Oral Naltrexone:
Not a Primary MAT – But Still Worth Knowing

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Disclosure Information

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IBM Watson/Truven Health Analytics, Rand Corp.
Purpose of the Webinar

- Oral naltrexone (NTX-PO) is a potent blocker at brain opioid receptors, so it was a natural consideration as a medication in addiction treatment (MAT) for Opioid Use Disorder (OUD).
- For most OUD patients, however, studies have not found NTX-PO to be any better than placebo or non-medication treatment – due to poor adherence by patients.
- Nevertheless, it is still used for patients whose pill-taking can be regularly monitored, for detoxification and induction onto extended-release naltrexone, and for patients who have completed MAT but encounter new stressors for which they may want temporary protection from relapse.

Objectives:

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

- Understand the brain receptor and clinical effects of oral naltrexone.
- Describe the limitations of oral naltrexone in practical clinical care.
- Understand the appropriate roles of oral naltrexone use in opioid use disorder.
Brain Reward:
With us throughout evolution

fMRI Cue Activation by Alcohol Images

Myrick et al. Psychiatry 2008;65(4):466-475
Brain Structure:
Two Regions – Cortex & Limbic

Cortex
Role:
• Decision making
• Thinking
• Reasoning
• Learning

Limbic Region
Role:
• Basic Drives
• Experience of Reward, Euphoria

Interventions
– Psychosocial Therapies
– 12 Step Programs
– Monitoring

Interventions
– Agonist Medications
– Antagonist Medications

Both Reward/Motivation ("Go" signals) & Inhibitory Control ("No Go") disrupted in addiction – address BOTH in prevention & treatment

Healthy Opioid Receptor Activity

**Dopamine**
- Eating when hungry
- Drinking when thirsty
- Rewards survival behavior

**Endorphins**
- Pain relief
- Stress relief
- Emotional bonding

**Opioid Agonists & Partial Agonists**

**Agonists**
- Opioid analgesics
- Illicit opioid (e.g., heroin)
- Methadone
- Activates opioid receptors
- Excess dopamine release

**Partial Agonists**
- Buprenorphine
- Same as agonists, but ceiling effect

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**Opioid Antagonist**

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

Ventral Tegmental Area → Nucleus Accumbens

Dopamine → Opioid Peptides

GABA → Arcuate Nucleus

Naltrexone
Full and Partial Agonists vs. Antagonists

An agonist has an active site of similar shape to the endogenous ligand binding to the receptor and producing the same effect. An antagonist is close enough in shape to bind to the receptor but not close enough to produce an effect. It also takes up receptor space and so prevents the endogenous ligand from binding.

Opioid Effect

- Full Agonist (Methadone)
- Partial Agonist (Buprenorphine)
- Antagonist (Naloxone)

Neurobiology of Opioid Use Disorder

- Opioids: at substantia nigra & VTA interneurons, rapidly & briefly bind MOP-r, GABAergic inhibition of DA neurons
- \( \uparrow \) Dopaminergic Reward: Initial positive reinforcement; later, regulatory changes via mRNA or protein/peptides
- Recurrent withdrawal negatively reinforces recurrent use, via regulatory changes that persist for weeks/months
- Negative Reinforcement: mediated via
  - Upregulation of the KOP-r/dynorphin system (may underlie aversion, dysphoria/anhedonia, and depression-like or anxiety-like states)
  - Stress-responsive brain areas via the hypothalamo-pituitary-adrenal (HPA) axis

(Kreek et al., J Clin Investigation 2012)
A Biopsychosocial Disorder Requires 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**: Not considered treatment; Detox without continued meds dominates; is **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 permit counseling
- **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
Primary Effects of NTX-PO

- It can block the reinforcing effects of opioids
- And markedly diminish or eliminate:
  - Opioid discrimination
  - Self-reported mood effects
  - Opioid self-administration
  - Opioid craving

Pharmacokinetics of NTX-PO

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

Benefits of NTX-PO

- Daily oral pill
- Not a controlled substance, no euphoria or reward
- Patients won’t “like it too much”

