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PSYCHIATRY ACADEMY

Naltrexone for Opioid Use Disorder

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Disclosures

I or my spouse have the following relevant financial relationships with a commercial interest to disclose:

Consultant

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Bay Cove, Gavin foundation consultant for Acute Treatment Services

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Lumin Health

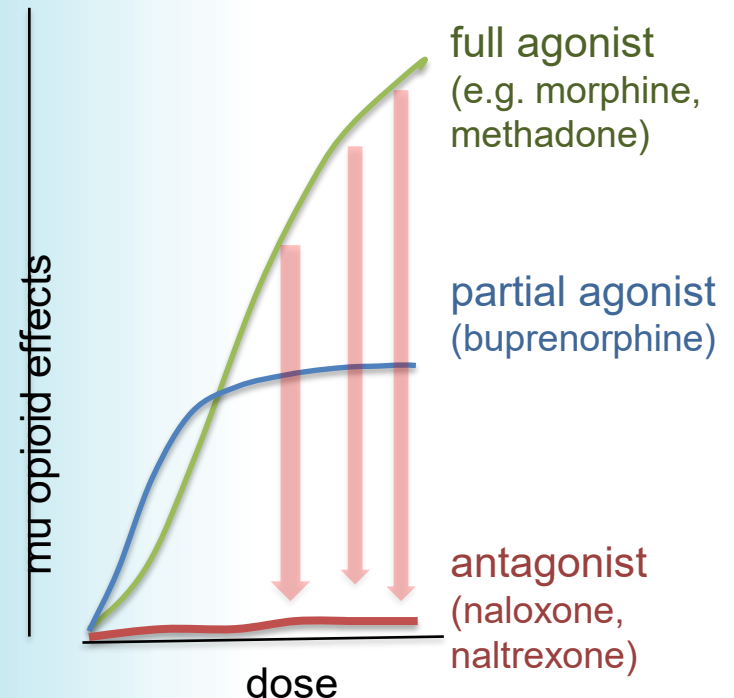
Naltrexone



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- Extended-release IM Naltrexone (Vivitrol®)
 - Monthly IM dosing
- Centrally-acting ANTAGONIST at mu opioid receptors
 - Blocks euphoric effect of opioid agonists
 - No dependence
 - Not scheduled
- High Affinity
 - Blocks other opioids
 - Can precipitate withdrawal



<https://www.ncbi.nlm.nih.gov/books/NBK537079/>

WWW.MGHCME.ORG

<https://www.vivitrol.com/content/pdfs/prescribing-information.pdf>

Oral Naltrexone for OUD



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- **NOT effective for OUD due to lack of adherence**
- Retention rates worse compared to ER
- Does not suppress cravings
- *Decreases* time to relapse
- No difference compared to placebo after treatment completion, unlike naltrexone ER

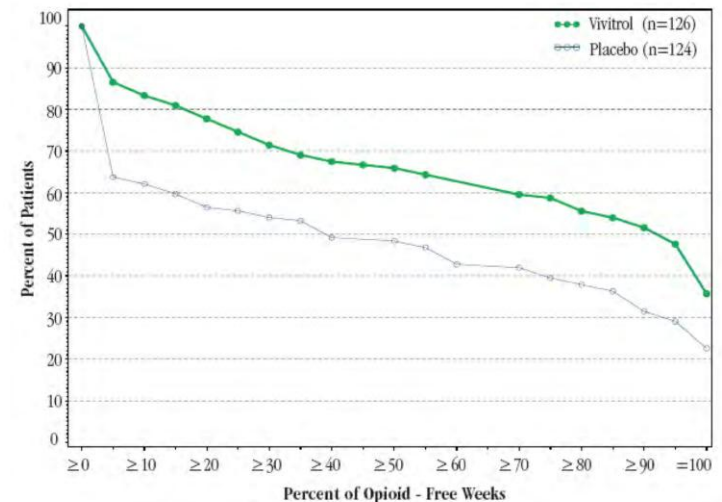


IM Naltrexone for OUD

FDA approved 2010 for OUD

- 3 U.S. trials showing IM superior to placebo & to usual (psychosocial) treatment
- Lower rate of relapse, longer time before return to opioid use (Lee 2016)
- **Not** studied as standalone treatment (without psychosocial component) unlike agonists

Figure 1: Subjects Sustaining Varying Percentages of Opioid-Free Weeks



A greater percentage of subjects in the VIVITROL group remained in the study compared to the placebo group.



