NALTREXONE

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Project Echo

How many of you have prescribed or worked with patients on naltrexone (Vivitrol)

- Yes
- No

OBJECTIVES

- Review the pharmacology of naltrexone
- What is the evidence of its effectiveness
- Patient selection
- Induction barriers
- Pain management in patients on Naltrexone
- Other indications for naltrexone

36 yo male with opioid use disorder presents to your clinic. He wants to try the naltrexone orally as he does not want to be on any medication that he can become physically dependent on. Is this likely to be successful long term?

A- Yes
B- No

PHARMACOLOGY OF NALTREXONE

- First synthesized in 1965
- First approved by FDA for treatment of opioid addiction in 1984 as oral preparation (Trexan)
- Oral version never proved to be very effective due to compliance issues and pharmacologic profile
- Approved for treatment of alcohol use disorders in 1994
- Injectable naltrexone approved for opioid use in 2010

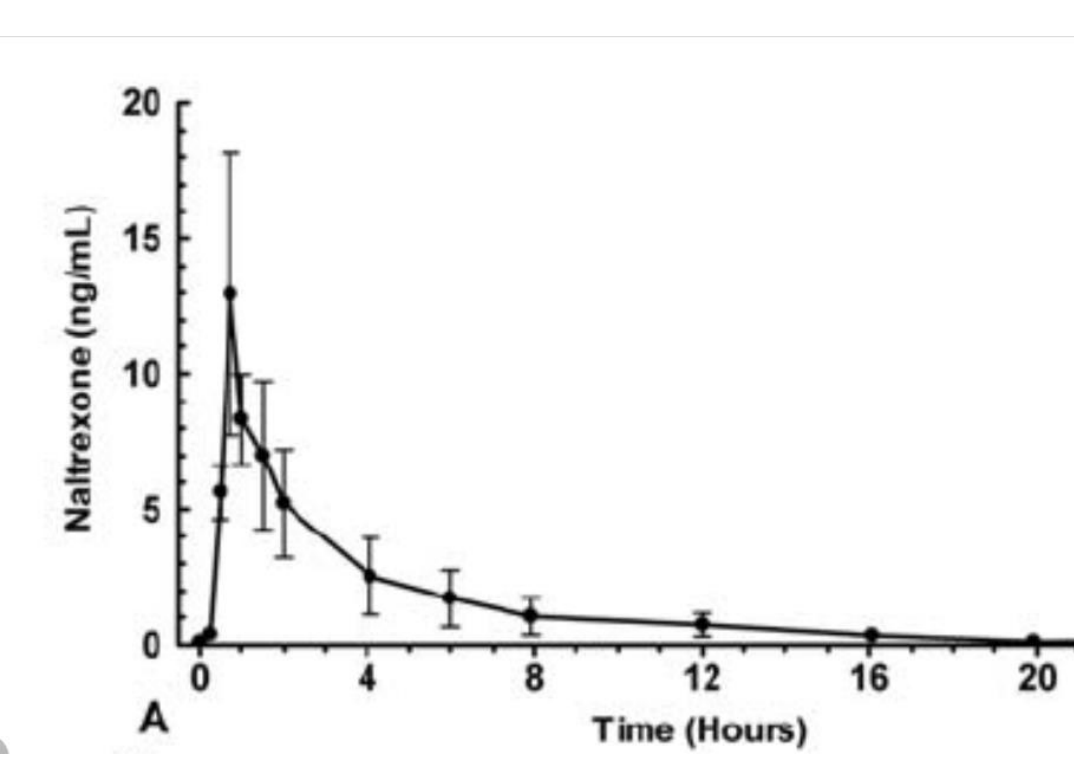
PHARMACOLOGY OF NALTREXONE

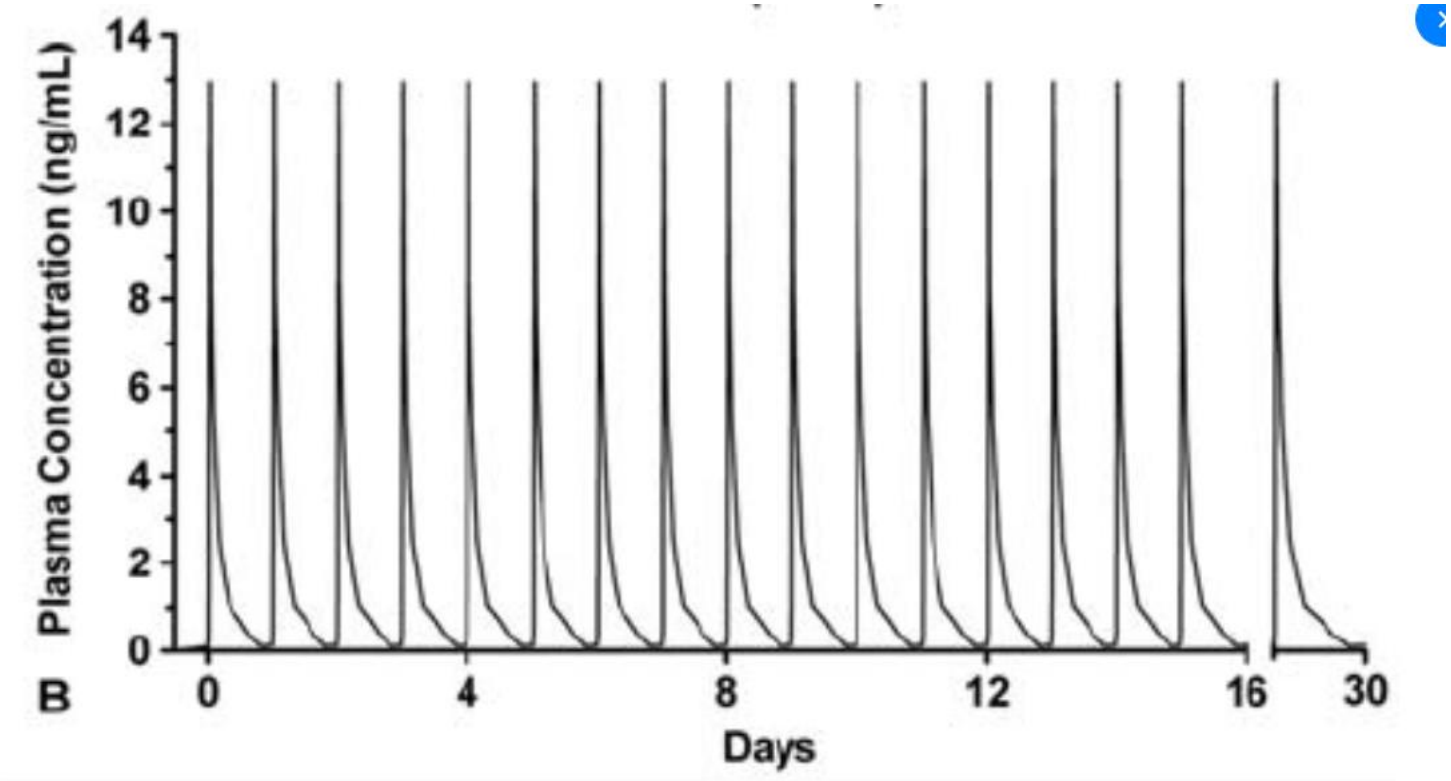
- ORAL|
  - rapidly and nearly completely (96%) absorbed into plasma within one hour
  - has a high first pass metabolism by the liver within one hour
  - naltrexone and 6 beta naltrexol are conjugated
  - renally excreted
  - metabolized to 6 beta naltrexol (less active metabolite)
  - Half lives of naltrexone 6 hrs, 6 beta naltrexol 13hrs