Problems of NTX-PO

- Daily oral pill
- Not a controlled substance, no euphoria or reward
- Patients won’t “like it too much”
Strengths of NTX-PO

- Single dose pill – no dose adjustments or taper on or off
- Any licensed healthcare professional can prescribe it
- No overdose risk
- No physical dependence to manage upon conclusion
- No diversion
- Testing the blockade: not essential to efficacy

(Sullivan MA, et al., 2013)

Limitations of NTX-PO

- Less effective than other MATs
- Not significantly more effective than placebo – for most
**Drug-Drug Interactions**

- Few with NTX-PO, except for opioid blockade
- Interacts with ALL opioids
  - Produces precipitated opioid withdrawal
  - Not a side effect, but is an adverse event
- Precipitated withdrawal
  - Worse than tapered withdrawal
  - Worse than cold turkey withdrawal
  - May cause patient to avoid treatment in the future

**Break**

- Reconvene in 5 minutes
The Declining Efficacy of Naltrexone Pharmacotherapy for Alcohol Use Disorders Over Time: A Multivariate Meta-Analysis

A. C. Del Re, Natalya Maisel, Janet Blodgett, and John Finney

Background: Oral naltrexone is an FDA-approved medication for treating alcohol use disorders. Although its efficacy has been supported in multiple clinical trials, an earlier review found that its effect sizes (ESs) on relapse to heavy drinking and, to a lesser extent, percent days drinking were smaller in more recent trials and in multicenter than in single-site studies. We examined whether these findings held when studies from 2004 to 2009 were taken into account, and whether single-site versus multicenter trials, the use of placebo run-in periods, and placebo group improvement accounted for variation in naltrexone effects and decreasing effects over time.

Methods: A multivariate meta-analysis of naltrexone pharmacotherapy trials for alcohol use disorders was conducted. All analyses simultaneously modeled ESs on outcomes of percent days abstinent and relapse to heavy drinking. Potential moderators of medication effects that were examined included publication year, multicenter design (vs. single site), placebo run-in period, and placebo group improvement.

Results: Statistically significant between-group differences on percent days abstinent (the inverse of percent days drinking) and relapse to heavy drinking favored naltrexone versus placebo. Year of publication was a significant moderator for both outcomes, with more recent trials having smaller ESs. Neither multi- versus single-site study, the interaction between multi- versus single-site study and year of publication, nor placebo run-in period was a significant moderator of naltrexone effects. Although placebo group improvement was modestly associated with smaller between-group naltrexone versus placebo ESs, only 21 studies provided usable information on placebo group improvement. Within those studies, there was no relationship between naltrexone ESs and time, so placebo group improvement was not examined as a moderator of that relationship.

Conclusions: Naltrexone ESs have attenuated over time. Moderators that explain why effects have been decreasing remain to be determined.

NTX-PO Trials: Less Benefit, Over Time

Percent Days Abstinent

(Del Re et al., 2013)
NTX-PO Trials: Less Benefit, Over Time

- Overall, NTX-PO’s effect is modest
- Effects have attenuated over time
- Factors that explain the decreasing effects of NTX-PO over time remain to be determined
Abstract

Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation

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NTX-PO Trial: Lack of Significant Benefit

Proportion drug free in those who remained on treatment (from Krupitsky et al., 200442)
NTX-PO Trials: Lack of Significant Benefit

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curran, 1976</td>
<td>1.00 (0.75 to 1.33)</td>
</tr>
<tr>
<td>San, 1991</td>
<td>1.35 (0.98 to 2.03)</td>
</tr>
<tr>
<td>Lerner, 1992</td>
<td>0.80 (0.35 to 1.73)</td>
</tr>
<tr>
<td>Shufman, 1994</td>
<td>1.14 (0.54 to 2.44)</td>
</tr>
<tr>
<td>Krupitsky, 2004</td>
<td>0.66 (0.43 to 0.95)</td>
</tr>
<tr>
<td>Hollister, 1978</td>
<td>0.97 (0.85 to 1.11)</td>
</tr>
<tr>
<td>Corrigh, 1997</td>
<td>0.73 (0.44 to 1.25)</td>
</tr>
<tr>
<td>Combined [fixed]</td>
<td>0.94 (0.84 to 1.06)</td>
</tr>
</tbody>
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Favours naltrexone  Favours placebo