Miracle drug?

Monthly injection that blocks euphoric effect of mu opioid agonists, does not create dependence, not as stigmatized, helps with relapse prevention over placebo



The Challenges

- Medication Initiation
 - Must be opioid-free for at least 7-10 days
 - Will precipitate withdrawal if taken too soon post-agonist
 - May experience subacute withdrawal post-induction
- Increased risk of overdose with return to use
 - Loss of tolerance to full agonist
 - Loss of antagonist blockade at end of month or with delayed injection
- Pain management
 - Opioid blockade can complicate pain management



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How does it compare to Buprenorphine?

First head-to-head trial: 2017 X-BOT trial



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- Randomized to daily SL buprenorphine vs monthly naltrexone ER during inpatient detox stay
- Followed for 24 weeks to assess relapse rate
- Per-protocol analysis (people who successfully start naltrexone ER): No difference between meds once treatment initiated
- **Intent-to-treat analysis** BUP-NLX superior to XR-NTX due to challenges inducing onto XR-NTX and high rates of relapse

	XR-NTX group (n=283)	BUP-NX group (n=287)	Treatment effect
Inducted to study medication			
Intention-to-treat group	204 (72%)	270 (94%)	OR 0.16, 95% CI 0.09–0.28; p<0.0001
Opioid relapse, weeks 3–24			
Intention-to-treat group	185 (65%)	163 (57%)	OR 1.44, 95% CI 1.02–2.01; p=0.036
Per-protocol group	106/204 (52%)	150/270 (56%)	OR 0.87, 95% CI 0.60–1.25; p=0.44
Relapse-free-survival (weeks), range 3–24			
Intention-to-treat group	8.4 (3.0–23.4)	14.4 (5.1–23.4)	HR 1.36, 95% CI 1.10–1.68; p=0.0040
Per-protocol group	20.4 (5.4–23.4)	15.2 (5.7–23.4)	HR 0.92, 95% CI 0.71–1.18; p=0.49
Total number of weekly opioid-negative urine samples, range 0–24			
Intention-to-treat group	4 (0–19)	10 (3–20)	p<0.0001
Per-protocol group	13 (3–21)	11 (3–20)	p=0.81
Total number of self-reported opioid-abstinent days, range 0–144			
Intention-to-treat group	39 (1–144)	81 (16–144)	p<0.0001
Per-protocol group	123 (18–144)	87 (20–144)	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.

Table 2: Opioid treatment outcomes



X-BOT Trial Summary

- XR-NTX less effective than BUP-NLX for prevention of opioid relapse following admission for inpatient detoxification
 - 28% dropped out of treatment before XR-NTX induction*
 - 6% dropped out before receiving BUP-NLX
- Nearly all induction failures had early relapse to opioids
 - 25% of XR-NTX group
 - 3% of BUP-NLX group
- Once on the medications, authors found both medications had similar effectiveness and safety
 - Suggest interpreting with caution as this disregards high risk initiation

*study required >3d from last opioid use, opioid-free urine, successful naloxone challenge

U.S. controversy: Marketed directly to judges, drug courts



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Amid a surging opiate crisis, the maker of the anti-addiction drug Vivitrol skirted the usual sales channels. It found a captive market for its once-a-month injection in the criminal justice system.

