Treatment Track

Extended-Release Naltrexone vs. Buprenorphine-Naloxone: A Comparative Effectiveness Trial

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Edward Nunes, MD, Professor of Psychiatry, Columbia University Medical Center / New York State Psychiatric Institute

Moderator: Judge David Tapp, JD, MS, 28th Judicial Circuit of Kentucky, and Member, National Rx Drug Abuse & Heroin Summit Advisory Board
Disclosures

- Joshua Lee, MD, MSc, and David Tapp, JD, MS, have disclosed no relevant, real, or apparent personal or professional financial relationships with proprietary entities that produce healthcare goods and services.

- Edward Nunes, MD – Contracted Research: Grants with NIDA (NIH); Braeburn and Alkermes
Disclosures

- All planners/managers hereby state that they or their spouse/life partner do not have any financial relationships or relationships to products or devices with any commercial interest related to the content of this activity of any amount during the past 12 months.

- The following planners/managers have the following to disclose:
  - Kelly J. Clark, MD, MBA, FASAM, DFAPA – Consulting fees: Braeburn, Indivior
Learning Objectives

- Describe how extended-release naltrexone and buprenorphine differ as opioid use disorder treatments.
- Explain the primary and key secondary findings of the National Institute on Drug Abuse National Drug Abuse Treatment Clinical Trials Network comparative effectiveness trial.
- Apply lessons learned from the National Institute on Drug Abuse National Drug Abuse Treatment Clinical Trials Network trial and related studies to clinical decision-making.
CTN-0051
Extended-Release Naltrexone vs. Buprenorphine for Opioid Treatment (X:BOT)
ClinicalTrials.gov NCT02032433

Joshua D Lee MS MSc
Associate Professor, NYU Langone Health
DrJoshuaDLee
Disclosures

- Trial sponsored by NIDA, run through NIDA CTN
- Suboxone donated by R-B/Indivior
- Vivitrol purchased by NIDA
- Vivitrol and funds from Alkermes for unrelated studies
- Suboxone and funds from R-B for unrelated studies
- No paid consulting, advisory board, activities (Lee, Rotrosen, Nunes)
- No equity
- (U10DA013046, UG1/U10DA013035, UG1/U10DA013034, U10DA013045, UG1/U10DA013720, UG1/U10DA013732, UG1/U10DA013714, UG1/U10DA015831, U10DA015833, HHSN271201200017C, and HHSN271201500065C) and K24DA022412
Design Overview

- Two-arm randomized *effectiveness* trial comparing two approved treatments (~400-600 participants, 8 sites)
- Recruitment from inpatient detoxification/residential settings
- Intent to characterize the “detox hurdle”
- Flexible point of randomization, defined early and late randomizers
- Defined high and low severity users
- Mitigation plan to address “detox hurdle”
- Six months of flexible treatment
- Follow-up through 9 months after randomization
- Primary endpoint = “time-to-relapse” (ITT and Per-Protocol)
  - 7 consecutive use days
  - 4 consecutive use weeks
  - Beginning no earlier than 21 days post-randomization
Secondary Outcomes

- Successful induction onto XR-NTX or BUP-NX
- Adverse events
- Opioid abstinence
- Opioid craving
- Sub-acute withdrawal
- Alcohol and other drug use
- Tobacco use
- Problems related to drug abuse
- HIV risk behavior
- Cognitive function
Candidate enters treatment program

Study is explained, candidate consents (can occur at any time-point between program admission and discharge)

Participant meets eligibility criteria

Participant is randomized

- **XR-NTX (n=200)**
  - Complete detoxification
  - Achieve 3+ days abstinence
  - Negative UDS
  - Negative NX challenge
  - First XR-NTX injection

- **BUP-NX (n=200)**
  - Achieve sufficient withdrawal (or have already completed detoxification) to induct onto BUP-NX
  - Initiate BUP-NX

Treat for 24 weeks
- Weekly visits

Refer to community-based treatment
- Follow up at week 28 and week 36

Treatment Failures, Dropouts

Phase 1

Phase 2

Phase 3

Phase 4

**Note:** A concerted effort will be made to assess all enrolled subjects at weeks 24, 28, and 36 post-randomization regardless of whether they have dropped out of study treatment.
Sites

