MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Naltrexone for Opioid Use Disorder

Jessica Gray, MD

February 2026

Disclosures

I or my spouse have the following relevant financial relationships 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

Prior salary support NIDA CTN 0800

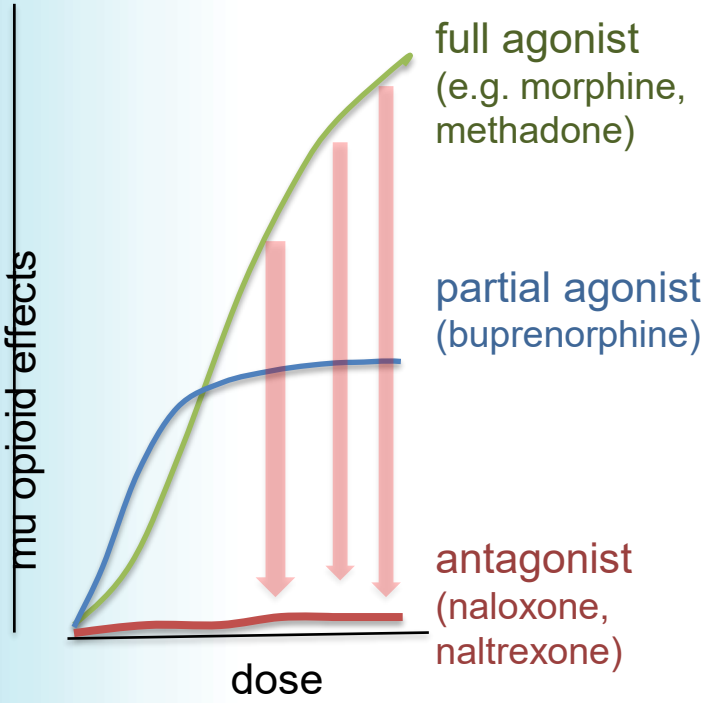
Lumin Health

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

Naltrexone

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

- 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/

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

Oral Naltrexone for OUD

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

- **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

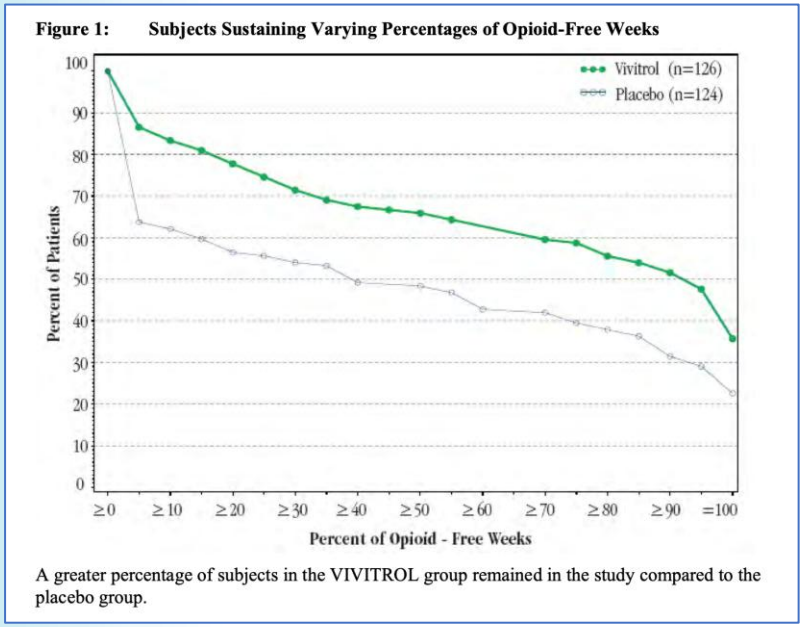
Bart G. J Addict Dis. 2012;31(3):207-25.
Lee J. N Engl J Med 2016; 374:1232-1242

IM Naltrexone for OUD

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

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



Comer 2006, Krupitsky 2011, Lee 2016

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

https://www.accessdata.fda.gov

How does it compare to Buprenorphine?