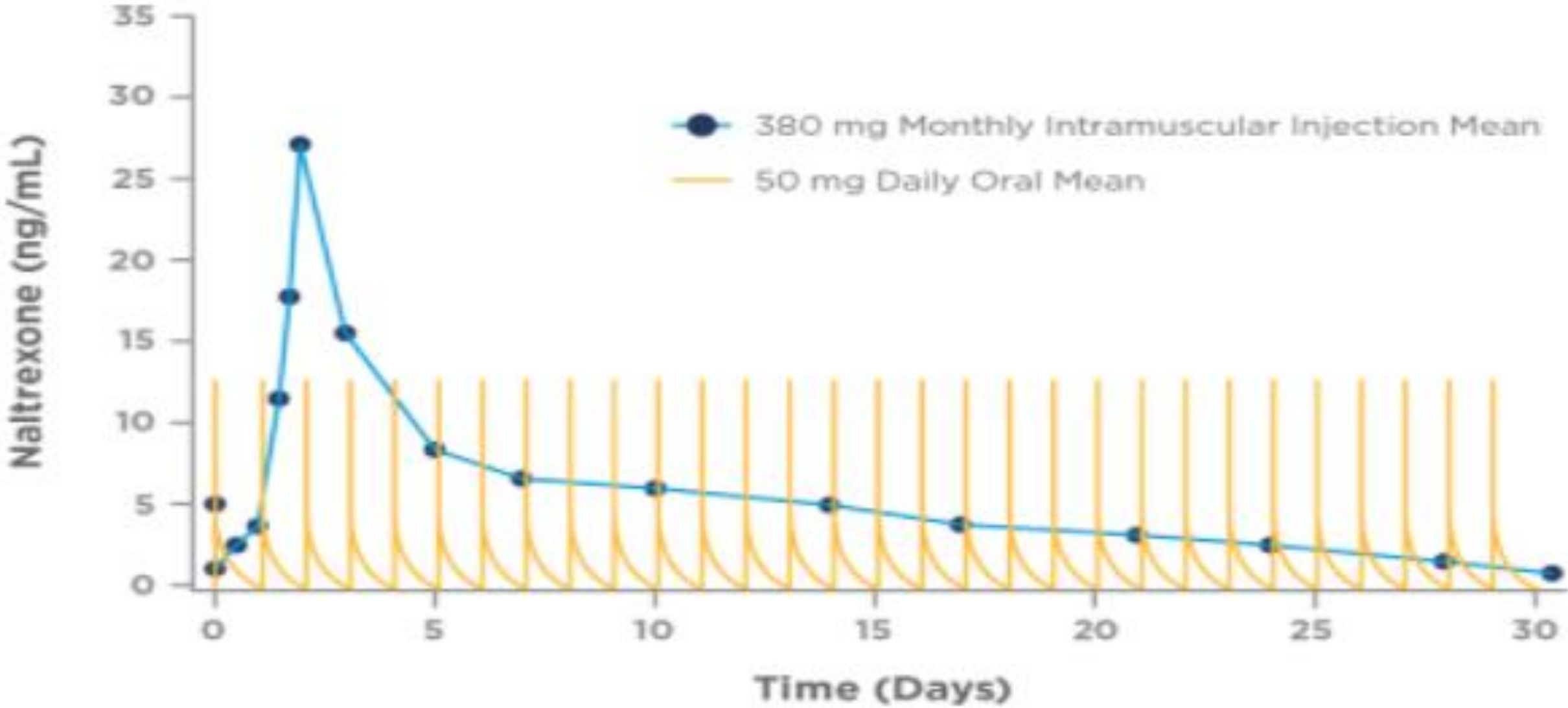
PHARMACOLOGY OF NALTREXONE

- Intermuscular
  - drug is embedded in microspheres to prolonged absorption
  - less first pass metabolism so levels of 6 beta naltrexol are less (2x vs 30x)
  - 6 beta naltrexol is peripherally selective
  - half life of 5 -10 days (25 days for 90% clearance)
  - while the total 28 day dose is less then oral (380mg vs 1200mg) the systemic exposure at steady state is 4x more (AUC)

Naltrexone/6 B- naltrexol levels






380 mg Monthly Intramuscular Injection Mean
50 mg Daily Oral Mean
Naltrexone (ng/mL)
35
30
25
20
15
10
5
0
0
5
10
15
20
25
30
Time (Days)

Administration of IM naltrexone

- Powder needs to be mixed in diluent then inject
  required vigorous mixing
- Thick and can solidify in needle
- Room temperature
- Painful, ice may help
- Give pt card with info on injection

Mechanism of Action for alcohol use disorder

- Blocks the release of dopamine in the reward system which may be mediated by the endorphin response created by alcohol
- Blocks release of endorphins or the binding of endorphins
- Reduces effect of environmental cues and associated cravings

- Reduced positive reinforcement when drinking
- Reduced cravings

Mechanism of action for opioid use disorder

- Competitive antagonist of opioid receptors
  - mu, < kappa, < delta
- Highest affinity for mu receptors , 10-20 x lower affinity for kappa and delta receptors
