32 (18.2%)</td>
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<tr>
<td></td>
<td>TOTAL</td>
<td>7 (7.9%)</td>
<td>12 (13.8%)</td>
<td>19 (10.8%)</td>
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<tr>
<td></td>
<td>IMPLANT SITE PAIN</td>
<td>4 (4.5%)</td>
<td>4 (4.6%)</td>
<td>8 (4.5%)</td>
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<td>IMPLANT SITE PRURITUS</td>
<td>1 (1.1%)</td>
<td>4 (4.6%)</td>
<td>5 (2.8%)</td>
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<tr>
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<td>IMPLANT SITE BRUISING</td>
<td>1 (1.1%)</td>
<td>1 (1.1%)</td>
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<td>IMPLANT SITE ERYTHEMA</td>
<td>1 (1.1%)</td>
<td>1 (1.1%)</td>
<td>2 (1.1%)</td>
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<tr>
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<td>IMPLANT SITE HAEMORRHAGE</td>
<td>0 (0.0%)</td>
<td>1 (1.1%)</td>
<td>1 (0.6%)</td>
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<tr>
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<td>OEDEMA PERIPHERAL</td>
<td>0 (0.0%)</td>
<td>1 (1.1%)</td>
<td>1 (0.6%)</td>
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<td>DEVICE EXPULSION</td>
<td>1 (1.1%)</td>
<td>0 (0.0%)</td>
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<tr>
<td></td>
<td>IMPLANT SITE DISCOLOURATION</td>
<td>1 (1.1%)</td>
<td>0 (0.0%)</td>
<td>1 (0.6%)</td>
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<tr>
<td>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</td>
<td>TOTAL</td>
<td>3 (3.4%)</td>
<td>3 (3.4%)</td>
<td>6 (3.4%)</td>
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<tr>
<td></td>
<td>CELLULITIS</td>
<td>1 (1.1%)</td>
<td>1 (1.1%)</td>
<td>2 (1.1%)</td>
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<tr>
<td></td>
<td>INCISION SITE INFECTION</td>
<td>1 (1.1%)</td>
<td>0 (0.0%)</td>
<td>1 (0.6%)</td>
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<tr>
<td></td>
<td>PURULENT DISCHARGE</td>
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<td>1 (1.1%)</td>
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<td>WOUND INFECTION</td>
<td>1 (1.1%)</td>
<td>1 (1.1%)</td>
<td>2 (1.1%)</td>
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</tbody>
</table>
Table 3: Adverse Events, Implant-site related

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Sublingual Buprenorphine (n=89)</th>
<th>Probuphine (n=87)</th>
<th>Total</th>
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<tbody>
<tr>
<td>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</td>
<td>TOTAL</td>
<td>3 (3.4%)</td>
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<td>DERMATITIS CONTACT</td>
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<td>RASH</td>
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<td>1 (0.6%)</td>
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<td>SKIN IRRITATION</td>
<td>1 (1.1%)</td>
<td>0 (0.0%)</td>
<td>1 (0.6%)</td>
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<tr>
<td>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</td>
<td>TOTAL</td>
<td>1 (1.1%)</td>
<td>2 (2.3%)</td>
<td>3 (1.7%)</td>
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<tr>
<td></td>
<td>CONTUSION</td>
<td>1 (1.1%)</td>
<td>0 (0.0%)</td>
<td>1 (0.6%)</td>
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<tr>
<td></td>
<td>INCISION SITE COMPLICATION</td>
<td>0 (0.0%)</td>
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<td>1 (0.6%)</td>
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<td>POSTOPERATIVE WOUND COMPLICATION</td>
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<td>NERVOUS SYSTEM DISORDERS</td>
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<td>PARAESTHESIA</td>
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<td>1 (0.6%)</td>
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<td>PERIPHERAL SENSORY NEUROPATHY</td>
<td>1 (1.1%)</td>
<td>0 (0.0%)</td>
<td>1 (0.6%)</td>
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## PRO-814 Demographic Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Probuphine® n=87</th>
<th>SL BPN n=89</th>
<th>Total n=176</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>59.8%</td>
<td>58.4%</td>
<td>59.1%</td>
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<tr>
<td></td>
<td>Female</td>
<td>40.2%</td>
<td>41.6%</td>
<td>40.9%</td>
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<tr>
<td>Age (yrs)</td>
<td>Mean (SD)</td>
<td>38 (11.2)</td>
<td>39 (10.8)</td>
<td>39 (11.0)</td>
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<tr>
<td>Race</td>
<td>White</td>
<td>94.3%</td>
<td>95.5%</td>
<td>94.9%</td>
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<td></td>
<td>Black</td>
<td>3.4%</td>
<td>2.2%</td>
<td>2.8%</td>
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<td>Asian</td>
<td>1.1%</td>
<td>0.0%</td>
<td>0.6%</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>1.1%</td>
<td>2.2%</td>
<td>1.7%</td>
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<tr>
<td>Ethnicity</td>
<td>Hispanic or Latino</td>
<td>3.4%</td>
<td>3.4%</td>
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<td></td>
<td>Not Hispanic or Latino</td>
<td>96.6%</td>
<td>96.6%</td>
<td>96.6%</td>
</tr>
<tr>
<td>Variable</td>
<td>Value</td>
<td>Probuphine n=87</td>
<td>SL BPN n=89</td>
<td>Total n=176</td>
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<td>----------------------------------------------</td>
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<td>-----------------</td>
<td>-------------</td>
<td>-------------</td>
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<tr>
<td>Time Since First Diagnosis</td>
<td>Mean (SD)</td>
<td>6.2 (5.93)</td>
<td>6.2 (6.95)</td>
<td>6.2 (6.45)</td>
</tr>
<tr>
<td>(subject-reported, yrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Opioid of Abuse</td>
<td>Heroin</td>
<td>17.2%</td>
<td>24.7%</td>
<td>21.0%</td>
</tr>
<tr>
<td></td>
<td>Rx Opioid Pain Reliever</td>
<td>75.9%</td>
<td>73.0%</td>
<td>74.4%</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>5.7%</td>
<td>2.2%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Daily Dose of Buprenorphine</td>
<td>2 mg</td>
<td>6.9%</td>
<td>3.4%</td>
<td>5.1%</td>
</tr>
<tr>
<td>at Time of Randomization</td>
<td>4 mg</td>
<td>13.8%</td>
<td>16.9%</td>
<td>15.3%</td>
</tr>
<tr>
<td></td>
<td>6 mg</td>
<td>9.2%</td>
<td>4.5%</td>
<td>6.8%</td>
</tr>
<tr>
<td></td>
<td>8 mg</td>
<td>70.1%</td>
<td>75.3%</td>
<td>72.7%</td>
</tr>
</tbody>
</table>