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

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

- 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**

Lee, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): A multicentre, open-label, randomised controlled trial. Lancet 2018

X-BOT Trial Summary

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

- 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

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

- Nearly all induction failures had early relapse to opioids
  - **25%** of XR-NTX group
  - **3%** of BUP-NLX group

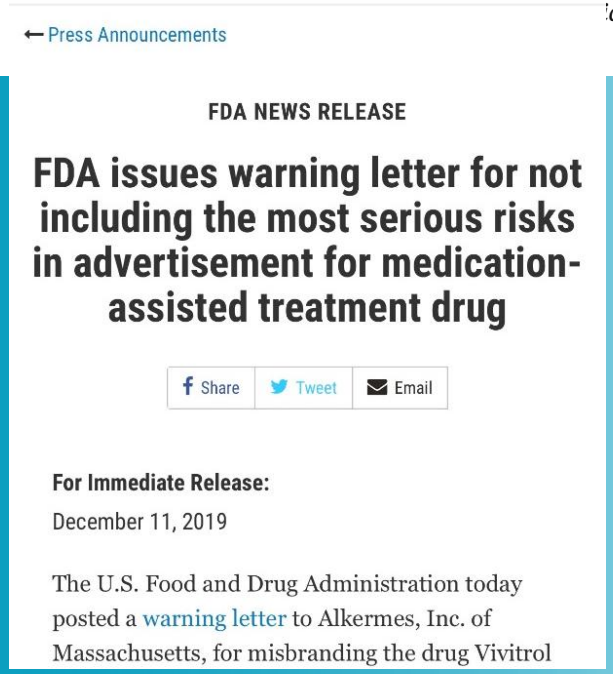
- Once on the medications, authors found both medications had similar effectiveness and safety
  - Suggest interpreting with caution as this disregards high risk initiation

Lee, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): A multicentre, open-label, randomised controlled trial. Lancet 2018

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

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

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

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

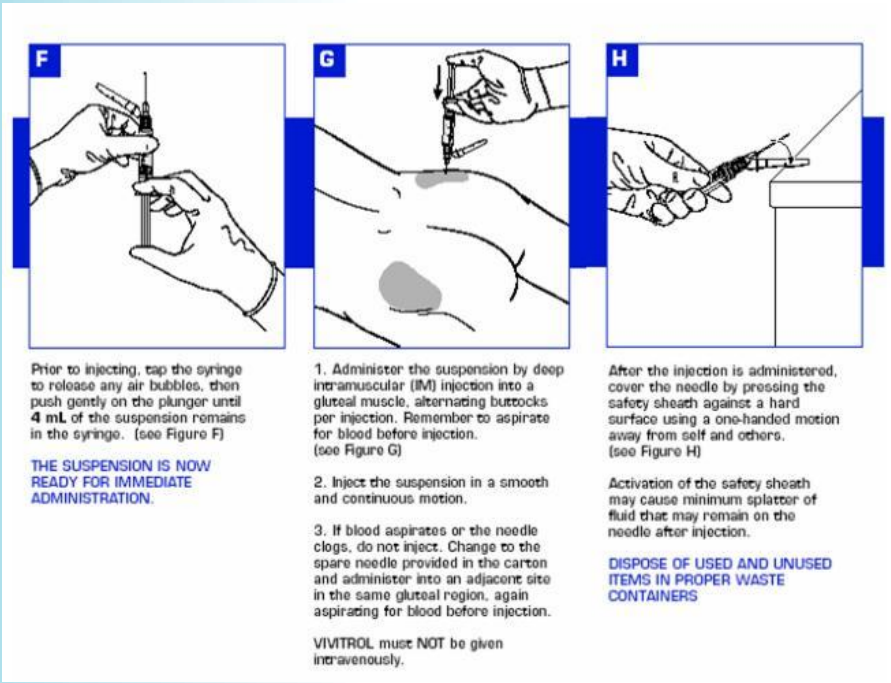
Brenna et al. Patients with Opioid Use Disorder Choosing Treatment with Extended-Release Naltrexone: A 6-Month Naturalistic Study. Eur Addict Res. 2025.
Gjersing et al. Mortality during and following treatment with extended-release naltrexone based on data from two clinical trials. Drug and Alcohol Dependence, 2025
Mordal et al. High induction rate onto extended-release naltrexone for people with opioid use disorder: experiences from a Norwegian naturalistic study. Addict Sci Clin Pract. 2025