- May have some very weak agonist properties also
- - single 50 mg dose blocks u receptors for 48-72 hours
  96% blockade of brain opioid mu receptors at 24hr
  86% at 48hr
  46% at 72hr

A patient on vivitrol can “override” the vivitrol if they inject enough fentanyl

- True
- False

BINDING AFFINITIES TO MU RECEPTOR

- Sufentanil 0.1
- Buprenorphine .21-1.5
- Naltrexone .4 -.6
- Fentanyl .70-1.9
- Methadone .70-5.6
- Naloxone 1.0-3.0
- Morphine 1.0-4.0

Pharmacytimes.com, Jan 6, 2018

Naltrexone carries a higher risk of overdose if the patient relapses after stopping it

- A- Yes
- B- No

DOES NALTREXONE REDUCE THE RISK OF OVERDOSE?

- Is the risk of overdose higher with patients who decide to stop naltrexone?
  - increase number and sensitivity of mu receptors in the CNS
  - there is a loss of tolerance to opioids with naltrexone that does not occur when the patient is on a full or partial agonist
  - there does not seem to be strong clinical evidence (mixed results) therefore it is not a contraindication to using naltrexone
  - however always warn the patient of the risks of overdose with relapse

Naltrexone is less effective in preventing relapse on opioids then buprenorphine?

- A- True
- B- False

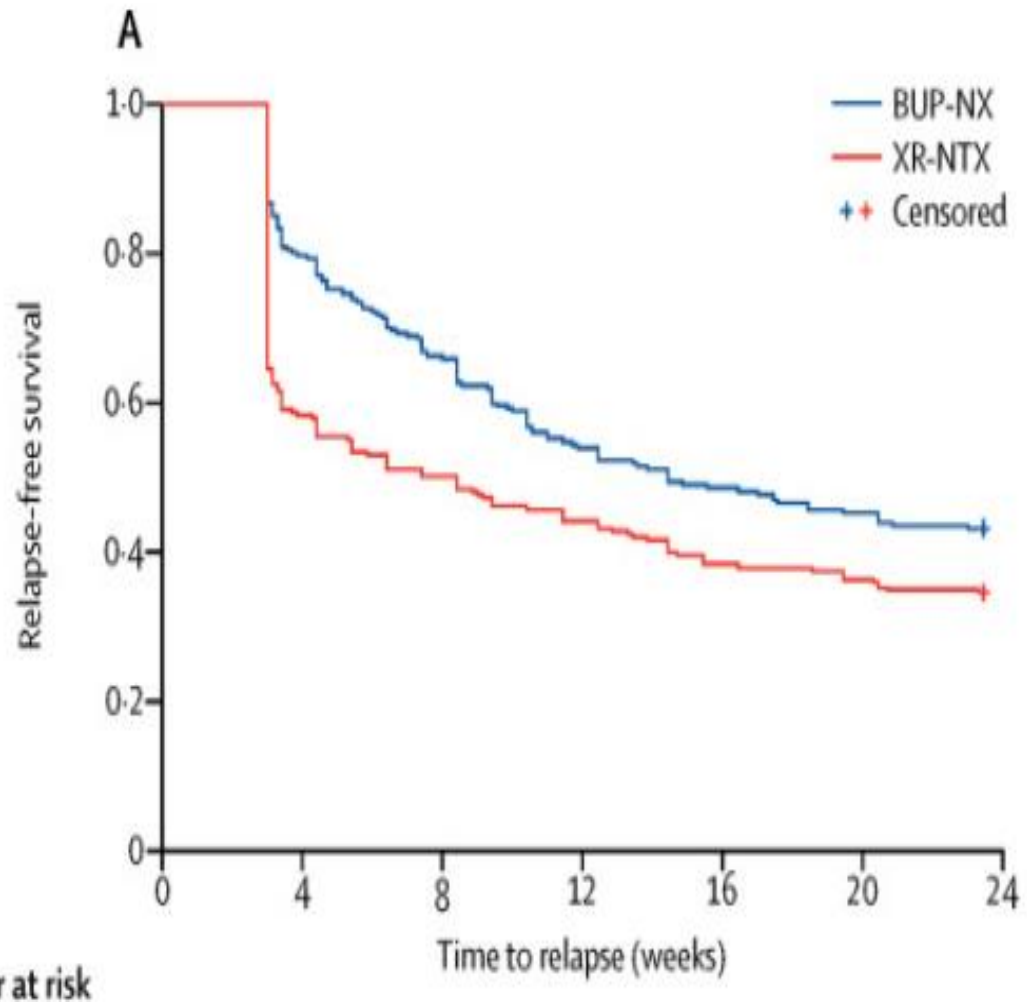
Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicenter, open-label, randomized controlled trial, Lee, J., et. Al., Lancet Vol 391, 2018