- Inpatient detoxification / short-term residential programs with capacity to continue medication for up to 24 weeks of outpatient treatment and follow patients for a total of 36 weeks

- Study Sites
  Avery Road (MD)  Bellevue (NY)
  ETS/RCKC (WA)  Gateway (FL)
  Maryhaven (OH)  SSTAR (MA)
  Tarzana (CA)  Turquoise
  Lodge (NM)
INCLUSION CRITERIA

- Male/Female
- ≥18 years
- Meet DSM-5 criteria for Opioid Use Disorder
- Used opioids other than as prescribed within past 30 days
- Seeking treatment and willing to accept agonist or antagonist Rx
- Good general health
- Able to provide consent
- English speaking
- If female of childbearing potential, willing to practice effective birth control

EXCLUSION CRITERIA

- Serious medical, psych or SUD making participation hazardous
- LFT values > 5 times upper limit
- Suicidal or homicidal ideation requiring immediate attention
- Known allergies to study meds or diluents
- Methadone maintenance of 30mg or more
- Pain requiring opioid Rx
- Pending legal action
- Currently pregnant/breast feeding
- Body habitus precluding gluteal IM injection
Demographics

- 30% Female / 70% Male
- 17% Hispanic / Latino
- 26% Non-White / 74% While
- 69% 25-45 years old
- 15% <25 years old
- 57% High school or less
- 66% Never married
- 63% Unemployed
Opioid Use

- **Primary Opioid**
  - 82% Heroin
  - 16% Opioid Analgesics
  - 1% Methadone
  - 1% Buprenorphine

- **Severity**
  - 63% are IV users
  - 40% are high severity users (IV and ≥ 6 bags per day)

- **Duration**
  - Age at first use = 21.3
  - Years of use = 12.5
Choice and Motivation

- **Choice**
  - All willing to take either medication
  - 29% preferred XR-NTX
  - 33% preferred BUP-NX

- **Motivation**
  - 86% intended to complete 6-months of XR-NTX
  - 87% intended to complete 6-months of BUP-NX
Induction Success (%)

All

By Randomization Timing

0-72hr days since last opioid

73hr+ since last opioid
Induction Success (%) X Site

Site 1: XR-NTX 57, BUP-NX 100
Site 2: XR-NTX 100, BUP-NX 95
Site 3: XR-NTX 91, BUP-NX 91
Site 4: XR-NTX 83, BUP-NX 100
Site 5: XR-NTX 98, BUP-NX 98
Site 6: XR-NTX 84, BUP-NX 97
Site 7: XR-NTX 64, BUP-NX 87
Site 8: XR-NTX 75, BUP-NX 100
**Induction Failures**

- Randomized to XR-NTX = 79
  - 70 met relapse criteria at day 21
  - 79 met relapse criteria by end of study
- Randomized to BUP-NX = 17
  - 10 met relapse criteria at day 21
  - 13 met relapse criteria by end of study
24-Week Relapse Rates (%)

**Intent-to-Treat Sample (ITT)**

- XR-NTX: 65%
- BUP-NX: 57%

**Per-Protocol Sample (PP)**

- XR-NTX: 52%
- BUP-NX: 56%

**Effect Sizes and Confidence Intervals**

- **Intent-to-Treat Sample (ITT)**
  - OR = 1.44
  - 95% CI: 1.02-2.01
  - p = 0.04

- **Per-Protocol Sample (PP)**
  - OR = 0.87
  - 95% CI: 0.60-1.25
  - p = 0.44
Relapse-Free Survival

Intent-to-Treat Sample (n=570) Per-Protocol Sample (n=474)

BUP-NX BUP-NX
XR-NTX XR-NTX

HR=1.36
95% CI: 1.10-1.68
p < 0.05

HR=0.92
95% CI: 0.71-1.18
p = NS
## Other Opioid Use Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intent-to-Treat Sample</th>
<th>Per-Protocol Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>XR-NTX</td>
<td>BUP-NX</td>
</tr>
<tr>
<td>Median Weeks Negative UDS</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Median Days Abstinent (TLFB)</td>
<td>39</td>
<td>81</td>
</tr>
<tr>
<td>Median Weeks Until Relapse</td>
<td>8.4</td>
<td>14.4</td>
</tr>
<tr>
<td></td>
<td>All Above, p &lt; 0.05</td>
<td>All Above, p = NS</td>
</tr>
</tbody>
</table>
Induction Success (%)

