THE PATIENT-CENTERED APPROACH TO EXTENDED-RELEASE NALTREXONE (XR-NTX)

David R. Gastfriend, MD DFASAM

Chief Architect, CONTINUUM - The ASAM Criteria Decision Engine, ASAM
Chief Medical Officer, DynamiCare Health, Inc.
Senior Research Scientist, Treatment Research Institute/Public Health Management Corp.

Disclosure Information

David R. Gastfriend M.D., DFASAM

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Purpose of the Workshop

- The FDA approved IM Extended-Release Naltrexone (XR-NTX) for prevention of opioid use disorder (OUD) relapse post-Detox.
- XR-NTX differs from previous Medication Assisted Treatments (MATs) in terms of:
  - Abstinence
  - Blockade
  - Duration of action
  - Psychological effects
  - Impact on behavior
- We will review XR-NTX’s pharmacology, clinical indication, formulation, patient selection issues, patient initiation protocols, counseling approaches, contraindications, adverse effects, & treatment completion.

Objectives:

As a result of this workshop, participants will be able to:

- Describe how the unique brain receptor actions and time-course of XR-NTX in OUD treatment impact patients.
- Implement clinically effective use of XR-NTX with psychosocial treatment.
- Help patients to understand, select, initiate and sustain XR-NTX treatment for effective relapse prevention and recovery in OUD.
Reward/Motivation ("Go" signals) & Inhibitory Control ("No Go") are disrupted & must be addressed in prevention & treatment

Brain Structure: Regions & Roles

Opioid Antagonist

**Antagonist**
- Naltrexone
- Blocks opioid receptor
- Preferentially binds to the opioid receptors
- Displaces opioids
Brain Reward: Clinical Pharmacology

Reward & Positive Reinforcement

- Pain: brain's natural signal to protect the body
- Proper goal of pain medicine: alleviate *but not eliminate* pain
- Exceeding pain alleviation – risks euphoria
- Euphoria = reward
- Repeated reward $\rightarrow$ positive reinforcement
- The “Go” System
Withdrawal & Negative Reinforcement

- Opioid drugs all wear off after a while
- When excessive opioid doses wear off, the brain is in withdrawal
- Withdrawal is an uncomfortable, even painful state even worse than the pain preceding the medicine
- This negative effect → wanting to keep taking opioids, known as negative reinforcement
- Disrupted ability of inhibitory control damages the “No Go” system

A Biopsychosocial Disorder: Treatment + Chemistry

Medications (All FDA-approved Agents)

Behavioral Therapies (Including Contingency Management*)

Medical Detoxification Services

Recovery Support Services

*Sanctions: measured, prompt, scientifically sound
### Goals of Anti-Opioid Pharmacotherapy

- **Withdrawal Management** alone: *inadequate care*
- **Early recovery protection:** period of highest risk for OD
  - Death rates upon prison release = 12-100x that of general population
  - Harm reduction, e.g., from HIV and HEP C transmission
- **Anti-craving:** stabilize urges/impulses to use long enough to permit counseling effects to take hold
- **Stress Response Normalization:** OUD disrupts ACTH/Cortisol
- **Extinction:** of both positive and negative cue response
- **Biological Stabilization:** Eating, diurnal cycle, sexual function, capacity for self-care / activities of daily living / treatment retention, general healthcare, relationship bonding
- **NOT Recovery:** Disease acceptance, coping skills, rehab

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### VIVITROL (extended-release naltrexone; XR-NTX)

- VIVITROL is indicated for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with VIVITROL
  - Patients should not be actively drinking at the time of initial VIVITROL administration
- VIVITROL is indicated for prevention of relapse to opioid dependence, following opioid detoxification
  - Opioid-dependent patients, including those being treated for alcohol dependence, **must be opioid-free for a minimum of 7–10 days** before starting VIVITROL treatment
- Treatment with VIVITROL should be part of a comprehensive management program that includes psychosocial support
- VIVITROL has a boxed warning related to hepatotoxicity
  (Alkermes, FDA-approved labeling)
**VIVITROL Pharmacokinetics**

Mean Steady-State NTX Concentration

- *Predicted concentrations based on rapid achievement of steady state and literature evidence*


Plasma concentrations do not necessarily correlate with clinical efficacy.

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**INJECTABLE EXTENDED-RELEASE NALTREXONE FOR OPIOID DEPENDENCE: A Double-Blind, Placebo-Controlled, Multicentre Randomised Trial**

(*The Lancet, 2011;377:1506-1513*)

E Krupitsky¹, EV Nunes², W Ling³, A Illeperuma⁴, DR Gastfriend⁴, BL Silverman⁴

¹ Bekhterev Research Psychoneurological Institute, St Petersburg State Pavlov Medical University, St Petersburg, Russia
² New York State Psychiatric Institute and Department of Psychiatry, Columbia University, New York, NY, USA
³ Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles, Los Angeles, CA, USA
⁴Alkermes, Inc., Waltham, MA

**Funding:** Alkermes Inc.

**Objective:** To assess the efficacy, safety and patient-reported outcomes of an injectable, once monthly extended-release formulation of the opioid antagonist naltrexone for the treatment of patients with opioid dependence after detoxification
Secondary Endpoint: Treatment Retention

![Graph showing treatment retention with Placebo (N=124) and VIVITROL (n=126)].

Log-rank P = 0.0042 (adjusted)

Secondary Endpoint: Craving

- Baseline craving scores: VIVITROL=18; Placebo=22
- VIVITROL patients had a 50% reduction from baseline in VAS-craving vs. no change for placebo

![Graph showing mean change in VAS-craving score over treatment weeks].