- 24 week multisite randomized controlled study
- Compared naltrexone injectable with buprenorphine
- Started with inpatients admitted for “detox”
- Outcome was opioid free survival

Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicenter, open-label, randomized controlled trial, Lee, J., et. Al., Lancet Vol 391, 2018

- 570 participants recruited
- 72% of naltrexone patients successful initiated
  94% of buprenorphine patients successful initiation
- 65% relapse events in naltrexone group
  57% relapse events in the buprenorphine group
- Almost all the relapse events in the naltrexone group occurred in those failing induction

EFFECTIVENESS OF NALTREXONE



Average opioid craving was initially less for the XR-NTX group (p=0·0012 at week 7) than fo the BUP-NX group, then converged by week 24 (p=0·20; figure 3).

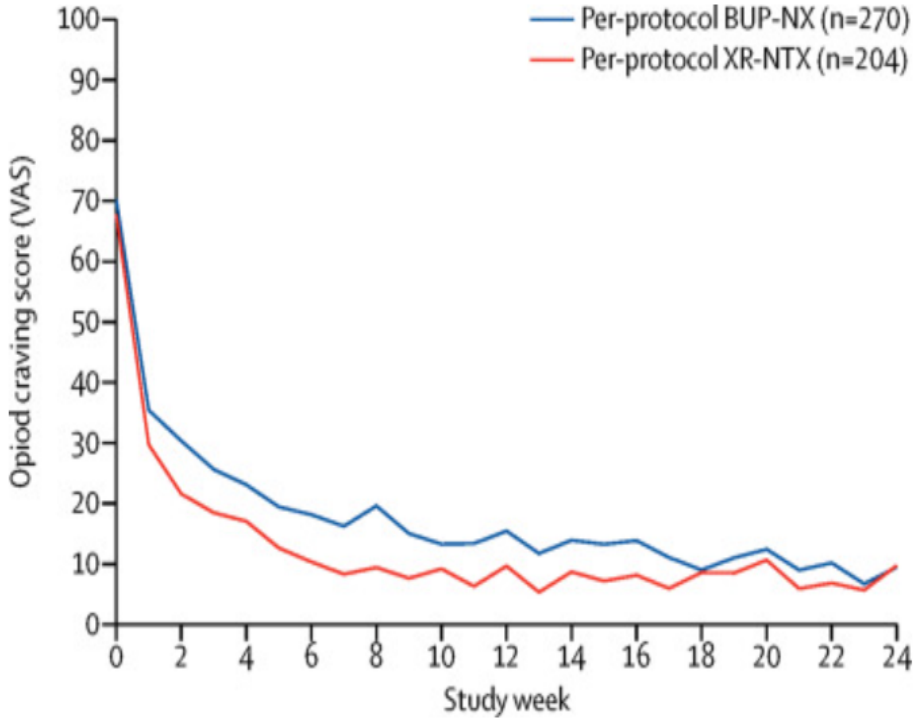


Figure 3

Opioid craving during the trial

Craving was self-reported with an opioid craving VAS, range 0–100. VAS=Visual Analogue Scale. XR-

Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence A Randomized Clinical Noninferiority Trial: Tanum, l., et.al., JAMA Psychiatry,

- 12 week randomized study (Norway)
- Outpatient addiction clinics but recruitment from inpatient detoxification units (patients were “detoxed” at time of enrollment)
- Outcomes: completion rates, proportion of negative urines and heroin use
- 159 participants

Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence A Randomized Clinical Noninferiority Trial: Tanum, l., et.al., JAMA Psychiatry,

- 56/80 completed in the naltrexone group
- 49/79 completed in the buprenorphine group