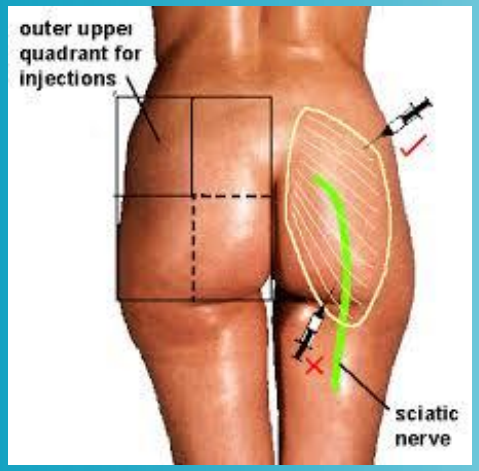
MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Logistics

Naltrexone ER Injection

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

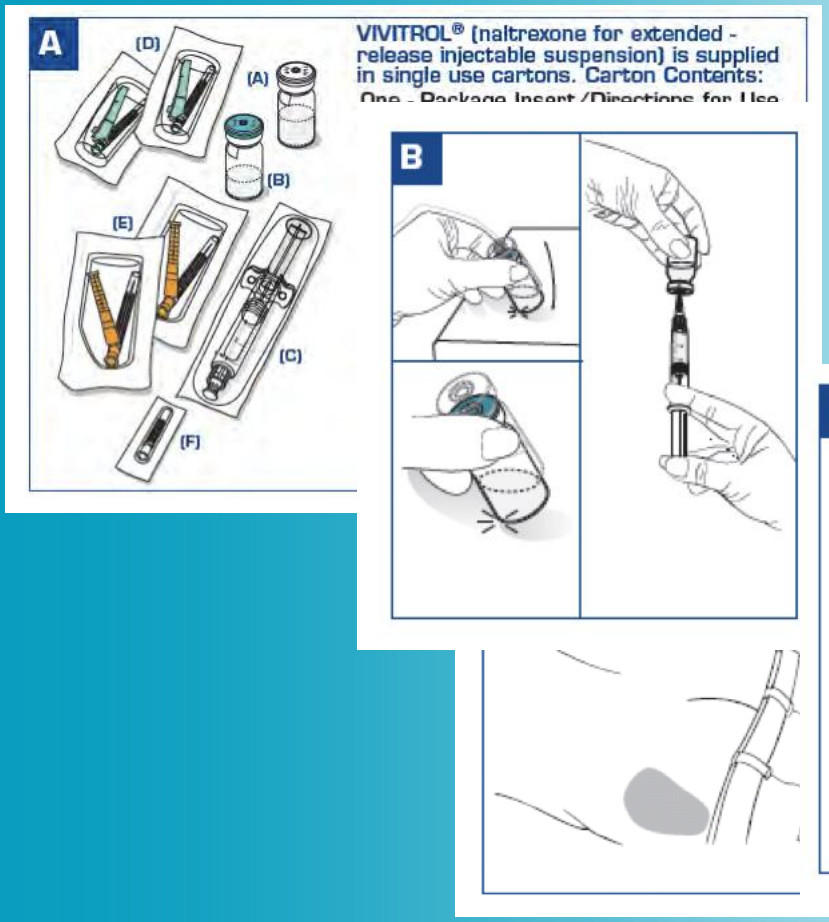




https://www.youtube.com/watch?v=lZBaDCIWSwg

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

Naltrexone IM injection



Naltrexone ER Side Effects

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

- 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

Liver disease and monitoring

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Baseline LFTs not required — avoid delaying treatment

HIV/HCV/HBV: do **not** require testing to start; offer routine screening + referral

Monitoring: no evidence for frequent labs; **quarterly LFTs reasonable** or if symptomatic

Counsel patients to report: relapse, new meds (incl. OTCs), hepatic symptoms

Stop NTX/XR-NTX if: AST/ALT >10× ULN with symptoms or hospitalization
→ evaluate other causes; **restart if symptoms resolve & LFTs <10× ULN**

https://pcssnow.org/wp-content/uploads/2014/10/PCSS-MAT-NTX-Liver-Safety-Guideline1.pdf

PCSS Guidance:
Monitoring of Liver Function Tests in Patients Receiving Naltrexone or Extended-Release Naltrexone. Reviewed and Re-released: May 2022

