EXTENDED-NALTREXONE for the Treatment of OPIOID USE DISORDER:

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Matt Iles-Shih, MD

Acknowledgement: Mark Duncan MD & Caleb Banta-Green MSW, MPH, PhD
GENERAL DISCLOSURES

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SPEAKER DISCLOSURES

✓ No conflicts of interest/disclosures
OBJECTIVES

1. Review pharmacology of extended-release naltrexone.
2. Distill the evidence around the use of extended-release naltrexone.
3. Identify clinical strategies for effective use of extended-release naltrexone.
OPIOID USE DISORDER TREATMENT BASICS

• Retention in treatment is KEY!
  – Medication assisted treatment
  – Psychosocial support

• Medication assisted treatment is the foundation for recovery in OUD
  – Help prevent relapse
  – Help prevent overdose
  – Extended duration of use → indefinite if needed

Medication-assisted Treatment (MAT) Options:

Agonists (Full & Partial Agonist) & Antagonist

- Full Agonist (Methadone)
- Partial Agonist (Buprenorphine)
- Antagonist (Naltrexone, Naloxone)
XR-NALTREXONE (XR-NTX)

• Use
  – relapse prevention for opioids and alcohol

• Mechanism of Action (MOA)
  – opioid receptor antagonist → (not abusable)

• Dose & Route
  – 380mg IM (gluteal, superior-lateral quadrant) Q4wks !!!

• Adverse Effects
  – headache, insomnia, dizziness, syncope, anxiety, low mood, fatigue, N/V, abdominal pain, body aches, suicidal ideation, low libido, rash, elevated liver enzymes
  – Common: injection site reaction

Injection Video: https://vimeo.com/101010120/940e72505d
XR-NALTREXONE
Pharmaco-dynamics/kinetics

• High Mu affinity
  – it will displace all opioids!

• Peak
  – biphasic w/ ~2hrs and then 2-3days

• Duration & Half-life
  – 4wks; 5-10 days
    • Plasma XR-NTX not detected at 42 days (healthy vol)

• Metabolism
  – Primarily hepatic, excreted in urine.

REVIEW OF EFFECTIVENESS FOR EXTENDED-RELEASE NALTREXONE
EFFECTIVENESS OF XR-NALTREXONE VS PLACEBO

• Improves treatment retention
  – At end of 24 week trial

<table>
<thead>
<tr>
<th>XR-Naltrexone (N=126)</th>
<th>Placebo (N=124)</th>
</tr>
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<tbody>
<tr>
<td>53%</td>
<td>37%</td>
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• Reduces opioid use

<table>
<thead>
<tr>
<th></th>
<th>XR-Naltrexone</th>
<th>Usual Treatment (counseling and referral)</th>
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</thead>
<tbody>
<tr>
<td>Median Time to Relapse</td>
<td>10 weeks</td>
<td>5 weeks</td>
</tr>
<tr>
<td>Lower Rate of Relapse</td>
<td>43%</td>
<td>64%</td>
</tr>
<tr>
<td>Higher rate of opioid negative urines</td>
<td>74%</td>
<td>56%</td>
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NRwegian Trial

- 3 months, N=149
- Open-label, randomized after inpt detox

**Results**
- Similar Efficacy
- Retention: no diff. (drop outs: 24 vs 29 – Bup)
- Opioid Neg Urine Tests: no difference
- Reported use of Heroin & Other Opioids: XR-Naltrexone superior
- Cravings: no diff
- Satisfaction w/Tx: XR-NTX>Bup

**Other Notes**
- Only 3 months
- Pts post-med managed w/d
- Observed *daily* Buprenorphine dosing
- Low mean Buprenorphine dose (11.2mg)

Tanum L, et al, 2017
XR-NALTREXONE VS BUPRENORPHINE-NAL

USA Trial

– 6 months, N=570

• Results

<table>
<thead>
<tr>
<th></th>
<th>XR-Naltrexone</th>
<th>Bup-Nal</th>
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<tbody>
<tr>
<td>Drop Out Before Induction</td>
<td>79 (28%)</td>
<td>17 (6%)</td>
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<tr>
<td>Higher risk of relapse</td>
<td>185 (65%)</td>
<td>163 (57%)</td>
</tr>
<tr>
<td>Weekly Opioid Negative Urines</td>
<td>4</td>
<td>10</td>
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<tr>
<td>Self-reported days abstinent</td>
<td>39</td>
<td>81</td>
</tr>
</tbody>
</table>

• Other Notes

– Similar efficacy if induction was successful
– All participants recruited from detox centers
– Retention challenge in both groups (43%-47%)
– Cravings: initially less w/NTX, no diff at 6mo

Lee JD, et al, 2018
BOTTOMLINE

XR-NTX will work...
if you can get someone on it
...and keep them on it.