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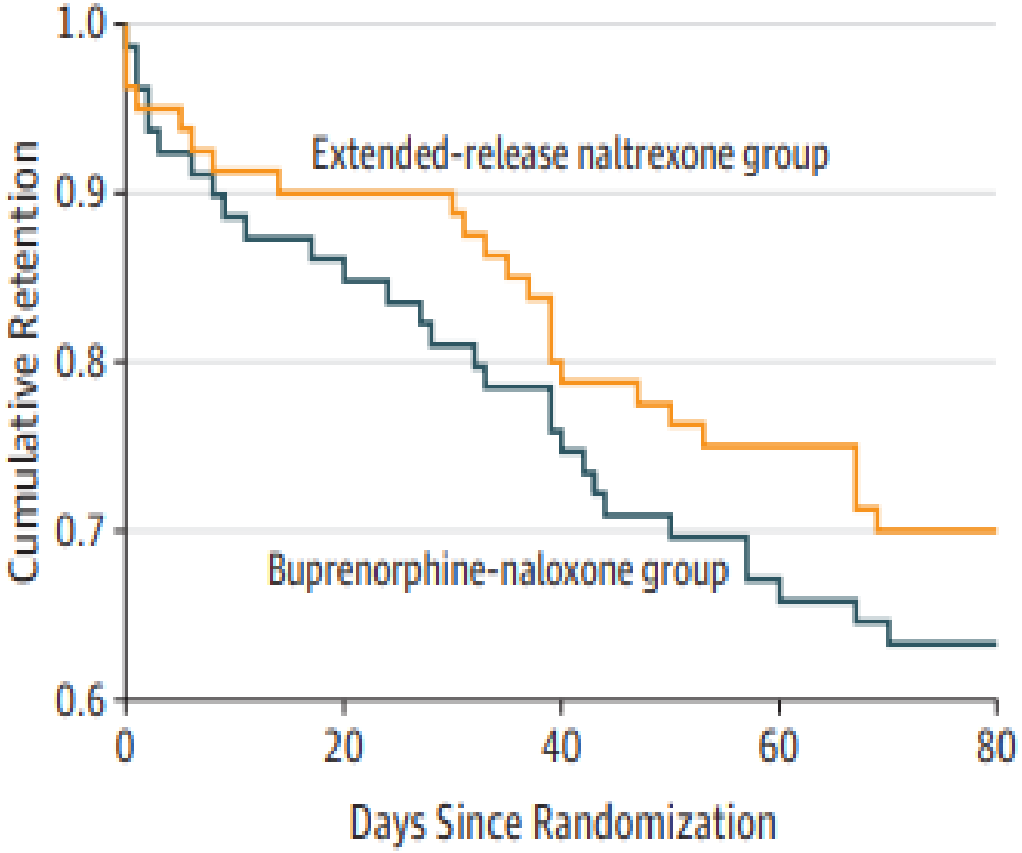