All

By Low- or High-Severity

# Gender (%)

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Men</th>
<th>Women</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction Failure (XR-NTX)</strong></td>
<td>27.9</td>
<td>29.2</td>
<td>25.0</td>
<td>0.46</td>
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<tr>
<td><strong>Induction Failure (BUP-NX)</strong></td>
<td>5.9</td>
<td>6.3</td>
<td>4.9</td>
<td>0.66</td>
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<tr>
<td><strong>24-Week Relapse Rate Per-</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XR-NTX</td>
<td>52.0</td>
<td>52.2</td>
<td>51.5</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>24-Week Relapse Rate Per-</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUP-NX</td>
<td>55.6</td>
<td>56.0</td>
<td>54.6</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>Prefer XR-NTX</td>
<td>Prefer BUP-NX</td>
<td>P-value</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------</td>
</tr>
<tr>
<td>Induction Failure (XR-NTX)</td>
<td>31.5</td>
<td>27.1</td>
<td>34.8</td>
<td>0.30</td>
</tr>
<tr>
<td>Induction Failure (BUP-NX)</td>
<td>9.8</td>
<td>18.7</td>
<td>1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-Week Relapse Rate P-P</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>XR-NTX</td>
<td>54.1</td>
<td>47.1</td>
<td>60.3</td>
<td>0.16</td>
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<tr>
<td>BUP-NX</td>
<td>55.8</td>
<td>55.7</td>
<td>55.8</td>
<td>0.99</td>
</tr>
</tbody>
</table>
Opioid Craving
Self-Reported Visual Analog Scale

P = 0.0012 overall
NS at week-24

Graph showing the trend of opioid craving score (VAS) over study weeks for Per-protocol BUP-NX (n=270) and Per-protocol XR-NTX (n=204). The craving scores decrease over time, with BUP-NX and XR-NTX showing different patterns.
Smoked Cigarettes in Past 30 Days (%)

For relapsers, only data collected before relapse is included.
Used Alcohol in Past 30 Days (%)

Participants do not provide TLFB data while in detox. Missing TLFB days not occurring during detox are imputed as use days. For relapsers, only data collected before relapse are included.
Used Any Other Drugs in Past 30 Days (%)

Participants do not provide TLFB data while in detox. Missing TLFB days not occurring during detox are imputed as use days. For relapsers, only data collected before relapse are included.
Figure 16: Boxplots of SOWS Score by Treatment Arm
Figure 15: Boxplots of HAM-D Score by Treatment Arm
Trails A

Figure 10: Boxplots of Trails A by Treatment Arm
## Treatment Emergent Adverse Events (Per-Protocol Sample Only)

<table>
<thead>
<tr>
<th>Treatment Emergent Adverse Events</th>
<th>XR-NTX</th>
<th>BUP-NX</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants with ≥1 Treatment Emergent Adverse Event</td>
<td>111 (54.4%)</td>
<td>141 (52.2%)</td>
<td>p=0.64</td>
</tr>
<tr>
<td>Number of Treatment Emergent Adverse Events</td>
<td>247</td>
<td>334</td>
<td></td>
</tr>
<tr>
<td>Study Medication Discontinued due to Adverse Event</td>
<td>6</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Type of Treatment Emergent Adverse Event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site reaction, mild or moderate</td>
<td>46</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>34</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>30</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>23</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>22</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>22</td>
<td>28</td>
<td></td>
</tr>
</tbody>
</table>
# Treatment Emergent Serious Adverse Events
(Per-Protocol Sample Only)

<table>
<thead>
<tr>
<th></th>
<th>XR-NTX</th>
<th>BUP-NX</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants with ≥1 Serious Adverse Event</strong></td>
<td>29 (14.2%)</td>
<td>29 (10.7%)</td>
<td>p=0.25</td>
</tr>
<tr>
<td><strong>Number of Treatment Emergent Serious Adverse Events</strong></td>
<td>39</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td><strong>Type of Treatment Emergent Serious Adverse Event</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>9</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>
# Overdose Events (ITT Sample)