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

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

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

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

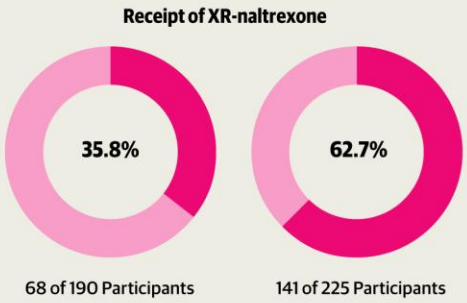
225 Rapid procedure
1 d Oral buprenorphine, 1 opioid-free d, 3-4 d oral naltrexone titration + adjunctive medications before XR-naltrexone initiation

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



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

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Cases

Case 1

- 28YO 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 for OUD
- 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?

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

- 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

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

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

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

- 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!

jgray7@mgb.org
@drjessgray

References

- Jarvis, B. P., Holtyn, A. F., Subramaniam, S., Tompkins, D. A., Oga, E. A., Bigelow, G. E., & Silverman, K. (2018). Extended-release injectable naltrexone for opioid use disorder: a systematic review. *Addiction (Abingdon, England)*, *113*(7), 1188–1209.
- Lee JD, Nunes EV Jr, Novo P, Bachrach K, Bailey GL, Bhatt S, Farkas S, Fishman M, Gauthier P, Hodgkins CC, King J, Lindblad R, Liu D, Matthews AG, May J, Peavy KM, Ross S, Salazar D, Schkolnik P, Shmueli-Blumberg D, Stablein D, Subramaniam G, Rotrosen J. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. Lancet. 2018 Jan 27;391(10118):309-318.
- http://pcssnow.org/wp-content/uploads/2017/02/Naltrexone_Step-by-Step_Virtual_Brochure-1.pdf
- https://www.vivitrol.com/content/pdfs/prescribing-information.pdf
- Brenna IH, Waleur KM, Benth JŠ, Solli KK, Mordal J, Løberg EM, Weimand B, Tanum L. Patients with Opioid Use Disorder Choosing Treatment with Extended-Release Naltrexone: A 6-Month Naturalistic Study. Eur Addict Res. 2025;31(1):1-12.
- Superior to placebo:
- Lee, J. D., Friedmann, P. D., Kinlock, T. W., Nunes, E. V., Boney, T. Y., Hoskinson, R. A., Jr., … O'Brien, C. P. (2016). Extended-release naltrexone to prevent opioid relapse in criminal justice offenders. New England Journal of Medicine, 374(13), 1232–1242.
- Comer, S. D., Sullivan, M. A., Yu, E., Rothenberg, J. L., Kleber, H. D., Kampman, K., … O'Brien, C. P. (2006). Injectable, sustained-release naltrexone for the treatment of opioid dependence: A randomized, placebocontrolled trial. Archives of General Psychiatry, 63(2), 210–218.
- Krupitsky, E., Nunes, E. V., Ling, W., Illeperuma, A., Gastfriend, D. R., & Silverman, B. L. (2011, April 30). Injectable extended-release naltrexone for opioid dependence: A double-blind, placebo-controlled, multicentre randomised trial. Lancet, 377(9776), 1506–1513.
- Comparison to Buprenorphine
- Lee, J. D., Nunes, E. V., Jr., Novo, P., Bachrach, K., Bailey, G. L., Bhatt, S., … Rotrosen, J. (2018). Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): A multicentre, open-label, randomised controlled trial. Lancet, 391(10118), 309–318.
- Norway studies:
- Brenna IH, Waleur KM, Benth JŠ, Solli KK, Mordal J, Løberg EM, Weimand B, Tanum L. Patients with Opioid Use Disorder Choosing Treatment with Extended-Release Naltrexone: A 6-Month Naturalistic Study. Eur Addict Res. 2025;31(1):1-12.
- L. Gjersing, L. Tanum, B. Weimand, K.K. Solli. Mortality during and following treatment with extended-release naltrexone based on data from two clinical trials,Drug and Alcohol Dependence, Volume 274, 2025
- Mordal J, Juya F, Holtan L, Vederhus JK, Opheim A, Brenna IH, Enger AE, Weimand B, Solli KK, Tanum L. High induction rate onto extended-release naltrexone for people with opioid use disorder: experiences from a Norwegian naturalistic study. Addict Sci Clin Pract. 2025 Jun 16;20(1):50.