**FIGURE 6** Relative risk of stopping treatment (meta-analysis plot, fixed effects) (Adi et al., 2007)

NTX-PO Retention, Across Studies

**FIGURE 7** Combined retention rate and 95% CI in naltrexone treatment (Adi et al., 2007)
NTX-PO Trials: Lack of Significant Benefit

- Data on retention from 7 trials of NTX-PO vs. placebo
- Meta-analysis suggests that dropout risk with NTX-PO is reduced by 6% vs. placebo, but this is not statistically significant

NTX-PO Trials: Benefit for Whom?

- Only a portion of OUD patients accept NTX-PO or persist
- Some evidence suggests that there is benefit for:
  - Patients who are employed & married
  - In public drug treatment programs, only 10–15% have been willing to try NTX-PO
- Efforts to improve patient retention show limited benefit
- For example, NTX-PO + Contingency Management (CM)
Improvement in naltrexone treatment compliance with contingency management

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Received 12 May 1998; accepted 20 August 1998

Abstract

The efficacy of a voucher-based incentive program for improving adherence to outpatient, thrice weekly naltrexone maintenance was tested in a three group, randomized, 12-week clinical trial. Voucher incentives were given as follows: contingent group (n = 19) for each consecutive naltrexone dose ingested; non-contingent group (n = 19) on unpredictable schedule independently taking naltrexone; no-voucher group (n = 20) none. Vouchers were exchangeable for goods and services. The contingent group had significantly longer treatment retention and ingested significantly more doses of naltrexone (consecutive and total) than either control group. Voucher incentives can significantly increase adherence to naltrexone maintenance in recently detoxified opiates

NTX-PO + Contingency Management (CM)
NTX-PO + Contingency Management (CM)

- Month-long mu-opioid competitive antagonism per IM injection
- **Why?** Oral NTX meta-analysis: 13 RCTs (N=1158)
  - NTX-PO did not reliably ↑ retention or abstinence rates
  - In Canada, NTX-PO associated deaths 3-7x > methadone
    (Minozzi et al., Cochrane 2011; Gibson AE, Degenhardt LJ, Drug Alc Rev 2007)
- XR-NTX: must be opioid-free 7-10 days (or rapidly detoxed)
- Detox causes loss of tolerance, patient must be cautioned
- Buttock muscle injection: site reactions; nausea, “NTX flu”
- Hepatic safety: even in chronic Hep C+ & HIV+; no black box
- No withdrawal upon treatment completion; self-tapering
- Not a controlled substance; no street value
- Treatment of choice for opioid + alcohol dependence
XR-NTX RCT: Retention

Placebo - Median days of treatment = 96
XR-NTX - Median days of treatment = 168

Log-rank P = 0.0042 (adjusted)


Retention Studies: NTX-PO vs. XR-NTX

1 Combined retention rate and 95% CI in all treatment groups
(Aoki et al., Health Technol Assess 2007)
**NTX-PO: Contraindications**

- Acute hepatitis, advanced liver disease
- Moderate to severe renal impairment
- Severe psychiatric disease, current suicidal/homicidal ideation, especially if patient is prone to worsen with withdrawal
- Opioid positive urine screen.
- Failed naloxone/naltrexone challenge test
- Chronic or acute pain that may require opioid analgesics
- Hypersensitivity to naltrexone

**NTX-PO: Other Considerations**

- **Pain:**
  - Chronic pain must be managed with non-opioids.
  - Acute pain requires anesthesia consult.
  - If patient expects surgery, delay start of NTX-PO
  - Can wait 1 day
  - Can override with anesthesia or high-dose opioids, but requires monitoring

- **Cirrhosis:**
  - NTX is extensively metabolized through the liver
  - Withold if AST/ALT >5x normal limits
**NTX-PO: Other Considerations**

