

Effectiveness of XR-Naltrexone for opioid and alcohol treatment

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Long-Acting Medications for Opioid Use Disorders

◆ Naltrexone

◆ Daily tablet 50 mg

- **Monthly IM Injection**
- Bi-monthly SC implant (RUS)
- 6-month SC implant (AUS, ~ UA)

◆ Buprenorphine

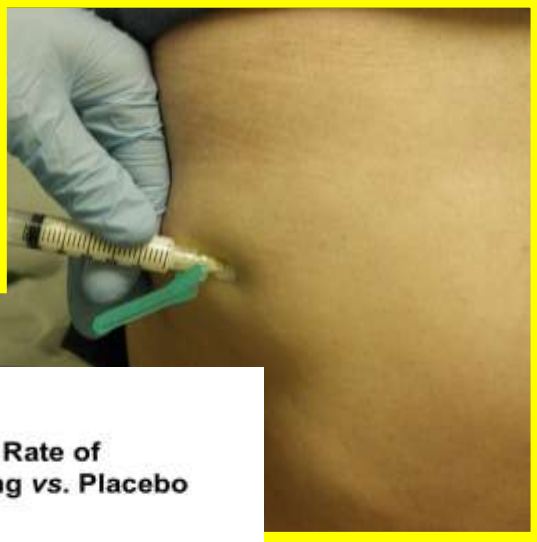
For OUD

- SL Daily BUP-NX (and BUP)
- Buccal Daily BUP-NX
- **Monthly SC Injection (USA)**
- **6 month SC implant (USA)**

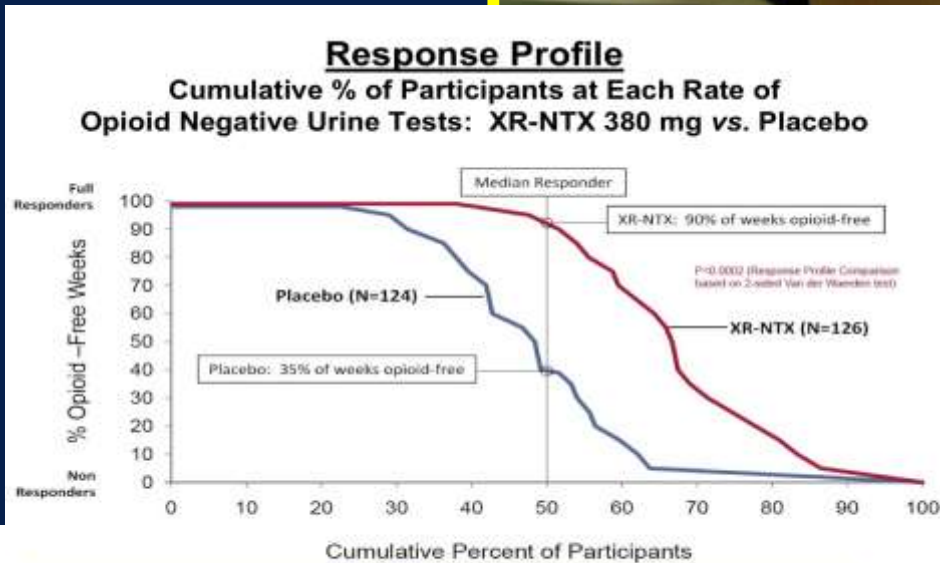
For Pain

- Injectable BUP
- Buccal and Transdermal BUP

Extended-Release Naltrexone (Vivitrol): mu opioid antagonist for opioid or alcohol use disorders