Adjusted P-value based on generalized estimation equation model assuming normal distribution and autoregressive correlation structure.
Norway Study: XR-NTX vs. BUP/NAL
(Tannum et al. JAMA Psychiatry 2017)

QUESTION: Is XR-NTX as effective for heroin-OUD as buprenorphine/naltrexone (BUP/NAL)?

DESIGN: 12-week, multicenter, outpatient, open-label Random-control Trial (RCT) at 5 urban addiction clinics in Norway with 232 adults from outpatient addiction clinics & detox units.

INTERVENTIONS: Randomization to either daily flex-dose BUP/NAL, 4 to 24mg/d, or XR-NTX 380mg IM every 4th week for 12 weeks.

SAMPLE: 159 participants, mean age 36 years, 27.7% women.

80 randomized to XR-NTX and 79 to BUP/NAL; 66.0% completed.
Norway Study: XR-NTX vs. BUP/NAL  
(Tannum et al. JAMA Psychiatry 2017)

RESULTS:
Retention:  
XR-NTX non-inferior to BUP/NAL: 69.3 vs. 63.7 days

Opioid (–) Urines:  
XR-NTX non-inferior to BUP/NAL: 90% vs. 80% (p<.001)

CONCLUSIONS:  
XR-NTX was effective as BUP/NAL for short-term abstinence from heroin & other illicit substances
Norway Study: XR-NTX vs. BUP/NAL  
(Tannum et al. JAMA Psychiatry 2017)

- Induction into XR-NTX treatment required full detox to a greater extent than into the BUP/NAL
- The Norwegian detox guidelines turned out to be insufficient
- Detox frequently produced withdrawal (WD) adverse effects on induction of XR-NTX and, to some extent, BUP/NAL
- The study therefore changed its detox strategy in the 1st year in accordance with the literature
- These changes reduced new adverse events from induction

NIDA XBOT Study  
(Lee et al., Lancet 2017)

QUESTION: How do XR-NTX vs. BUP-NAL differ in relapse rates?

METHODS:
24 week, open-label, comparative effectiveness RCT, at 8 US inpatient services with outpatient follow-up. Participants were ≥18 years with DSM-5 OUD, & used non-Rxed opioids in the past 30 days.

INTERVENTION: Vivitrol vs. Suboxone SL film

OUTCOME:
Opioid relapse-free survival: Relapse was 4 consecutive weeks of any non-study opioid use by urine or self-report, or 7 consecutive days of self-reported use
**NIDA XBOT Study** *(Lee et al., Lancet 2017)*

**XR-NTX Induction Process**

- **Detox, length of stay (LOS):** not protocol-derived; varied by site.
  
  **Detox Options:**
  
  - **Opioid-free:** No opioids; clonidine/comfort meds (2 sites)
  - **Short Stay:** 3–5 day methadone taper (4 sites)
  - **3–14 day BUP taper:** (2 sites)
  
  - Before XR-NTX induction, patients had to:
    
    - complete detox (≥3 days from last opioid)
    - have opioid-negative urine
    - have a negative Naloxone Challenge Test
      (= no/minimal opioid WD after naloxone ≥0.4 mg IM/SQ/IV)

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**NIDA XBOT Study** *(Lee et al., Lancet 2017)*

- 570 randomly assigned

- 283 randomly assigned to XR-NTX treatment
  
  - Randomisation timing status: <3 days vs. ≥3 d
  - 107 early randomisation group: 53% completed
  - 176 late randomisation group: 84% completed
  - Induction status
  - 204 inducted to XR-NTX treatment
  - 79 induction failures: 39%

- 287 randomly assigned to BUP-NX treatment
  
  - Randomisation timing status
  - 110 early randomisation group
  - 177 late randomisation group
  - Induction status
  - 270 inducted to BUP-NX treatment
  - 17 induction failures: 6%

**XR-NTX induction success varied by site:**

- Short Stay, methadone-taper unit: 52%
- Opioid-free extended-stay site: 95%

No difference in induction or relapse for either medication **in men vs. women**
Opioid Craving: Visual Analog Scale self-report, range 0–100

- Per-protocol BUP-NX (n=270)
- Per-protocol XR-NTX (n=204)

*p=0.0012 at wk 7  
*p=NS at wk 24

NIDA XBOT Study (Lee et al., Lancet 2017)

Retention in All Randomized Patients (N = 570)  
Retention in All Inducted Patients (N = 474)
### XR-NTX group (n=283) vs. BUP-NX group (n=287)

#### Treatment effect

<table>
<thead>
<tr>
<th>Induced to study medication</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat group</td>
<td>0.16 (0.09-0.28)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Opioid relapse, weeks 3-24</td>
<td>OR 1.44 (1.02-2.01)</td>
<td>0.036</td>
</tr>
<tr>
<td>Per-protocol group</td>
<td>OR 0.87 (0.60-1.25)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

#### Relapse-free survival (weeks), range 3-24

| Intention-to-treat group | HR 1.36 (1.10-1.68) | p=0.0040 |
| Per-protocol group       | HR 0.92 (0.71-1.18)  | p=0.49   |

#### Total number of weekly opioid-negative urine samples, range 0-24

| Intention-to-treat group | 4 (0-9) | <0.0001 |
| Per-protocol group       | 13 (3-21) | p=0.81  |

#### Total number of self-reported opioid-abstinent days, range 0-144

| Intention-to-treat group | 39 (1-144) | <0.0001 |
| Per-protocol group       | 123 (18-144) | p=0.67   |

Data are n (%), n/N (%), or median (IQR). XR-NTX=extended-release naltrexone. BUP-NX=buprenorphine-naloxone. OR=odds ratio. HR=hazard ratio.