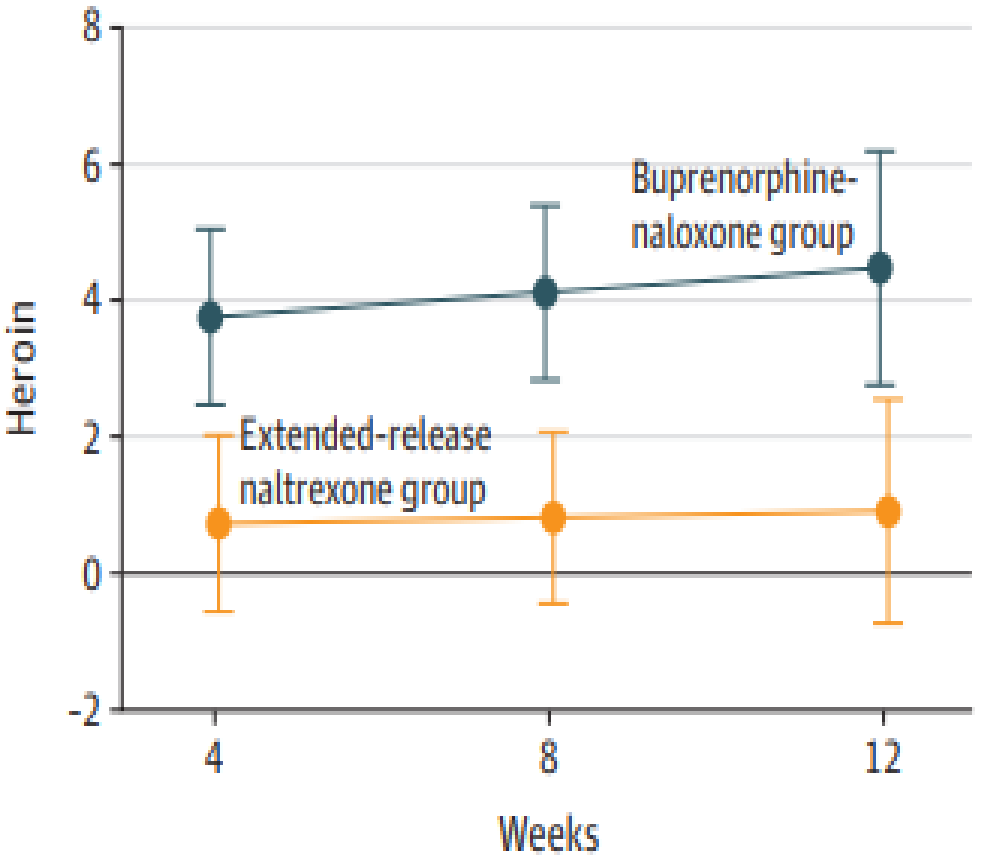

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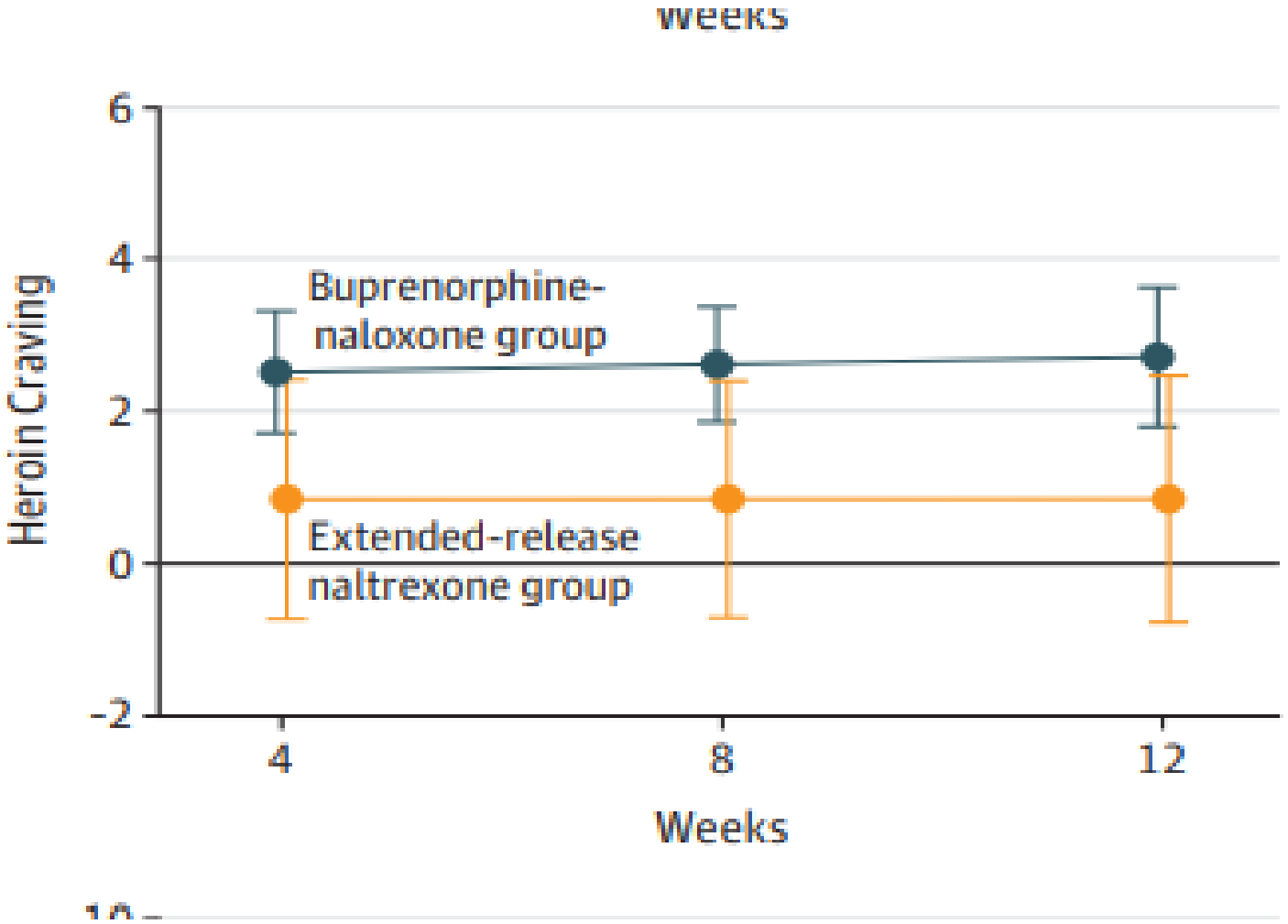


36 yo female with opioid use disorder severe, heroin, presents to your clinic for MAT. Since she may be going to jail in 2 months she prefers to try naltrexone since she will not have to worry about withdrawal if incarcerated. How long will she have to stop the heroin before starting naltrexone?

- A- 2-3 days
- B- 3-5 days
- C- 5-7 days
- C- 8-10 days

Naltrexone Induction Strategies

- 7-10 days of abstinence generally required (pt has to be willing to be sick for awhile)- for short acting opioids 3-5 days ?
- Most difficult transition methadone (10-14 days)
- Structured inpatient settings with documented abstinence/naloxone challenge if admission is short term
- Outpatient
  - daily support during withdrawal phase
  - supplemental non-opioid withdrawal medications
  - does urine need to be negative?
  - test dose with 12.5mg/6.25mg?
  - can start injectable after 1-2 days of oral formulation tolerated
- Has fentanyl use changed our approach with naltrexone ?