- **Pregnancy:**
  - Insufficient research to assess safety/efficacy of NTX-PO in pregnancy
  - NTX-PO & XR-NTX are Category C medications
  - Provider must assess risk/benefit with consent

- **Breastfeeding:**
  - Naltrexone passes into breast milk
  - Breast feeding should be avoided on naltrexone

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**NTX-PO: For Whom?**

- Not currently using, but OUD history & at risk for relapse
- High degree of motivation for abstinence from opioids
- Motivated to undergo detox & be opioid-free
- Rejects agonist treatment or has failed agonist treatment
- Succeeded with agonist treatment & wants to conclude it
- Wants shorter-term medication that can be easily concluded
- History of or active alcohol use disorder
### NTX-PO: For Whom?

- Preparing to leave rehab or jail/prison opioid-free
- Monitored & may not be allowed agonist treatment
  - by judges, professional boards
  - employers
  - schools or sports teams
- Structure & social supports in place
  (however, chronicity & severity can be either mild or severe)
- Late adolescent/emerging adult with shorter duration addiction

### NTX-PO: For Whom?

- Monitored & may not be allowed agonist treatment
  - by judges, professional boards
- Example: Health professionals in recovery
- May be compelled to undergo daily NTX-PO
  under direct visual observation
  by a non-relative or significant other

- AND…for short-term induction onto XR-NTX
  in low dose escalation protocols
Naltrexone vs Placebo for the Treatment of Alcohol Dependence
A Randomized Clinical Trial

David W. Oslin, MD; Shirley H. Leong, PhD; Kevin G. Lynch, PhD; Wade Berrettini, MD, PhD; Charles P. O'Brien, MD, PhD; Adam J. Gordon, MD, MPH; Margaret Rukstalis, MD

**Importance** Alcohol use disorder is one of the leading causes of disability worldwide. While effective pharmacological treatments exist, they are efficacious only in certain individuals, contributing to their limited use. Secondary analysis of clinical trial data suggests that a functional polymorphism (rs1799971, Asn40Asp) of the μ-opioid receptor gene (OPRM1) is associated with the risk of relapse to heavy drinking following treatment with the opioid antagonist naltrexone.

**Objective** To prospectively examine whether rs1799971 is predictive of naltrexone treatment response.


**NTX-PO: For Whose Genes?**

- A genetic polymorphism (rs1799971, Asn40Asp) of the μ-opioid receptor gene (OPRM1) has been proposed as a candidate for enhanced efficacy of NTX-PO in alcohol treatment
- A definitive (N=221), multi-site, 12-week, double-blind, randomized clinical trial of NTX-PO vs. placebo was conducted
- There was no evidence of a genotype effect on heavy drinking, other drinking outcomes, or any secondary outcomes
- The study did not support the hypothesis that the Asp40 allele is a biomarker for response to NTX-PO in alcohol dependence

(Oslin et al., 2015)
**NTX-PO: Care Planning**

- Reinforce with patient the need for frequent appointments
- Evaluate: Is this realistic?
- Have appropriate Level of Care in place or work towards establishing this
- NTX-PO is compatible with ALL ASAM Levels of Care
- Obtain psychiatric consultation if mental health concerns
**NTX-PO: Care Planning**

- **Labs:**
  - If clinically indicated, check LFTs < 5x normal
  - If female, HCG negative; If positive HCG, engage with OB
  - Drug test: negative for opioids

- **Discharge Papers:**
  - If patient is referred from Detox/Rehab/Hospital, obtain discharge paperwork, including medications
  - Confirm no opioids were given (including methadone or BUP) or this will delay NTX induction due to precipitated WD

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**NTX-PO: Naloxone Challenge**

- Drug screen: Negative for all opioids.
- Off short-acting opioids ≥ 3-7 days
- Off long acting opioids (methadone, BUP) ≥ 7-10 days
- Obtain baseline Blood Pressure & Heart Rate
- Obtain baseline Clinical Opiate Withdrawal Score (COWS) or Clinical Institute Narcotic Assessment Score (CINA)
- If + opioid withdrawal signs, even with – drug screen, do not perform Naloxone Challenge (will be positive)
- Administer Naloxone HCl 0.8-1.2 mg IM (2 divided doses reduces risk of severe withdrawal)
- Repeat COWS at 15 min & again at 30 min after injection
- If no WD signs/symptoms, give 2nd dose of 0.4 - 0.8mg
- Repeat COWS at 15 min & again at 30min
NTX-PO: Naloxone Challenge