<table>
<thead>
<tr>
<th></th>
<th>XR-NTX</th>
<th>BUP-NX</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overdose Events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants with ≥1 Overdose Event</td>
<td>15</td>
<td>8</td>
<td>p=0.15</td>
</tr>
<tr>
<td>Number of Overdose Events (overall)</td>
<td>18</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Number of Overdose Events (per-protocol)</td>
<td>10</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td><strong>Fatal Overdose Events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Fatal Overdose Events (overall)</td>
<td>2</td>
<td>3</td>
<td>p&gt;0.99</td>
</tr>
<tr>
<td>Number of Fatal Overdose Events (per-protocol)</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
## Overdoses per Weeks-at-Risk

<table>
<thead>
<tr>
<th></th>
<th># ODs</th>
<th>Weeks-at-Risk</th>
<th>ODs/Weeks-at-Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Sample</strong></td>
<td>28</td>
<td>18,779</td>
<td>0.0015</td>
</tr>
<tr>
<td><strong>Not Inducted</strong></td>
<td>9</td>
<td>2,730</td>
<td>0.0033</td>
</tr>
<tr>
<td><strong>On Study XR-NTX</strong></td>
<td>1 or 2</td>
<td>3,471</td>
<td>0.0003 - 0.0006</td>
</tr>
<tr>
<td><strong>On Study BUP-NX</strong></td>
<td>0</td>
<td>5,532</td>
<td>0.0000</td>
</tr>
<tr>
<td><strong>On Study Medication</strong></td>
<td>1 or 2</td>
<td>9,003</td>
<td>0.0001 - 0.0002</td>
</tr>
<tr>
<td><strong>Not On Study Medication</strong></td>
<td>26 or 27</td>
<td>9,776</td>
<td>0.0027</td>
</tr>
</tbody>
</table>
Conclusions

1. In these settings more difficult to start XR-NTX
2. Short LOS and methadone or buprenorphine detoxes make XR-NTX induction harder
3. Nearly all induction failures quickly relapsed
4. Better overall opioid outcomes for BUP-NX group in Intent-to-Treat Sample directly related to differential induction failure
5. Essentially equivalent safety and effectiveness for XR-NTX and BUP-NX in Per-Protocol Sample
6. No differences in AEs, SAEs, ODs and fatal ODs
7. Medication appears to reduce OD risk
Take-Home Messages

- Once-initiated, XR-NTX and BUP-NX are equally safe and effective
- For some patients, a detox hurdle complicates XR-NTX initiation but we know more about that now and can, in part, address it
- Patients, families, providers can now make important and long-term treatment choices based on preference, lifestyle, experience and hard data
- Because of the many agonist/antagonist differences these are real choices
- The research community needs to develop better NTX induction strategies and better treatment retention strategies
- Policy-makers need to expand treatment options and get more people into treatment
- More to come – genetics, health economics, moderator analyses
Thanks

- Study Participants
- Study Site Teams
  Avery Road  Bellevue
  ETS/RCKC  Gateway
  Maryhaven  SSTAR
  Tarzana  Turquoise Lodge
- EMMES CCC
- EMMES DSC
- NIDA CCTN
- PRB / DSMB
- Lead Node Team
Extended-Release Naltrexone vs Buprenorphine for Opioid Treatment (X:BOT):
Who Responds to Which Treatment? Moderator Analysis and Clinical Impressions

Edward Nunes MD
New York State Psychiatric Institute
Columbia University Medical Center
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Disclosures (presenters)

- Nunes
  - Study medication and study funding from Alkermes; unpaid consultant to Alkermes; study funding from Braeburn-Camerus; unpaid consultant to Alkermes, Braeburn-Camerus
Acknowledgement

- CTN-0051 acknowledgements listed previously
- Statisticians, Jennifer Scodes and Dr. Martina Pavlicova
Overall Goal

- Given that sublingual buprenorphine-naloxone (BUP-NX) and extended release injection naltrexone (XR-NTX) appear to be close in effectiveness:
  - How to begin to think about patient-treatment matching?
  - How to select the best treatment for a given patient based on his/her demographic and clinical characteristics?
  - What are the pragmatic clinical issues in implementing these two medication treatments in real world treatment settings?
Outline