CASE: CONVERSION FROM BUP TO NALTREXONE

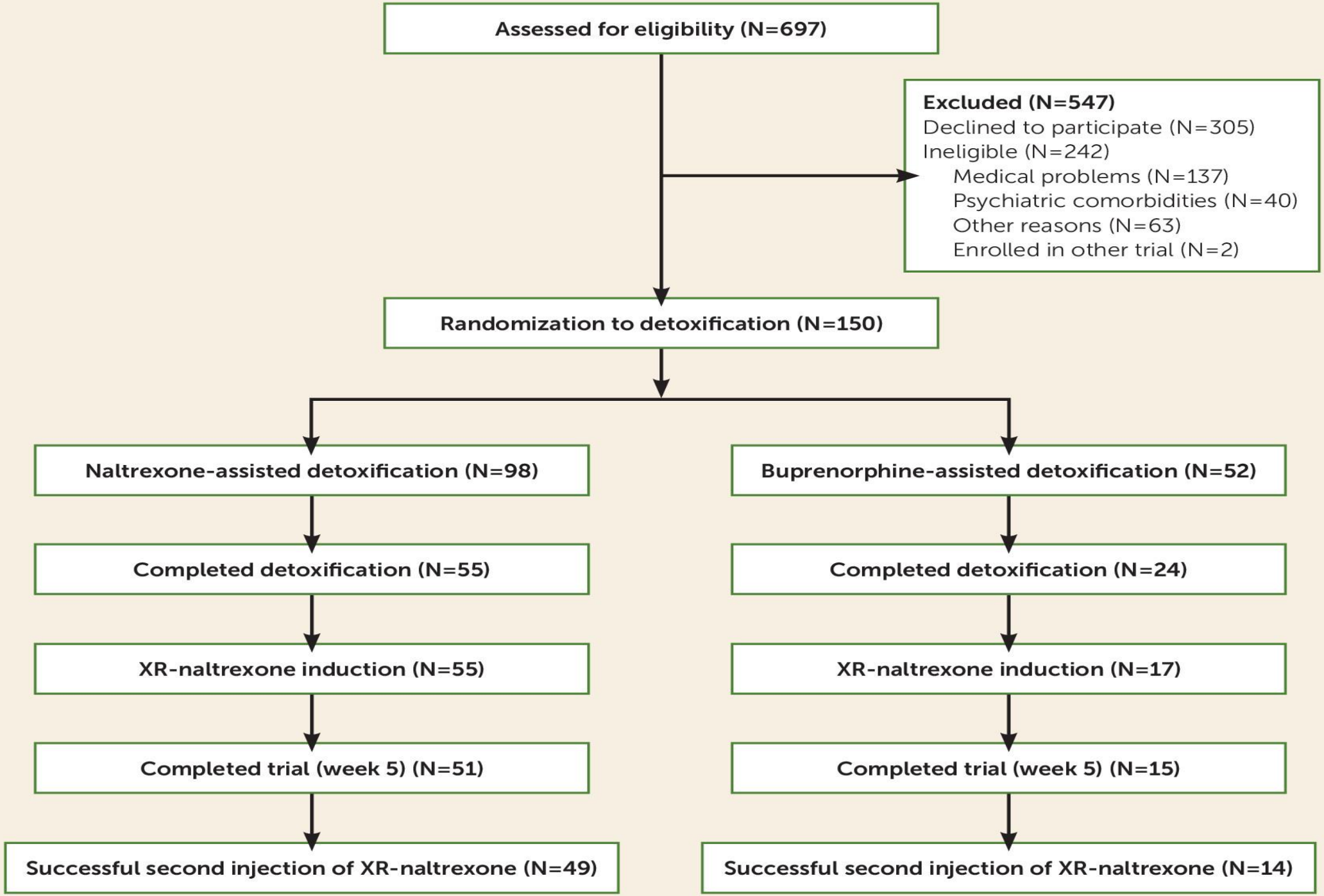
- Patient with opioid use disorder who was placed on buprenorphine. Since being on buprenorphine the patient has done poorly with continued heroin use, despite engagement in groups and individual therapy. His wife is now reporting he is selling some of his buprenorphine. You wish to convert him to naltrexone and offer this to the patient. What would your strategy be on making this conversion.

Long-Acting Injectable Naltrexone Induction: A Randomized Trial of Outpatient Opioid Detoxification With Naltrexone Versus Buprenorphine: Sullivan M., et al., The American Journal of Psychiatry, 2017

- 150 patients randomized to 2 different conversion strategies

TABLE 1. Outpatient Opioid Detoxification Regimen, by Treatment Arm, in a Study of Oral Naltrexone Versus Buprenorphine as Detoxification Strategies for Extended-Release Injectable Naltrexone Induction in Opioid Dependence

Protocol Day	Naltrexone-Assisted Detoxification	Buprenorphine-Assisted Detoxification
1	Ancillary medications[a] to support abstinence	
2	Buprenorphine, 2 mg sublingually every 1–2 hours, up to 8 mg	
3	(Washout)	Buprenorphine, 6 mg
4	Naltrexone, 1 mg	Buprenorphine, 4 mg
5	Naltrexone, 3 mg	Buprenorphine, 4 mg
6	Naltrexone, 12 mg	Buprenorphine, 2 mg
7	Naltrexone, 25 mg	Buprenorphine, 1 mg
8	Extended-release injectable naltrexone, 380 mg i.m.	