### NIDA XBOT Study (Lee et al., Lancet 2017)

#### OVERDOSE EVENTS

<table>
<thead>
<tr>
<th></th>
<th>XR-NTX (N=283)</th>
<th>BUP/NAL (N=287)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants with one or more overdose event (all)†</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Participants with one or more overdose event (per protocol)‡</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Number of overdose events (all)§</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Number of overdose events (per protocol)</td>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>

#### Fatal overdose events

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of fatal overdose events (all)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Number of fatal overdose events (per protocol)</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

†p=0.14 (Fisher’s exact). ‡p=0.31 (Fisher’s exact).
§4 participants reported >1 OD. 3 of the 4 were randomly assigned to XR-NTX (2 were induction failures, 1 successfully inducted); each reported 2 ODs. One of the 4 was assigned to BUP/NAL (successfully inducted) & reported 3 ODs. None of these 9 overdoses were fatal.
**NIDA XBOT Study** (Lee et al., Lancet 2017)

**FINDINGS (n=570): XR-NTX (n=283) vs. BUP-NAL (n=287)**

- Fewer initiated XR-NTX 72% vs. BUP-NX 94%; \( p<0.0001 \)
  Overall (intention-to-treat population, n=570)
  24 week relapse events: XR-NTX 65% vs. BUP-NX 57%

- Almost all of the difference was due to early relapse in 89% of XR-NTX induction failures

- Among successfully inducted participants (n=474),
  24 week relapse events were similar.

- Self-reported opioid craving was initially less with XR-NTX \( (p=0.0012) \), then converged by week 24 \( (p=0.20) \)

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**NIDA XBOT Study** (Lee et al., Lancet 2017)

- Aside from mild-to-moderate XR-NTX injection site reactions, adverse events did not differ between groups

- 5 fatal ODs occurred (2 XR-NTX; 3 BUP-NAL).

- Most ODs occurred months after the last dose
  Or, for participants who were not inducted, long after detox

- Thus, it is difficult to attribute an association between study med & overdose

**CONCLUSION:**

- More difficult to initiate XR-NTX

- But once initiated, both meds were equally safe & effective

- Need to focus on induction
NIDA XBOT Study (Lee et al., Lancet 2017)

570 randomly assigned

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No difference in induction or relapse for either medication in men vs. women

Percent of patients with Good Clinical Response (≥ 90% urine-confirmed abstinent weeks) (Nunes et al., 2015)

<table>
<thead>
<tr>
<th>Baseline Predictor Variable</th>
<th>Percent of Patients with Good Clinical Response (≥ 90% Urine-Confirmed Abstinent Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower Severity XR-NTX</td>
</tr>
<tr>
<td>Clinical Global Impression Severity (CGI-S)</td>
<td>58.6% (17/29)</td>
</tr>
<tr>
<td>SF-36 Mental Component</td>
<td>48.4% (31/64)</td>
</tr>
<tr>
<td>EQ-5D Health</td>
<td>58.0% (29/50)</td>
</tr>
<tr>
<td>Craving at Baseline</td>
<td>42.7% (29/68)</td>
</tr>
<tr>
<td>HIV Sero-status</td>
<td>HIV Negative</td>
</tr>
<tr>
<td></td>
<td>48.7% (36/74)</td>
</tr>
</tbody>
</table>

Descriptive analysis of baseline predictor-by-treatment interactions, significant at p ≤ 0.15 – ≥ 0.05. Baseline predictor variables that are continuous or count variables are dichotomized at the median split into lower and higher groups.

* None of the putative predictor variables yielded significant (p<0.05) interactions with treatment.
XR-NTX Warnings & Precautions

- Unintended Precipitation of Opioid Withdrawal
- Opioid Overdose at the End of a Dosing Interval, After Missing a Dose and Following an Attempt to Overcome Opioid Blockade
- Pain Management
- Injection Site Reactions
- Hepatotoxicity
- Eosinophilic Pneumonia
- Hypersensitivity Reactions
- Depression and Suicidality
- Interference with Laboratory Tests

Adverse Events (AEs)

- Side effects can occur with any medication
- AEs fall into basic categories:
  - Serious Adverse Events (SAEs) – rare, but need to anticipate; may require Emergency Dept. (ED)
  - Routinely advise patients to expect common, mild to moderate side effects
- Of greatest concern early; mentoring helps
  - With experience, these become less frequent
- Vivitrol precipitated opioid withdrawal: not a side effect but is an adverse event due to inadequate withdrawal.
- Phone mentors to report these episodes, so they can help improve success with detox and induction.
Common Clinical Adverse Events (AEs)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>VIVITROL (N=126)</th>
<th>Placebo (N=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine aminotransferase increased</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>Gamma-glutamyltransferase increased</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td>Influenza</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Toothache</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Headache</td>
<td>3%</td>
<td>2%</td>
</tr>
</tbody>
</table>

| > 1 serious adverse event               | 2%               | 3%              |
| Discontinued due to serious adverse event| 2%               | 2%              |

No overdose events or other severe AEs were reported.

In the Placebo group, 4 patients reported 5 SAEs: 2 infectious, 1 drug dependence, 1 psychotic disorder and 1 peptic ulcer.
In the VIVITROL group, 3 patients reported 4 SAEs: consisting of infectious process, e.g., AIDS/HIV or other infection.
Krupitsky E et al. Lancet. 2011;1506-13
Data on File. Alkermes, Inc.