- Moderator analysis of CTN-0051/X:BOT Trial
  - What characteristics of patients (if any) indicate that a patient is more likely to respond well to buprenorphine (BUP-NX), as opposed to injection naltrexone (XR-NTX), and vice versa

- Clinical impressions and issues with real world implementation
Moderator Analysis

- Moderator analysis asks whether characteristics of patients, measured at baseline, predict a different response (better/worse) to one treatment than another
  - For example: Homelessness (yes/no) is a moderator if:
    • Naltrexone works better than buprenorphine if the patient is homeless
    • Buprenorphine works better than naltrexone if the patient is not homeless
- Outcome: Relapse to opioid use during the 6 month trial (yes/no)
- Two samples
  - Intent to Treat (all randomized)
  - Per protocol (patients who initiated medication)
- Logistic regression models:
  - Relapse (yes/no) = treatment (BUP-NX, XR-NTX) + Moderator (yes/no) + interaction term (Treatment X Moderator)
Relapse Binary (yes/no) by the End of 6 Month Trial

Intent to Treat N = 570

Per Protocol N = 474
Moderator Variables Examined

- Demographics (including homelessness, criminal justice involvement)
- Severity
  - Opioid severity: IV use, heroin vs rx opioids, severity stratification factor, age at onset, duration of opioid use disorder
  - Other drug/alcohol severity: current use (yes/no), DSM-5 diagnosis
  - Psychiatric severity and physical pain severity
- Friends or family using drugs, living with drug/alcohol users
- Preference for BUP-NX or XR-NTX
- Treatment History
- Past experience with opioid withdrawal (how tolerable/intolerable?)
- Timing of randomization (early in detox hospitalization vs later)
Moderator Analysis: Results

- Few significant moderators, modest effects
- Two moderators significant after correction for multiple comparisons
  - Homelessness
  - Timing of Randomization (Early vs Late)
- Three moderators significant (P < .05) before correction
  - Hispanic
  - DSM-5 cocaine diagnosis
  - First treatment episode
- Trends
  - Current cigarette smoker, current heroin user, duration opioid use, Friends/family opioid users
Moderator: Homelessness

- If not homeless, better outcome (less relapse) on buprenorphine (BUP-NX)
- If homeless, better outcome (less relapse) on naltrexone (XR-NTX)

Percent of patients with No Relapse over 6 month trial:

<table>
<thead>
<tr>
<th></th>
<th>All Randomized Sample</th>
<th>Per Protocol Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Naltrexone XR-NTX</td>
<td>Buprenorphine BUP-NX</td>
</tr>
<tr>
<td>Not Homeless (N = 427)</td>
<td>29</td>
<td>44</td>
</tr>
<tr>
<td>Homeless (N = 143)</td>
<td>45</td>
<td>28</td>
</tr>
</tbody>
</table>
Proportion Not Relapsed after 6 Months

<table>
<thead>
<tr>
<th></th>
<th>XR-NTX¹</th>
<th>BUP-NX</th>
<th>XR-NTX²</th>
<th>BUP-NX²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Homeless</td>
<td>29</td>
<td>44</td>
<td>45</td>
<td>28</td>
</tr>
<tr>
<td>Homeless</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Series1          | Series2 |
Moderator: Timing of Randomization

- **All Randomized sample: Late randomization, better outcome on BUP-NX**
- **Per Protocol sample, early randomization, better outcome on XR-NTX**
- **Percent with No Relapse over 6 month trial:**

<table>
<thead>
<tr>
<th></th>
<th>All Randomized Sample</th>
<th>Per Protocol Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Naltrexone XR-NTX</td>
<td>Buprenorphine BUP-NX</td>
</tr>
<tr>
<td>Early Randomization (N = 217)</td>
<td>31</td>
<td>29</td>
</tr>
<tr>
<td>Late Randomization (N = 353)</td>
<td>34</td>
<td>47</td>
</tr>
</tbody>
</table>
Moderators Significant (p < 0.05) but not after correction for multiple comparisons

- Hispanic
  - Naltrexone worse outcome among Hispanics, only in Intent to Treat (All Randomized) sample