← Press Announcements

FDA NEWS RELEASE

FDA issues warning letter for not including the most serious risks in advertisement for medication-assisted treatment drug

f Share t Tweet e Email

For Immediate Release:

December 11, 2019

The U.S. Food and Drug Administration today posted a [warning letter](#) to Alkermes, Inc. of Massachusetts, for misbranding the drug Vivitrol

By **Mark Herz**

March 25, 2022

Updated March 25, 2022

The Massachusetts Trial Court has agreed to stop ordering and pressuring its drug court defendants to take a specific medication for opioid use disorder, and will instead leave medical decisions to licensed prescribers and treatment programs.

2019 WARNING LETTER

“Vivitrol is being promoted in a way that does not adequately present important risk information in a truthful and non-misleading manner. This is concerning from a public health perspective because of the potential for fatal opioid overdose in this vulnerable patient population.”

-Thomas Abrams, Director of FDA Office of Prescription Drug Promotion

[https://www.npr.org/sections/health-shots/2017/06/12/523774660/a-](https://www.npr.org/sections/health-shots/2017/06/12/523774660/a-drugmaker-tries-to-cash-in-on-the-opioid-epidemic-one-state-law-at-a-time)

[drugmaker-tries-to-cash-in-on-the-opioid-epidemic-one-state-law-at-a-time](https://www.npr.org/sections/health-shots/2017/06/12/523774660/a-drugmaker-tries-to-cash-in-on-the-opioid-epidemic-one-state-law-at-a-time)

<https://www.wgbh.org/news/local/2022-03-25/mass-drug-courts-settle-with-us-attorneys-office-over-interfering-with-treatment>

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2025 Literature updates

- Findings from Norway
 - For highly-motivated patients, longer duration of treatment was better (Brenna)
 - Risk of death remained high in year post-treatment discontinuation (Gjersing)
 - Inductions most successful for patients in controlled setting who had **not** been on methadone (Mordal)
- Limited applicability to U.S.:
 - Illicitly-manufactured Fentanyl (IMF) not prevalent in Norway
 - ER NTX not approved for OUD treatment in Norway, only used in research



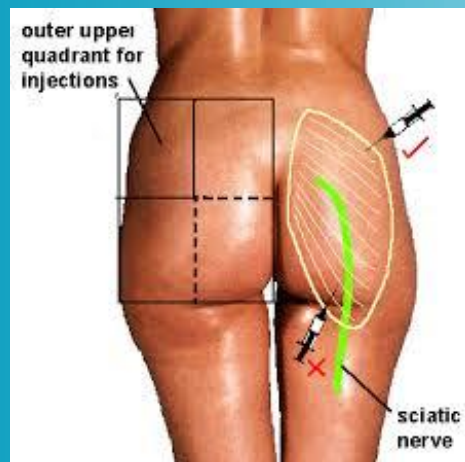
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Logistics



Naltrexone ER Injection



Prior to injecting, tap the syringe to release any air bubbles, then push gently on the plunger until 4 mL of the suspension remains in the syringe. (see Figure F)

**THE SUSPENSION IS NOW
READY FOR IMMEDIATE
ADMINISTRATION.**

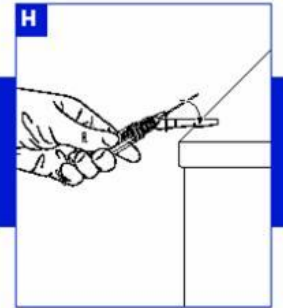


1. Administer the suspension by deep intramuscular (IM) injection into a gluteal muscle, alternating buttocks per injection. Remember to aspirate for blood before injection. (see Figure G)

2. Inject the suspension in a smooth and continuous motion.

3. If blood aspirates or the needle clogs, do not inject. Change to the spare needle provided in the carton and administer into an adjacent site in the same gluteal region, again aspirating for blood before injection.

VIVITROL must NOT be given intravenously.