XR-NTX and Hepatic Safety

- Originally FDA required Black Box Warning
- Oral NTX trials found Liver Function Tests (LFTs) — BUT, this was based on doses at 5-7x normal
- NTX-PO is safely used to treat pruritis in jaundiced patients with severe liver disease
- Two studies with XR-NTX found no clinically significant LFTs One each in alcohol and opioid dependence; the latter with 40% HIV+ and 90% chronic HepC+ patients (Mitchell et al., 2015)
- FDA subsequently removal of Black Box Warning for Vivitrol
HCV & HIV+ Sub-groups: LFT Increases >3x Upper Limits of Normal (ULN) After Initial Dose

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Extended-release naltrexone 380 mg N = 107</th>
<th>Placebo N = 85</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>21 (19.6%)</td>
<td>11 (12.9%)</td>
<td>.876</td>
</tr>
<tr>
<td>AST</td>
<td>15 (14.0%)</td>
<td>9 (10.6%)</td>
<td>.713</td>
</tr>
<tr>
<td>GGT</td>
<td>25 (23.4%)</td>
<td>18 (21.2%)</td>
<td>.811</td>
</tr>
</tbody>
</table>

ALT: Alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase

Subanalysis: patients (N=250) with chronic Hep C (88.8%) or HIV+ (42%)

ALT, AST & GGT >3X ULN normal: XR-NTX & PBO not significantly different

Elevations >3X ULN were primarily, but not exclusively in Hep C+ patients

In patients with elevations >3X ULN, AST levels returned toward baseline during follow up. No specific symptoms were associated with these elevations. (Mitchell et al., 2012)

Drug-Drug Interactions

- Few with the current MAT options, but require prospective awareness/monitoring
- Precipitated opioid withdrawal
  - not a side effect, an adverse event from incomplete detox
  - worse than Cold Turkey withdrawal
  - avoiding this is the goal of effective MAT Induction

FINAL WORDS OF WISDOM...

- Encourage patient to call
- Call the patient to check-in
- REVISE THE PLAN, including escalating Level if needed
### XR-NTX & Pleasure (Alcohol)

#### % Reporting Daily Activities as Pleasurable (N=72)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Very much</th>
<th>Quite a bit</th>
<th>Moderately</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gambling (N=26)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shopping (N=70)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eating sweets (N=72)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Exercising or participating in sports (N=57)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eating spicy foods (N=56)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Playing cards or games (N=41)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reading (N=71)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watching sports (N=51)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual relationships (N=55)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Being with friends (N=70)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eating good food (N=74)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Listening to music (N=71)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drinking alcohol (N=53)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

O’Brien et al., Am J Addiction 2011

### XR-NTX Continuation Post-Pain

(Earley et al., 2013)

- ~92% of subjects reporting receipt of a pain med for a pain-related AE received at least one more XR-NTX dose
- ~95% of all pain-related AEs reported were not associated with study discontinuation*

*As defined by no additional XR-NTX doses after the dosing of pain medication for a pain-related AE (Note: AEs or SAEs occurring >7 weeks after previous XR-NTX dosing were omitted from our analysis).
Pregnancy

- XR-NTX: Category C; opioid withdrawal can lead to spontaneous abortion or premature labor and delivery
- NTX exposure during pregnancy does not appear to alter rodent maternal health or result in congenital malformations
- NTX can prevent pregnancy-induced hypoalgesia, requiring NSAID coverage/local-regional anesthesia
- NTX-PO & Implants: Limited naturalistic studies show no adverse fetal effects; neonatal outcomes generally within normal limits
- NTX & metabolites appear in breast milk, but overall dose to the infant is 1% of the mother’s dose


Be Vigilant For Risks

- MAT blockade testing & override attempts
- Seeking prescribed opioids (either excessive agonist MAT doses or analgesics) to divert them for income – despite MAT
- Not adhering to prescribed regimens
- Returning late for refills
- Premature discontinuation.
- Address risks proactively: advise patient, supportive others, providers; monitor attendance & drug tests; communicate among addiction/medical/justice teams in timely fashion; re-assess & modify plan/ escalate as needed, over & above MAT
XR-NTX: Testing the Blockade

- As many as half of patients will “test” blockade
- Usually during the 1st month after detox; many on discharge day
- Thus, 1st injection is better 2d before discharge; if given on last day & risk of testing, supplement with NTX-PO
- Most, after unsuccessfully testing 1-3 times, stop testing
- Rarely, (but reported) patient could use high amounts such that physical dependence could recur

XR-NTX: 4th Week Effect

- Anecdotally, patients report XR-NTX wearing off by 4th week
- Russian Phase IV RCT analyzed week-by-week findings
- Week 4 did show:
  - Increased craving
  - Increased drug use
  - Increased dropout
- However, these changes occur at same rate in BOTH XR-NTX and Placebo patient groups
- Conclusion:
  - There is a 4th Week Effect
  - It is non pharmacological
  - Therefore, need counseling to address expectancy & ambivalence
  - Counseling must anticipate the 4th week effect from start of treatment
**4th Week Effect? Discontinuation**

Gastfriend, et al., 2013

- There is no single proven method, however, success has been found with Inpatient AND Outpatient approaches

- Success = No precipitated withdrawal AND >50% of patients retained through 1st XR-NTX injection

- KEY: Close contact & attention to the patient’s changing needs

- Setting expectations, providing support AND structure
### XR-NTX: WD Symptoms on Initiation