- DSM-5 cocaine diagnosis
  - Buprenorphine (BUP-NX) better outcome if no cocaine diagnosis in All Randomized sample
  - Naltrexone (XR-NTX) trend better outcome if DSM-5 cocaine use disorder in Per Protocol sample

- First treatment episode
  - Buprenorphine (BUP-NX) better outcome if not the patient’s first treatment episode, in all randomized sample
  - Naltrexone (XR-NTX) better outcome if it was the patient’s first treatment episode in the Per Protocol sample
Trends favor buprenorphine (BUP-NX) if not a current smoker, no current heroin use, shorter duration heroin use. BUP-NX and naltrexone (XR-NTX) relatively even if current smoker, current heroin user, longer duration of opioid use.

Trend favored buprenorphine if patient expressed preference for buprenorphine

Trend favors BUP-NX if no friends or family members use heroin. BUP-NX and XR-NTX relatively even if friends or family members are using heroin.
Moderator Analysis: Conclusions

- Few significant moderators
  - Homelessness, Timing of randomization
  - Hispanic ethnicity, First treatment episode, DSM-5 cocaine diagnosis—did not survive correction of p level

- Effects are modest, of heuristic interest
  - Not large enough to provide definite advice to an individual patient on treatment choice

- Most moderator variables not significant
  - Age, most other demographics, and most of the severity variables (substance use severity, psychiatric severity, pain)

- Baseline patient characteristics don’t provide strong guidance on choice of BUP-NX or XR-NTX for an individual patient
Relapse Binary (yes/no) by 6 Months: Focus on Failure to Initiate

Intent to Treat N = 570
Per Protocol N = 474
CTN-0051: Induction Success (%) by Site

<table>
<thead>
<tr>
<th>Site</th>
<th>XR-NTX</th>
<th>BUP-NX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site 1</td>
<td>57</td>
<td>100</td>
</tr>
<tr>
<td>Site 2</td>
<td>55</td>
<td>95</td>
</tr>
<tr>
<td>Site 3</td>
<td>91</td>
<td>98</td>
</tr>
<tr>
<td>Site 4</td>
<td>83</td>
<td>100</td>
</tr>
<tr>
<td>Site 5</td>
<td>52</td>
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<td>Site 6</td>
<td>64</td>
<td>87</td>
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<tr>
<td>Site 7</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Site 8</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>
CTN-0051 Program Level Factors Associated with Greater Naltrexone Initiation Success

- Non opioid detoxification (clonidine based)
  - Methadone or buprenorphine taper puts a lot of long acting agonist-partial agonist onboard
  - Slow washout delays time when naltrexone can be started without precipitating withdrawal
  - Patients don’t always tolerate waiting: “I gotta go…” syndrome

- Availability of flexible longer length of stay
  - Ability to wait out that 7 to 10 days from last opioid exposure in a protected environment
CTN-0051 Patient Level Factors Associated with Naltrexone Initiation Failure/Success

- **Initiation Failure > 35%**
  - Hispanic
  - Preference for buprenorphine
  - Current methadone use
  - High level of discomfort with opioid withdrawal (based on past experience)
  - (Current Pain)
  - Early Randomization (randomized while <= 3 days after last opioid use)

- **Initiation Failure < 20%**
  - Age less than 25 years
  - Homeless
  - Opioid analgesic user
  - Lives with an alcoholic or drug user
  - Late Randomization (randomized > 3 days after last opioid use)
Conclusions

- Characteristics of patients are of limited usefulness
  - Predicting success/failure to initiate buprenorphine or injection naltrexone
  - Predicting 6 month relapse

- Characteristics of treatment programs may be more important in determining treatment success
  - Medication initiation: inpatient versus outpatient, length of stay
  - Methods of managing patients over the long term: counseling, other supports, incentives
Extended-Release Naltrexone vs. Buprenorphine-Naloxone: A Comparative Effectiveness Trial

Joshua Lee, MD, MSc, Professor, Department of Population Health, New York University School of Medicine

Edward Nunes, MD, Professor of Psychiatry, Columbia University Medical Center / New York State Psychiatric Institute

Moderator: Judge David Tapp, JD, MS, 28th Judicial Circuit of Kentucky, and Member, National Rx Drug Abuse & Heroin Summit Advisory Board