After the injection is administered, cover the needle by pressing the safety sheath against a hard surface using a one-handed motion away from self and others. (see Figure H)

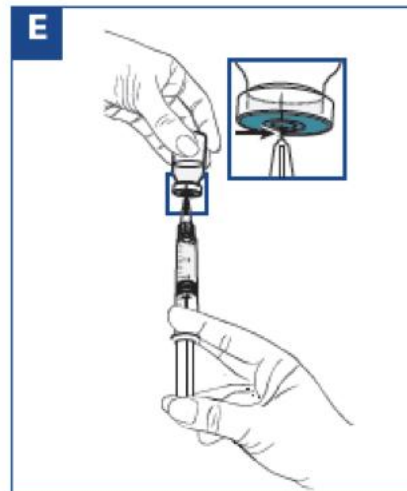
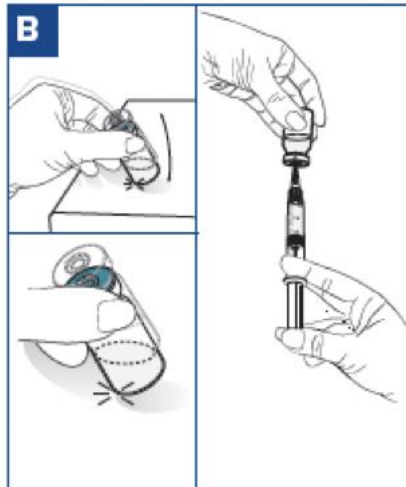
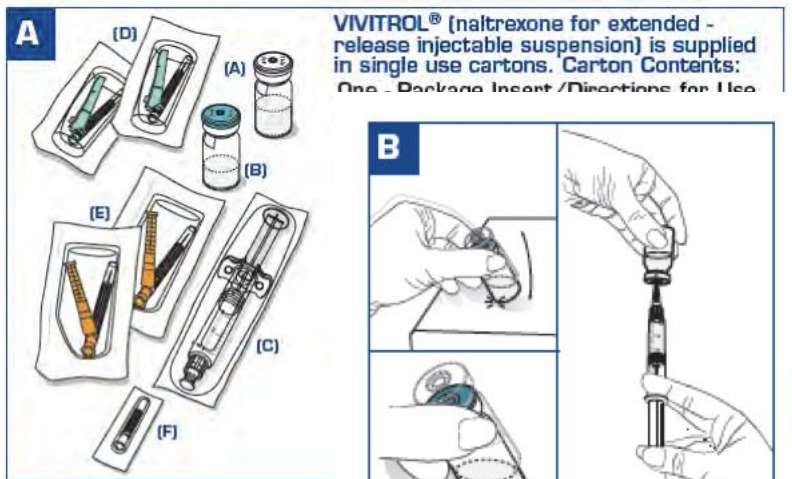
Activation of the safety sheath may cause minimum splatter of fluid that may remain on the needle after injection.

**DISPOSE OF USED AND UNUSED
ITEMS IN PROPER WASTE
CONTAINERS**

<https://www.youtube.com/watch?v=IZBaDCIWSwg>

<https://pcssmat.org/overview-of-mat/naltrexone/>

Naltrexone IM injection



ension by deep intramuscular (IM)
muscle, alternating buttocks per
**number to aspirate for blood before
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Naltrexone ER Side Effects

- Generally well tolerated if after period of abstinence
- Injection site reactions
- GI upset
- Diarrhea
- Headache
- Allergic pneumonitis



Storage

- Requires refrigeration
 - Do NOT freeze
 - May be kept in room temperature for up to 7 days prior to administration
- Warm to room temp (~45 min) before injection



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Inductions



Induction

- FDA guideline/manufacturer website: opioid-free interval of minimum 7-10 days for patients previously dependent on short-acting opioids
- Transition from methadone/buprenorphine may require opioid-free period of up to 2 weeks
- Oral lead-in to injection not required