- Withdrawal is commonly compared to the flu
  - Aches, pains, insomnia, nausea, anergia
  - Anxiety, irritability, dysphoria, anhedonia
- **Aggressive** symptomatic treatment helps
  - Insomnia: zolpidem, trazodone, quetiapine
  - GI distress: H2 blockers
  - Anxiety/hyperarousal: clonazepam, clonidine
- Most symptoms remit in 2-4 weeks
  - Prolonged symptoms are rare
    & likely represent additional psychopathology

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### Clinical Opioid Withdrawal Score

1. **Resting pulse rate:**  
   - 0 80 or below  1 81–100  2 101–120  4 >120

2. **Sweating:** over past half hour  
   - 0 None  
   - 1 Subjective chills or flushing  
   - 2 Flushed or moisture on face  
   - 3 Beads of sweat on brow or face  
   - 4 Sweat streaming off face

3. **Restlessness:** during assessment  
   - 0 Able to sit still  
   - 1 Reports difficulty sitting still  
   - 3 Frequent movements  
   - 5 Unable to sit still >few seconds

4. **Pupil size**  
   - 0 Pupils pinned or normal size  
   - 1 Possibly larger than normal  
   - 2 Pupils moderately dilated  
   - 5 Dilated; only rim of iris visible

5. **Bone or joint aches:** (due to WD)  
   - 0 None  
   - 1 Mild diffuse discomfort  
   - 2 Severe diffuse joint/muscle ache  
   - 4 Rubbing joints/muscles

6. **Runny nose or tearing:** not from cold  
   - 0 None  
   - 1 Stiffness or unusually moist eyes  
   - 2 Nose running or tearing  
   - 4 Constant nose running or tearing
Clinical Opioid Withdrawal Score

7. GI upset: over last half hour
   - 0 No GI symptoms
   - 1 Stomach cramps
   - 2 Nausea or loose stool
   - 3 Vomiting or diarrhea
   - 5 Episodes of diarrhea or vomiting
8. Tremor: observe outstretched hands
   - 0 No tremor
   - 1 Tremor felt, but not observed
   - 2 Slight tremor observable
   - 4 Gross tremor or muscle twitching
9. Yawning: during assessment
   - 0 No yawn
   - 1 Yawning 1-2x during assessment
   - 2 Yawning ≥3X during assessment
   - 4 Yawning several times/minute
10. Anxiety or irritability
    - 0 None
    - 1 Fells increasingly irritable/anxious
    - 2 Patient obviously irritable, anxious
    - 4 Difficult participating in assessment
11. Gooseflesh skin
    - 0 Skin is smooth
    - 3 Arm hair standing up
    - 5 Prominent piloerection

Total: sum of all 11 items
- 5–12=Mild; 13–24=Moderate; 25–36=Mod. severe; >36=Severe

(Adapted from Wesson et al., 1999)

WD Severity: Untreated vs. Treated
Balancing the Intensity & Duration of Withdrawal

Kosten & O’Connor, 2003
Improving NTX-PO Effectiveness

- Development of novel methods of detoxification
  - Clonidine become available to treat withdrawal
  - Rapid Detox: detoxification was accelerated by administering antagonist and emerging symptoms are treated with clonidine
  - General anesthesia and an Ultra-Rapid Detox (1 day detox) was introduced
  - Buprenorphine was introduced as a step-down from methadone during detoxification

- Using antagonists during detox became an opportunity to start naltrexone as a relapse prevention agent: **Rapid Naltrexone Induction**

- Work continued on **improving adherence to oral preparations** using tailored behavioral therapy

- Several **long-acting preparations** of naltrexone become available to deal with compliance issue

Rapid XR-NTX Induction - 2017
Columbia Protocol – In- OR Outpatient

- Patients abstain from opioids for ≤12 hours (e.g., Sun. afternoon)
- Mon. AM, BUP begins with adjunctive meds PRN withdrawal
- Clinic is daily, M-F during induction, for 1-3 hours for monitoring
- Assess patient on arrival, 1 hr post meds, & before leaving clinic
- Patient gets daily from nurse/physician:
  - Medical Assessment
  - Medication Management
  - Study meds & take-home meds
- Patients also receive weekly therapy sessions
Rapid XR-NTX Induction - 2017  
Columbia Protocol – In- OR Outpatient

- **Day 1**: Using Clinical Outcome Withdrawal Scale (COWS)  
  If score ≥ 6 → BUP 2 mg  
  If tolerated, add 2-4 mg in the clinic  
  Plus 2 mg dose at home that evening

- **Days 3, 4, & 5**: NTX-PO, in split doses if 1st daily dose tolerated  
  Adjust depending on the clinical situation

- **Day 5**: XR-NTX IM, usually 1 hour after total of NTX-PO 25 mg

- Ancillary meds are standing doses during days 2-5

- Start ancillary doses PRN the night prior to the 1st BUP dose  
  and for 2 weeks after the XR-NTX injection