Question:
Are there patient traits that have emerged to suggest who might have more success starting and staying on XR-Naltrexone?
TRAITS ASSOCIATED WITH SUCCESSFUL INDUCTIONS

- Post long-term detox (>21 days)
- Induction prior to release from prison
- 8 day naltrexone-assisted detox
- Fewer daily opioids
- Prescription opioid users
- Older age
- Pre-enrollment cannabis use
- Contingency Management

TRAITS ASSOCIATED WITH LONGER TREATMENT RETENTION

Characteristics associated with 6 mo of Tx

- Baseline employment
- Higher education
- Private health insurance
- Fewer mental health problems
- Less drug use

**NO CLEAR EVIDENCE BASE TO SUGGEST WHICH OF THESE TRAITS ARE MEANINGFUL**
MATCHING PATIENT/CLIENT TO THE APPROPRIATE THERAPY
MAT: Who is Appropriate for Which Rx?

Opioid agonists (full & partial)

- 1\textsuperscript{st} line for most pts w/moderate-severe OUD
  - h/o overdoses
  - Unable to tolerate detox
  - Chronic pain requiring opioid treatment
  - Advanced liver disease
  - Serious mental illness

- Advantages:
  - Easier to initiate (higher tx retention)
  - Larger, generalizable body of evidence
MAT: Who is Appropriate for Which Rx?

Who is appropriate for extended release naltrexone (XR-NTX)?

• **Group #1:** Are highly motivated and...
  – OUD of limited duration, mild severity &/or
  – Work related proscriptions against OAT (e.g., CDLs, pilots, some healthcare workers), &/or
  – Clinical context w/enhanced supervision/structure
  – Strong personal preference to be abstinent of all opioids.
  – Already abstinent
MAT: Who’s Appropriate for Which Rx? (cont)

Who is appropriate for XR-NTX?
• **Group #2**: Pts with behaviors/circumstances that substantially impact safety, rx compliance
  – Concurrent EtOH/Sed-Hypnotic misuse despite treatment
  – Cont. illicit opioid-use despite adequate agonist MAT
  – Evidence of diversion
  – Significant, unstable psychiatric disorders
  – Medical comorbidities w/risk of opioid-assoc. symptom exacerbation (e.g., ongoing acute pain-management, severe pulmonary ds.)

• **Group #3**: agonist therapy is not available
  – Institutional barriers, lack of local prescribers, etc.
NALTREXONE: SPECIAL POPULATIONS

• Infant
  – excreted in breast milk
  – avoid if possible

• Pregnancy
  – not well studied; some developmental abnormalities found in animal studies
  – check pregnancy test as indicated

• Geriatric
  – same as adult

• Adolescents
  – same as adult
GETTING STARTED (FINALLY!)

XR - Naltrexzone Induction
NALTREXONE: CAUTIONS & MONITORING

Potential Side Effects / Issues:

- Hepatocellular injury (rare, dose-dependent)
- Injection site rxs (vivitrol)—rarely clinically signif.
- Precipitated w/d (→ rx discontinuation)
- Analgesic blockade complicating pain management
  • Provide med alert bracelet
- Risk of OD: if pt stops (loss of tolerance) or attempts to overcome blockade

Monitoring:

- LFTs at initiation, at 1 mo, then annually
1. The “traditional” approach
   – Med-managed withdrawal (for patients actively using):
     • ≤ 7 days w/agonist or clonidine vs.
     • Stabilization & taper w/agonist
   – Patient should be opioid-free for “7-10 days” prior to XR-NTX induction
   – Withdrawal symptom management with ancillary medications
   – Often with:
     • Naloxone challenge prior to induction (most common), or
     • Trial PO naltrexone 25mg to ensure tolerability (less common)
# "TRADITIONAL" XR-NTX INDUCTION PROTOCOLS

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8</th>
<th>Day 15</th>
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<tr>
<td><strong>Non-Opioid</strong></td>
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<td>Ag/Ant</td>
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<td><strong>7 day washout</strong></td>
<td><strong>XR-NTX</strong></td>
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<tr>
<td>Supportive Meds</td>
<td><strong>Clonidine 0.1-0.2mg qid, Loperamide, Hydroxyzine, Prochlorperazine, Ibuprofen, Diazepam</strong></td>
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<th>Day 8</th>
<th>Day 15</th>
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<tbody>
<tr>
<td><strong>Bup</strong></td>
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<td></td>
<td><strong>Abstinent</strong></td>
<td><strong>Wash-out</strong></td>
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<td><strong>XR-NTX</strong></td>
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XR-NTX INDUCTION: HOW TO GET STARTED

2. Newer Protocols for Faster Induction

  • Randomized, open-label, controlled trial
  • 150 patients with DSM-IV OUD (heroin, prescribed opioids)
  • Randomized 2:1 to NTX- vs. Buprenorphine-assisted outpatient withdrawal protocol
  • Primary outcomes:
    – Successful XR-NTX induction
    – Receipt of 2\textsuperscript{nd} XR-NTX injection (5wk s/p induction)

Sullivan et al, 2017
### SULLIVAN’S NTX- & BUP.-ASSISTED PROTOCOLS

<table>
<thead>
<tr>
<th>Naltrexone (Exp Arm)</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8</th>
<th>Day 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag/Ant</td>
<td>Wash-out</td>
<td>Bup 2mg q1-2hr</td>
<td>Wash-out</td>
<td>NTX 1mg</td>
<td>NTX 3mg</td>
<td>NTX 12mg</td>
<td>NTX 25mg</td>
<td>XR-NTX</td>
<td></td>
</tr>
</tbody>
</table>