5-7 Day “Rapid” Induction

JAMA
Network | **Open.**

RCT: Rapid Initiation of Injection Naltrexone for Opioid Use Disorder

POPULATION

205 Men, 210 Women



Adults admitted with opioid use disorder who chose treatment with extended-release (XR) naltrexone

Mean age, 33.6 y

SETTINGS / LOCATIONS



**Six inpatient
hospital units in
the US**

INTERVENTION

415 Participants randomized



190 Standard procedure

3-5 d Oral buprenorphine taper followed by 7-10 d opioid-free period before XR-naltrexone initiation

225 Rapid procedure

1 d Oral buprenorphine, 1 opioid-free d, 3-4 d oral naltrexone titration + adjunctive medications before XR-naltrexone initiation

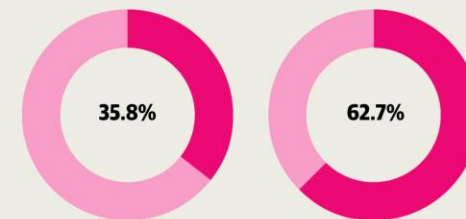
PRIMARY OUTCOME

Receipt of XR-naltrexone injection prior to inpatient discharge (yes/no), with noninferiority demonstrated if the lower bound of the 95% CI for the primary outcome odds ratio was >0.67

FINDINGS

The rapid procedure was noninferior to the standard procedure for initiation of XR-naltrexone

Receipt of XR-naltrexone



68 of 190 Participants

141 of 225 Participants

Odds ratio, 3.60 (95% CI, 2.12-6.10); $P < .001$

Shulman M, Greiner MG, Tafessu HM, et al. Rapid initiation of injection naltrexone for opioid use disorder: a stepped-wedge cluster randomized clinical trial. *JAMA Netw Open*. 2024;7(5):e249744. doi:10.1001/jamanetworkopen.2024.9744

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Cases



Case 1

- 28M active OUD presents asking for help getting onto XR NTX as outpatient
 - Key questions:
 - Why naltrexone?
 - Prior treatment history?
 - Current use pattern?
 - You express your concerns in a patient-centered way

Pt adamant. What do you do?



Case 2

- 42yo father who comes for his 36th IM NTX. Swears by this medicine: has kept him sober, no cravings, allowed him to get his life back.
 - Chose this medicine because he is not allowed to be on OAT in his union
- You ask him to share how he was successful



Which Patients Are Good Candidates for Antagonist Therapy?

- Patients not interested in, or able to be on, agonist maintenance
- Shorter history of use
- High degree of motivation for abstinence
- Professions where treatment with agonist is controversial or restricted (healthcare professionals, pilots)
- Patients successful on agonist but who want to try antagonist
- Patients who are abstinent but at risk for return to opioid use
- *ALWAYS document discussion of OD risk at each visit*



Case 3

- 28F remission from OUD, on IM naltrexone x 1 year
- Sees you for pre-conception counseling visit
- Asks if she should remain on naltrexone



IM Naltrexone: Emerging data for prenatal OUD

Australian studies gave initial safety data (NTX implant)

- Possible increase in early pregnancy loss, no increased anomalies or pregnancy outcome differences

U.S. Studies

- High rates of incomplete induction
- No difference in birth outcomes vs OAT
- 2024 systematic review
 - No RCT comparing OAT vs NTX
 - Similar obstetric outcomes b/t OUD in 5 cohort studies
 - All studies had selection bias
 - Shared decision-making approach until have more data
- 2024 prospective case series of women/infants *already on* NTX reassuring to 1 year postpartum
 - (N=7 mix of aud/oud and PO/IM ntx)



IM naltrexone for prenatal OUD

- Appealing to some patients (avoids NAS + reporting)
- NOT first line treatment (limited safety data)
- Individualize:
 - Benefit > risk of continuation if stable
 - Less evidence to initiate de novo
- Any MOUD is safer than untreated OUD



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Thank you!

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