---

### Rapid XR-NTX Induction - 2017  
Columbia Protocol – In- OR Outpatient

<table>
<thead>
<tr>
<th>Study Day</th>
<th>BUP</th>
<th>NTX</th>
<th>Clonidine&lt;sup&gt;a&lt;/sup&gt;&lt;sup&gt;,b&lt;/sup&gt;</th>
<th>Clonazepam&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Prochlorperazine&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Zolpidem&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Trazodone&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td></td>
<td></td>
<td>0.1 HS prn</td>
<td>0.5 HS prn</td>
<td>10 HS prn</td>
<td>10 HS prn</td>
<td>100 HS prn</td>
</tr>
<tr>
<td>Day 1</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td></td>
<td></td>
<td>0.1 qid</td>
<td>0.5 qid</td>
<td>10 qHS</td>
<td>100 qHS</td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>1 + 2</td>
<td>0.1 qid</td>
<td>0.5 qid</td>
<td>10 bid</td>
<td>10 qHS</td>
<td>100 qHS</td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td>3 + 3</td>
<td>0.1 qid</td>
<td>0.5 qid</td>
<td>10 bid</td>
<td>10 qHS</td>
<td>100 qHS</td>
<td></td>
</tr>
<tr>
<td>Day 5</td>
<td>6 + 6 + 12</td>
<td>0.1 qid</td>
<td>0.5 qid</td>
<td>10 bid</td>
<td>10 qHS</td>
<td>100 qHS</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> clonidine is held if SBP<100  
<sup>b</sup> adjunctive meds as needed, evening prior to 1st BUP dose & 2 wks after XR-NTX

*Personal communication, Bisaga A., March 2013*
Rapid XR-NTX Induction - 2017
Columbia Protocol – In- OR Outpatient

- 57% retention overall
- 78% retention among prescription opioid users

Choosing Withdrawal Management Setting Based on Drug Use Severity Alone

- Based on biological/pharmacological parameters:
  - Amount (e.g., number of bags, total mg per day)
  - Frequency (times per day – reflects reinforcement)
  - Duration (< 1 year – number of years)
  - Route of administration (PO, XR, IN, IV)
    - Reflects: Speed of onset
## Rapid XR-NTX Induction Algorithm

**Columbia Protocol – In- OR Outpatient**

<table>
<thead>
<tr>
<th>Severity (physical dependence/anticipated withdrawal)</th>
<th>NONE</th>
<th>MILD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Setting</strong></td>
<td>Outpatient</td>
<td>Outpatient or partial hospital</td>
</tr>
<tr>
<td><strong>Buprenorphine Dose</strong></td>
<td>None</td>
<td>None or 4mg, day 1</td>
</tr>
<tr>
<td><strong>Clonidine</strong></td>
<td>None</td>
<td>0.1-0.2 mg TID to QID</td>
</tr>
<tr>
<td><strong>Clonazepam</strong></td>
<td>None</td>
<td>0.5 mg BID</td>
</tr>
<tr>
<td><strong>Ancillary medications</strong></td>
<td>None</td>
<td>Sleep, pain (e.g. NSAID)</td>
</tr>
<tr>
<td><strong>Hydration</strong></td>
<td>Routine</td>
<td>Aggressive oral hydration (e.g., sports drinks)</td>
</tr>
<tr>
<td><strong>Time to first NTX dose</strong></td>
<td>Day 1</td>
<td>Day 3</td>
</tr>
<tr>
<td><strong>Initial oral NTX dose</strong></td>
<td>25-50 mg</td>
<td>12.5 mg QD</td>
</tr>
<tr>
<td><strong>Time to Vivitrol injection</strong></td>
<td>Days 1-2</td>
<td>Day 4; (or Day 5-6 after titrating oral naltrexone to 25-50mg QD)</td>
</tr>
</tbody>
</table>

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## Rapid XR-NTX Induction Algorithm

**Columbia Protocol – In- OR Outpatient**

<table>
<thead>
<tr>
<th>Severity (physical dependence/anticipated withdrawal)</th>
<th>MODERATE</th>
<th>SEVERE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Setting</strong></td>
<td>Partial hospital with inpatient backup</td>
<td>Inpatient or partial hospital with inpatient backup</td>
</tr>
<tr>
<td><strong>Buprenorphine Dose</strong></td>
<td>4-8 mg, day 1 or 2</td>
<td>8 mg, day 1 or 2, or &gt;8 mg as needed</td>
</tr>
<tr>
<td><strong>Clonidine</strong></td>
<td>0.2 mg (TID to QID)</td>
<td>0.2-0.3 mg QID</td>
</tr>
<tr>
<td><strong>Clonazepam</strong></td>
<td>1.0-2.0 mg (TID to QID)</td>
<td>1.0-2.0 mg QID</td>
</tr>
<tr>
<td><strong>Ancillary medications</strong></td>
<td>Sleep, pain, GI distress</td>
<td>Sleep, pain, GI distress</td>
</tr>
<tr>
<td><strong>Hydration</strong></td>
<td>Aggressive oral hydration</td>
<td>Aggressive oral or IV hydration</td>
</tr>
<tr>
<td><strong>Time to first NTX dose</strong></td>
<td>Days 3-4</td>
<td>Day 4-5 (later if needed)</td>
</tr>
<tr>
<td><strong>Initial oral NTX dose</strong></td>
<td>6 mg BID</td>
<td>3-6 mg QD-BID</td>
</tr>
<tr>
<td><strong>Time to Vivitrol injection</strong></td>
<td>Days 4-5; or days 5-7 after titrating oral naltrexone to 25-50 mg QD</td>
<td>Day 5-6; (or Day 6-7 after titrating oral naltrexone to 25-50mg QD)</td>
</tr>
</tbody>
</table>
Choosing Withdrawal Management Setting Based on Drug Use Severity Alone

- Based on biological/pharmacological parameters:
  - Amount (e.g., number of bags, total mg per day)
  - Frequency (times per day – reflects reinforcement)
  - Duration (< 1 year – number of years)
  - Route of administration (PO, XR, IN, IV)
    - Reflects: Speed of onset