**Supportive Meds**

- **Clonidine 0.1mg qid, Clonazepam 0.5mg q6hr (max 2mg/day)**

**PRN**

- **Clonidine q2hr, Prochlorperazine 10mg TID, Traz 100mg qhs**

### Bup (Cont Arm)

<table>
<thead>
<tr>
<th>Bup (Cont Arm)</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8-14</th>
<th>Day 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag/Ant</td>
<td>Abstinence</td>
<td>Tapering Bup Dose</td>
<td>Wash-out</td>
<td>XR-NTX</td>
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**Supportive Meds**

- **PRNs given per clinic discretion**

Sullivan, et al., 2017
NTX- vs. BUPRENORPHINE-ASSISTED OUTCOMES
Outcomes:
• Week #1 dropout and w/d severity comparable
• XR-NTX induction & 2\textsuperscript{nd} dose (wk#5) \uparrow for NTX arm
• Pts using heroin faired worse, across the board

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Treatment Arm (n=150)</th>
<th>Population</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Naltrexone (n=98)</td>
<td>Buprenorphine (n=52)</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>XR-NTX Induction</td>
<td>56.1%</td>
<td>32.7%</td>
</tr>
<tr>
<td>2nd NTX Inj (5wks)</td>
<td>50.0%</td>
<td>26.9%</td>
</tr>
<tr>
<td>Complete 8-day Detox</td>
<td>56.1%</td>
<td>46.2%</td>
</tr>
<tr>
<td>Absent wk 4-5 (s/p induction)</td>
<td>78.2% (43/55)</td>
<td>88.2% (15/17)</td>
</tr>
<tr>
<td>Mod-Severe Withdrawal</td>
<td>Treatment-Time Interaction: Bup = faster improvement in withdrawal scores vs. NTX (\dagger)</td>
<td></td>
</tr>
</tbody>
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\(\dagger\) Statistically significant at \(\leq 0.05\)
OTHER STRATEGIES

1. Inpatient/residential settings:
   - expensive & not scalable
   - still w/high rates of AMA discharges & return to use

2. Minimize washout period for short-acting opioid users:
   - Risk of precipitated withdrawal exp w/subsequent tx aversion

3. Stabilize on an agonist for ≥ 1 week, then gradually taper to XR-NTX
   - Not rigorously studied
   - May not be practical for many pts heading towards NTX
OTHER SUGGESTIONS
For facilitating MAT with XR-NTX

• Well-managed withdrawal & induction (as we’ve discussed)
  – Tailored to the client/patient & to your clinic or practice
• Careful initial assessment; regular re-assessment
  – The shortest route to “there” depends on where “here” is
• Patient empowerment:
  – Longitudinal pt. education & collaborative treatment planning
• Strengthen patient-clinician relationship:
  – Nurture trust & communication
• Proactive maintenance rx (don’t let pt fall through the cracks)
  – Reach out to drifting pts
  – Pt tracking & reminders
  – scheduling appointments to coincide w/monthly injections
• Don’t give up!
  – Induction is a first step, sometimes repeatedly taken
  – Relapse prevention-planning
OTHER CONSIDERATIONS: Subacute Withdrawal

• Protracted Withdrawal
  – Insomnia, GI issues, hyperalgesia
  – Anxiety, irritability, dysphoria, anhedonia

• Address Symptomatically
  – Insomnia: Trazodone, Gabapentin
  – GI: H2 blockers, antinausea
  – Anxiety: Clonidine

• Should Remit by 2-4 Weeks

Bisaga, A, PCSS-MAT 2015
OTHER CONSIDERATIONS: Testing the Opioid Blockade

• Testing the Block
  – Up to 50% of patients will do this
    • May be on first day of discharge
    • May be frequent
    • Low dose opioids
OTHER CONSIDERATIONS:

Pain

• Pain Management
  – Emergency pain management
    • Regional anesthesia/nerve blocks
    • Non-opioid option
    • If opioids needed → approp. clinical setting, monitoring
  – Non-emergency pain management
    • Non-opioid options
OTHER CONSIDERATIONS:
Relapse

• Relapse Prevention & Management
  – Close follow-up: consider weekly at first
  – Cravings may persist over first 3-4 weeks
    • Consider oral naltrexone supplementation
    • Sobriety Support, Skill-building, other psychosocial tx
  – Signs of instability
    • Missed appointments
    • Positive urine drug screens
  – Consider Transition to agonist
    • Wait until week 4-no point to try earlier
    • No withdrawal needed to wait for
OTHER CONSIDERATIONS:

Logistics

– WA State Apple Health: no PA required, no limits
– No waiver needed
– Stored in the fridge
– Warm up 45min before injection
– Can return to fridge after getting to room temperature for further storage

– Think through plan/workflow for induction
  • Actively using opioids
  • Not using opioids
  • Naloxone challenge
DISCUSSION AND QUESTIONS

• What’s been your experience with XR-NTX?

• What challenges & benefits have you run across (or might anticipate) for your clinic and patients?
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