Assessed for eligibility (N=697)
Excluded (N=547)
Declined to participate (N=305)
Ineligible (N=242)
Medical problems (N=137)
Psychiatric comorbidities (N=40)
Other reasons (N=63)
Enrolled in other trial (N=2)
Randomization to detoxification (N=150)
Naltrexone-assisted detoxification (N=98)
Buprenorphine-assisted detoxification (N=52)
Completed detoxification (N=55)
Completed detoxification (N=24)
XR-naltrexone induction (N=55)
XR-naltrexone induction (N=17)
Completed trial (week 5) (N=51)
Completed trial (week 5) (N=15)
Successful second injection of XR-naltrexone (N=49)
Successful second injection of XR-naltrexone (N=14)

Extended release naltrexone injection is performed in the majority of opioid dependent patients receiving outpatient induction: A very low dose naltrexone and buprenorphine open label trial: Mannelli, P., et al, Drug and Alcohol Dependence, 2014

Day	NTX Mean (SD) mg	Dose range mg	BUP mg
1	0.43 (0.02)	0.25–0.5	4
2	0.43 (0.082)	0.25–0.5	2
3	0.83 (0.082)	0.5–1	2
4	2.94 (1.81)	2–6	–
5	5.30 (0.626)	3–15	–
6	12.21 (6.03)	5–35	–
7	31.30 (8.14)	13–50	–

- 15/20 patients completed the 7 day transition
- No reported precipitated withdrawals in those who completed the detox

Adverse side effects

- Hepatic monitoring
  - hepatically metabolized so requires functional liver
  - contraindicated of liver function tests > 3-5 times normal
- Most common (> 10%)
  - insomnia
  - nausea, diarrhea
  - anxiety
  - headache
- Injection site pain

Patient is a 60 to male on naltrexone for OUD. He has been doing very well for the last year. He has a planned hip replacement in 2 months. Which strategy would you recommend for managing post op pain.

- A- stop IM naltrexone one month prior and convert to oral. Stop oral 5 days before surgery
- B- Continue IM naltrexone and allow anesthesiologist to use high dose opioids for pain management
- D- Stop naltrexone one week prior and use nonsteroids
- E – I have another option

Pain management while on naltrexone

- Nonmedication approaches (Physical techniques, Cognitive approaches)
- Nonopioid pain medications (Tylenol, nsaids, gabapentin…)
- Ketamine
- Nerve blocks (local anesthetics)
- High dose potency opioids (hydromorphone or fentanyl) at doses 10-20 times normal
  - variable dosing depending on level of NTC blockade
  - done in monitored setting by experienced provider

Pain management while on naltrexone

If Opioids are required:

- XR-NTX: dc >30 days before surgery (switch to PO NTX if needed to bridge)
- PO NTX: dc >48-72hrs before surgery if anticipated need for opioids
- Plan for re-induction of XR-NTX: short-acting opioid washout 3–7 days; provide naloxone challenge.

IN THE CHAT BOX LIST SOME OF THE REASONS A PATIENT MIGHT BE A BETTER CANDIDATE FOR NALTREXONE VS BUPRENORPHINE/METHADONE

WHEN NALTREXONE vs BUPRENORPHINE

- Can the patient withstand the necessary timeframe for the induction
- What is the patient's prior experience with MAT
- What is the patient's preference (informed consent of viable options)
- Some patients do not want to be on a "opioid" or medication they become dependent to
- Are there cost concerns
- Does the patient have concurrent alcohol use disorder"
- Does the patient have history of diversion or misuse of their prior MAT
- Is compliance with taking pills a barrier (traveling, work schedules…)
- Are there concurrent pain issues
- Concurrent sedative use disorder
- Criminal justice involvement

WHEN NALTREXONE vs BUPRENORPHINE

- Are there concerns about side effects (low testosterone levels, constipation, sedation) of methadone or buprenorphine
- Does the patient want to get away for “pill taking”
- Is the patient afraid of injections
- Is the patient on other medications that might interact with buprenorphine/naltrexone
- Does the patient have sleep apnea or other respiratory illnesses that potentially would be exacerbated with the use of a respiratory depressant
- Has the patient overdosed while taking methadone or buprenorphine

Low Dose Naltrexone

Low Dose Naltrexone Mechanism of Action

- In addition to its antagonist activity at the mu receptor it is also an antagonist at the “nonopioid receptors TLR4” found on macrophages
- Macrophages are essential in inflammation
- These receptors are also found in the microglial cells in the brain
- At very low levels causes an increase levels of endorphins and increase the sensitivity of unoccupied mu receptors

Other indications investigated

- Fibromyalgia
- Chronic pain
- Complex regional pain syndrome
- Personality Disorder
- Kleptomania
- Gambling Disorder
- Other substances (stimulants)
- Weight gain
- Multiple sclerosis
- Chron’s Disease

Low Dose Naltrexone (Micro dosing)

- 4.5 mg or less
- Theory: Low doses of naltrexone causes increased production of endorphins
- Improved pain control, fibromyalgia, Chrons
- Case studies
  - 4 for Chron's all showing improvements in disease and patient satisfaction
  - 2 for fibromyalgia showing improvements (30%-50% improvement)

CASE: HOW LONG IS ENOUGH

- Patient with opioid use disorder severe in remission for last 10 months. Is on vivitrol after failing buprenorphine. Is enrolled in the drug court and will be finishing in 2 more months. The patient is requesting to stop the vivitrol as he wants to see if he has cravings when he stops and while he still is in the court system.

- Any thoughts on how to advise this patient
- Would it be in the best interest in stopping the vivitrol?