- Does not account for:
  - Motivation/reward/socialization, e.g., ritualization
  - Impulsivity, e.g., craving, cue reactivity, distractability
  - Environment, e.g., supports, structural order/chaos

The Stages of Change Model of Recovery
Level of Care for MAT Support

- Based on the ASAM Criteria decision rules
- **Level 3-Withdrawal Management (WM) Inpatient Care**
  Severe withdrawal, with med/psych issues & unlikely to complete
- **Level 2-WM Intensive Outpatient (IOP) Care**
  Moderate, needing daytime support & supervision, But with a supportive evening/night environment
- **Level 1-WM Outpatient Care**
  Mild withdrawal and stability across all 6 dimensions
- **Level OTS Opioid Treatment Services**
  Need for daily opioid agonist meds, plus counseling
  For severe, unstable addiction & chaotic life environment

XR-NTX in Opioid Dependence in the Inpatient Rehabilitation Setting

DL Leslie PhD¹, W Milchak LCSW¹, DR Gastfriend MD², P Herschman PhD³, EO Bixler PhD¹, RE Meyer, MD¹

¹Penn State U/Hershey Medical Center, ²Alkermes Inc, ³CRC Health Group Inc

**Funding:** Research services agreement from Alkermes Inc. to Penn State University

**Objective:** A naturalistic study of patient characteristics, feasibility & hospital course of opioid dependent patients post-detox, in the midst of residential rehabilitation treated with (or without) once-monthly XR-NTX

Leslie et al., 2015
**XR-NTX in Rehab: Data Sources**

- Administrative records from 3 inpatient CRC, Inc. rehabs in PA
- CRC is the largest U.S. provider of specialized behavioral healthcare, treating >30,000 individuals daily
- Electronic records characterized 7,687 opioid dependent detox/rehab inpatients in terms of demography, diagnosis, payer & hospital course.
- The largest site provided data on how many patients attended their 1st post-discharge visit by day 10.
- 3 Groups were compared, with groups 2 & 3 as controls:
  - 1: **Injected** – with at least 1 XR-NTX
  - 2: **Not Injected** – but wanted & was prescribed XR-NTX
  - 3: **Not Prescribed** – neither offered nor prescribed XR-NTX

*Leslie et al., 2015*

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**XR-NTX in Rehab: Results**

<table>
<thead>
<tr>
<th></th>
<th>Injected</th>
<th>Not injected</th>
<th>Not Prescribed</th>
<th>p &lt; .001 vs XR-NTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Complete</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attended Post-discharge visit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of Stay (Days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Leslie et al., 2015*
XR-NTX in Rehab: Conclusions

- **Limitations**: Retrospective data (from PA), possible cohort differences, lack of clinical info, & short-term temporal focus.
- **Strengths**: Data reflect real world clinical experience, both commercial insurance & Medicaid populations; cohorts similar in baseline demographic, clinical & payer characteristics; consistent findings across 3 sites.

**Conclusions**

1. XR-NTX patients were significantly less likely to leave against medical advice, more likely to complete rehab, have longer LOS & greater entry to continuing care.

2. Women: as likely as men to receive XR-NTX; Race did not appear to be a factor in treatment selection.

3. XR-NTX can be successfully administered to opioid dependent patients after detox & before discharge from inpatient rehab.

Leslie et al., 2015

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### ASAM PLACEMENT CRITERIA

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Levels:</th>
<th>Out-patient</th>
<th>Opioid Treatment Program</th>
<th>Day Treatment</th>
<th>Residential Rehabilitation</th>
<th>Hospital (Medically Managed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5</td>
<td>1</td>
<td>OTP</td>
<td>2.1, 2.5</td>
<td>3.1, 3.3, 3.5, 3.7</td>
<td>4</td>
</tr>
</tbody>
</table>

1. **Intox/WD**
   - **Sub-levels:** Withdrawal Management (L-1, 2, 3.2, 3.7, 4)

2. **Biomedical**
   - Biomedical Enhanced (L-3.7)
   - Co-Occurring Disorders

3. **Emot'l/Behav'l**
   - Capable (L-2, 3)
   - Enhanced (L-2, 3)
   - Co-Occurring Disorders

4. **Readiness**

5. **Relapse Potential**

6. **Environment**
The Phases of Treatment

- **Withdrawal Management** – Medical Detoxification
- **Post-Withdrawal Anti-Craving Medication**
  – stabilizing brain chemistry
- **Counseling** – for the real *work* of recovery
  – Accept the disease
  – Know one’s vulnerabilities
  – Anticipate risk factors
  – Insulate from re-encountering the drug of abuse, even under stress
  – Master new coping behaviors
  – Construct healthy relationships
  – Find purpose in life/spiritual grounding

Counseling VIVITROL Patients for Recovery

- **Why?** Because addiction is TOUGH & recovery is painful
- **What?** Integrated XR-NTX + counseling yields BEST results
- **Who?** Patients who are *prepped* for long-term treatment
- **How?** With realistic expectations, supports, monitoring & program internal accountability structures, discontinuing by planned criteria
Counsel the Patient Regarding...

- Mood effects: Anxiety, Depression
- Cognitive effects: Slowing, dizziness: initially, avoid driving
- Naltrexone “Flu” and nausea - tend to be mild, for a few days
- Note prior daily reinforcement on short-acting opioids, & even on methadone & less so, buprenorphine
- Notifying prescriber in case of pregnancy/breast-feeding

Counseling For MAT Induction: What?

- What is the Clinical Risk/Benefit?
- What Detox Approach Should I Go Through?
- What is the Time Frame?
- What is the Patient Role?
- What are the Side Effects?
Counseling During MAT Induction: HOW?