- Negative Naloxone Challenge:
  - No subjective or objective WD
  - Proceed with NTX-PO 50 mg, 1 daily

- Positive Naloxone Challenge:
  - ANY WD signs/symptoms
  - Stop Naloxone Challenge – no more naloxone
  - WD usually emerges in 5-10 min, but dissipates in 30 min
  - WD Symptoms are usually mild
    - increase in anxiety
    - increase in heart rate
  - If positive, repeat Naloxone Challenge in 1-2 days

NTX-PO: Vulnerabilities/Education Needs

- Following detox & NTX-PO, patients lose opioid tolerance
- Thus, patients are vulnerable to potentially fatal overdose, if a dose is missed or when treatment is discontinued
- Attempting to break through blockade can also be fatal
- If patients no-show, attempt to reengage them
- Hepatic Injury: There have been cases of hepatitis
  Patients should be made aware of this risk
- Depression and Suicide:
  Overall infrequent, but risk can be elevated
  Patients should be monitored & treated
  Patients, families & caregivers should be educated
NTX-PO: Maintenance

- Once stable, clinic visits every 2 to 4 weeks.
- Goal: Clinic visits every month, with monthly refills
- Decreases in visit frequency require treatment team review
- At visits
  - Perform drug testing
  - Assess patient’s status using the 6 ASAM Dimensions
- Monitor for adherence, ambivalence & adverse reactions: hepatic complications, GI distress, depression, etc.
- If history of alcohol problems consider breathalyzer or ETG
- If Liver Function Tests were elevated, consider rechecking within 1-2 months or sooner depending on degree of elevation. Continue to regularly monitor LFTs.

Healthcare Costs with MAT

- 6-mo retrospective insurance cost study: all meds + inpt + outpt services (N=10,413) casemix controlled with instrumental variable analysis

(Baser O, Chalk M, Fiellin DA, Gastfriend DR. AJMC 17: S235-S246, 2011)
Objectives:

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

- Understand the brain receptor and clinical effects of oral naltrexone.
- Describe the limitations of oral naltrexone in practical clinical care.
- Understand the appropriate roles of oral naltrexone use in opioid use disorder.

Conclusions: Opioid Dependence

- OUD: a chronic disease needing long-term rehab with both meds AND counseling.
- Goals of treatment/rehabilitation: saving lives, stabilizing behavior & establishing social function
- Agonists & antagonists are superior to counseling alone
- All FDA-approved agents are appropriate 1st-line approaches
- Therefore, programs should provide ALL options, so that patients can be informed of and offered ALL options
- Low initial costs can become high costs longer-term
  High initial costs can result in lower costs longer-term
  Therefore, cost should NOT be a consideration
- Patient choice may be the BEST basis for drug selection.
- If one agent is unsuccessful, other options should be tried.
Conclusions: NTX-PO

- NTX-PO is a potent blocker at brain opioid receptors, so it was a natural consideration for OUD MAT.
- For most OUD patients, however, studies have not found NTX-PO to be any better than placebo or non-medication treatment – due to poor adherence by patients.
- Genetic studies have not found a biomarker for better NTX-PO efficacy for alcohol use disorder
- Nevertheless, it is still used for patients whose pill-taking can be regularly monitored, for detox & induction onto XR-NTX, and for patients who have completed MAT but encounter new stressors for which they may want temporary protection from relapse.

References

References


- Oslin DW, Leong SH, Lynch KG, Berrettini W, O'Brien CP, Gordon AJ, Rukstalis M. Naltrexone vs Placebo for the Treatment of Alcohol Dependence A Randomized Clinical Trial. *JAMA Psychiatry* 2015 Volume 72; 430-437
