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PSYCHIATRY ACADEMY

Naltrexone for Opioid Use Disorder

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Disclosures

I have the following relevant financial relationship with a commercial interest to disclose:

Consultant
- MCSTAP (Massachusetts Consultation Service for Treatment of Addiction and Pain) funded by Massachusetts government
- Bay Cove, Gavin foundation consultant for Acute Treatment Services

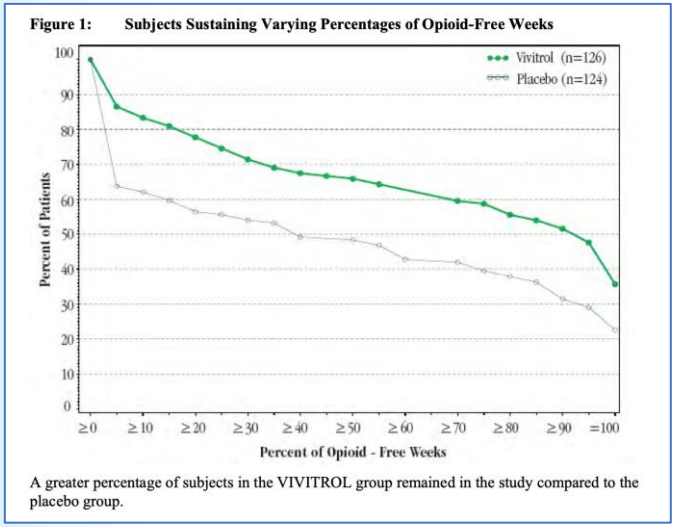
Salary support NIDA CTN 0800
Lumin Health

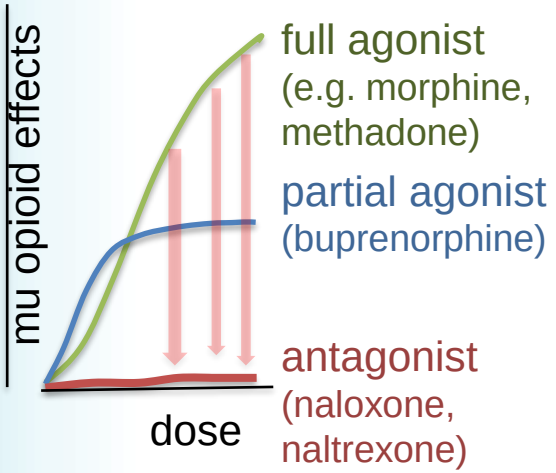
Thank you to Laura Kehoe for an earlier version of this presentation

Naltrexone

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- Extended-release IM NTX (Vivitrol) FDA approved 2010 for treatment of OUD
  - 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





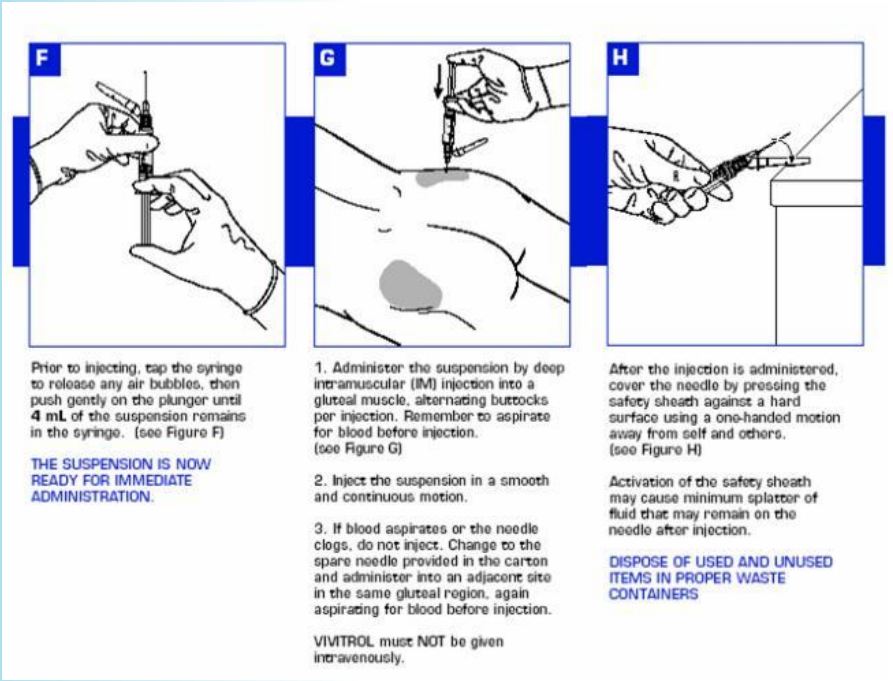
https://www.ncbi.nlm.nih.gov/books/NBK537079/