- Explore the Patient’s Perceptions
- How Is Hydration, Sleep, Appetite, Energy?
- How Is Craving Changing?
- “Pulling Off the Band-aid”: Slowly or All-At-Once
- How to Cope? Accepting Neediness, Taking Comfort Measures
- Light Activity/Exercise is Acceptable & May Be Helpful

Counseling During MAT Induction: HOW?

- Anticipate & recognize discomfort
- Foster Self-Efficacy: You can do it!
- Setbacks & Contingencies
- How Long Should Induction & Comfort Meds Be Continued?
- Talk to Significant Others
MAT Induction Program Best Practices

- MAT Adherence Champion – responsible for ongoing adherence monitoring for all patients undergoing induction
  - Medication Access – get support from sales reps for med availability/reimbursement
  - MAT Patient Tracking System – call patient (& Supportive Other) if late or no-shows
- Referral Affiliation Agreements – for continuity of care
- Have alternative plans ready, just in case:
  - Change in Level of Care (escalation)
  - Buprenorphine
  - Methadone

Treatment Program Best Practices

- Support from Current MAT Patients – may volunteer to provide first-hand accounts to prospective and newly initiated MAT patients.
- MAT Groups – Provide educational and emotional support, excellent for patients considering MAT
- Telephone Support – Enhances persistence with MAT and counseling engagement
- Ongoing Clinical Self-report Surveys – e.g., BAM - Brief Addiction Monitor, to clarify to patient his/her own risks AND protections and to objectively guide psychosocial support/counseling
XR-NTX: Managing Discontinuation

- Patients discontinue prematurely for innumerable reasons: it’s the disease
- Better to regularly anticipate ambivalence & explore it in counseling
- If patient discontinues, remember that blockade can continue for as long as 6 weeks after injection
- It is not uncommon for a patient to want to restart XR-NTX later; This is a good sign that predicts a longer retention
- If patient restarts XR-NTX after cessation, must review need for detox

Med Discontinuation & Follow-Up

- Opioid substitution is necessarily a long-term treatment since withdrawal causes frequent relapse upon taper.
- Vivitrol – no withdrawal, used to stabilize craving, establish disease acceptance, & engage in recovery – which may ensue in weeks or months.
- Team should work with patient to determine MAT duration
- Offer MAT based on engagement in psychosocial treatment, recovery efforts & functional progress.
- Assessment for MAT review: www.ASAMcriteria.org
- See FADAA’s MAT Completion Protocol webinar: http://www.fadaa.org/page/Training_Library, Medication Assisted Treatment Completion Criteria and a Proposed Protocol
Post Medication Outcome Tracking

- Opioid Use Disorder is chronic & relapse is common
- Track after MAT to determine if patient needs to restart
- Preferably before physiological dependence is reinstated
- Before other morbidity occurs,
- During the window of opportunity to quickly re-engage
- Ask for follow-ups reports on post-MAT outcomes
- Advise patient of the need to return for re-assessment and re-initiation of medication

Summary: Who Responds? (Nunes et al., 2015)

- Traditional consensus on oral naltrexone in opioid use dis.: OK for narrow range of good prognosis patients, e.g., professionals, high motivation & good social supports
- Monthly formulation: designed for good adherence
- No significant predictor variable interactions (p<.05)
- Trend interactions (p<.15) indicate good efficacy of XR-NTX vs. placebo in higher severity patients, i.e., with worse global severity with the Clinical Global Index, higher baseline craving, lower functional EuroQual-5D quality of life & HIV
- Results suggest that XR-NTX was effective in promoting abstinence from opioids & preventing relapse after detox across a range of demographic and severity characteristics
- Genetics: Not a predictor, at least for now (Oslin et al., 2015)
Summary: Offer XR-NTX If Patient…

- Just withdrawn from opioids; or abstinent but intense craving
- Leaving inpatient rehab or incarceration
- Has begun intermittent use, but not yet dependent relapse
- Despite maintenance agents, frequently uses opioids anyway
- Discontinuing maintenance – as a “landing pad” transition
- Young adult or late adolescent
- Subject to drug testing or job sanctions for maintenance
- Dependent on both opioids and alcohol

- Treatment Matching is key: There is no superior approach – except the one that works for the particular patient!
- Segregated care = BAD care; patients need integrated care

HOW?

- Losing the:
  Craving (good!); High/Euphoria (OK); Escape (Uggh...)
- How Does Vivitrol Promote The 1st Step?: Awareness
- How Will I Cope?! Emotion Without Escape
- How to Talk About Vivitrol In A.A.
- Is There Spirituality After Technology?
- Foster Self-Efficacy: Via exploration, NOT discontinuation
- Remembering Vulnerability: Notes, Journals, Rating Scales
- Setbacks & Contingencies: Plan ahead, Restart
- How Long Should Vivitrol Be Continued?
  6 mos? 12 mos? 13 mos? Or, based on criteria...
Summary: Optimizing in Real-Time

- 50% success rates – are still not that successful!
- Patients vary widely, both objectively & subjectively
- Decision logic for MAT induction placement is but an aid
- So...encourage patients & supportive others to call
- Call patients to check-in – DAILY is not too often
- Review med-taking, doses, timetable, symptom progress
- Bring the patient back in, whenever uncertain
- REVISE THE PLAN, including escalating Level if needed

REFERENCES

- ASAM Criteria. Mee-Lee D, Editor. American Society of Addiction Medicine, 2013
REFERENCES