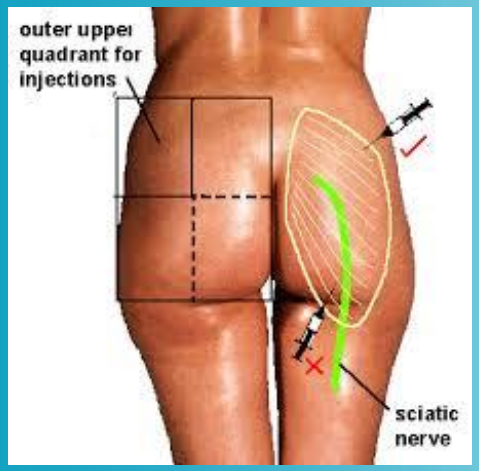
https://www.vivitrol.com/content/pdfs/prescribing-information.pdf

Naltrexone ER Injection

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https://www.youtube.com/watch?v=lZBaDCIWSwg

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

Miracle drug?

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

Naltrexone ER Cautions

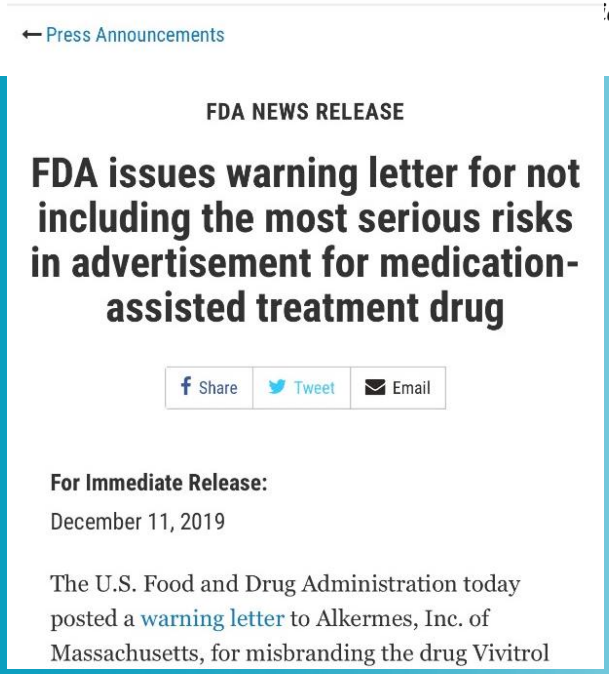
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- Will precipitate withdrawal if agonists (full or partial) are occupying mu receptors
- Must be 7-10+ days opioid free
- May experience subacute opioid withdrawal when starting right after medically supervised opioid withdrawal
- Can use a trial dose of intranasal naloxone if unclear safety
- Will blockade all opioids, including those for pain
- Increased risk of overdose if patients try to overcome blockade
- Increased risk of overdose end of month or missed dose because of loss of tolerance

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

Share Tweet 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-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

Naltrexone ER Side Effects

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

Oral Naltrexone

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- **Oral naltrexone *ineffective for OUD* re: 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

Bart G. J Addict Dis. 2012;31(3):207-25.

Lee J. N Engl J Med 2016; 374:1232-1242

2017 X-BOT trial: Somewhat Misleading Press

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- Voluntary inpatient medically managed withdrawal
- Patients randomized to daily buprenorphine vs monthly naltrexone ER
- Followed 24 weeks to assess relapse rate
- Per-protocol analysis (people who successfully start naltrexone ER) showed no difference
- **Intent-to-treat analysis showed buprenorphine superior to naltrexone ER**

	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

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- Difficult to initiate naltrexone ER
  - Only 72% assigned received first dose
  - And among those assigned during detox, only 53% started the medication
  - ***Vs… 94% assigned to buprenorphine started Rx***
- Relapses earlier and more likely with NTX ER vs. BUP
  - Intention to treat analysis
    - 65% relapse NTX ER vs. 57% buprenorphine
  - Relapse immediate
    - Very early on as so difficult to initiate NTX (25% day 21 NTX vs 3% buprenorphine)
- More overdoses in those randomized to NTX ER vs. BUP

Lee, Joshua D et al. The Lancet , Volume 391 , Issue 10118 , 309 - 318

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?

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- 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

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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)

Jones, Addiction 2013; Wachman JAM 2024; Towers AJOG 2020; Alturu Ob&Gyn 2024

IM naltrexone for prenatal OUD

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- 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

Thank you!

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