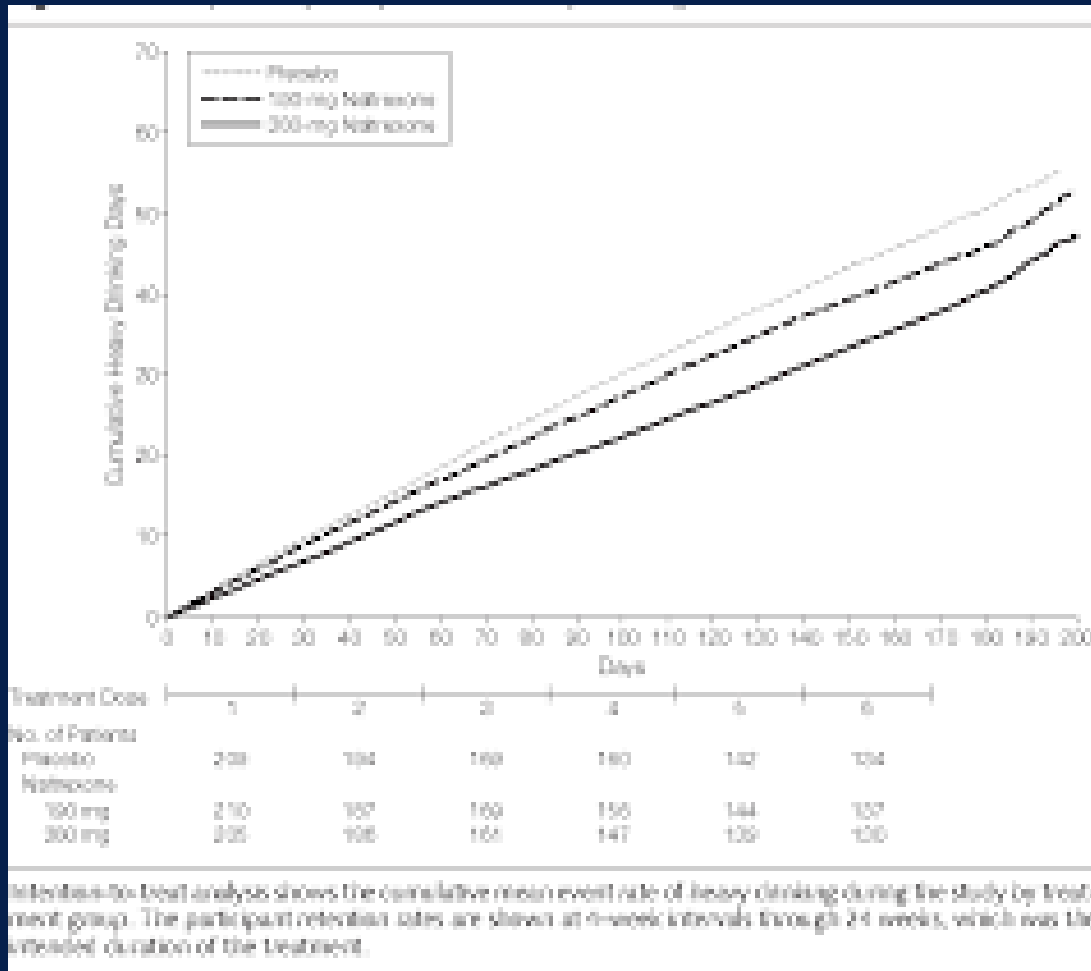


- Monthly intramuscular injection
- Given by nurse, PA, MD, pharmacist
- Non-narcotic, not a controlled substance
- Must detox off opioids first!
 - Jail, prison, detox, rehab, other
- Not for use if:
 - Pregnancy
 - Chronic pain requiring opioids



• Total abstinence (100% opioid-free weeks) during Weeks 5-24 was reported in 45 (35.7%) of subjects in the XR-NTX group versus 28 (22.6%) subjects in placebo group ($P=0.0224$).

XR-NTX for Alcohol Treatment



- ◆ Naltrexone with Medical Management is first line treatment for alcohol use disorders in US (Anton, COMBINE Study, 2005)
- ◆ XR-NTX is superior to placebo (Garbutt, 2006)
- ◆ XR-NTX may or may not be superior to Oral Naltrexone

viral load

- ◆ 2x placebo-controlled RCTs of XR-NTX for alcohol (N=100) and opioid (N=93) use disorders in HIV+ adults leaving prison/jail
- ◆ Only alcohol or opioid RCTs linking an addiction medication to HIV suppression after prison

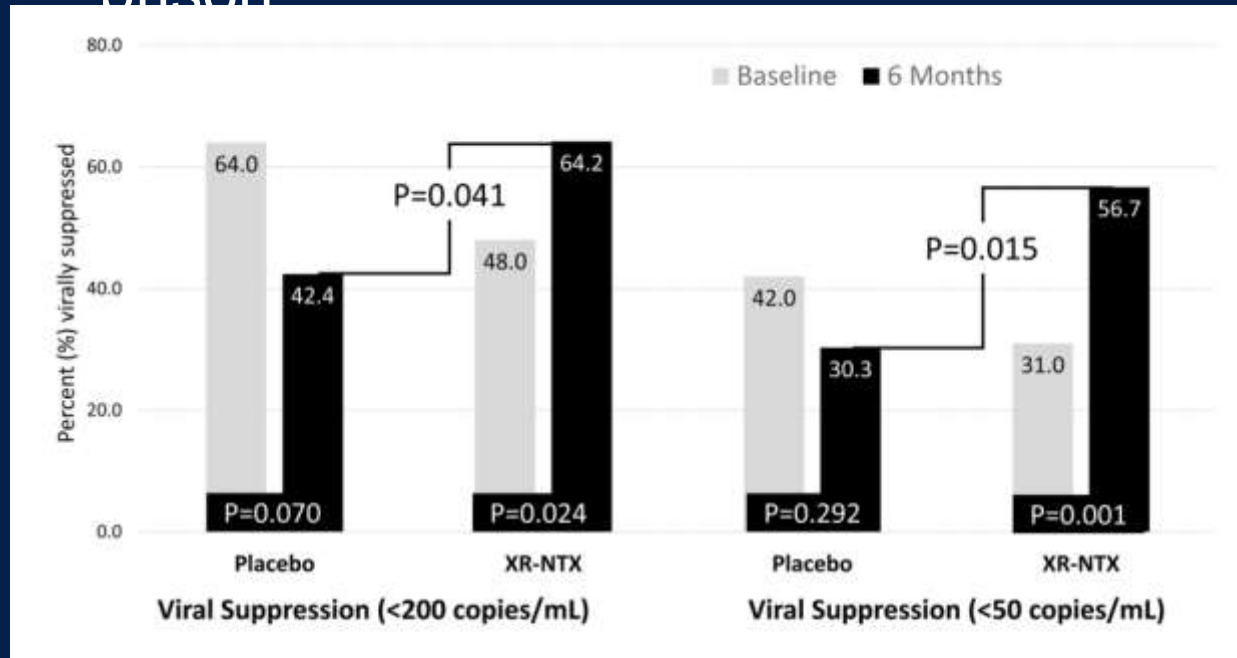


Figure 2. Intention-to-Treat Analysis: Comparison of viral suppression levels at <200 copies/mL and <50 copies/mL for participants receiving extended-release naltrexone or placebo (N=100)

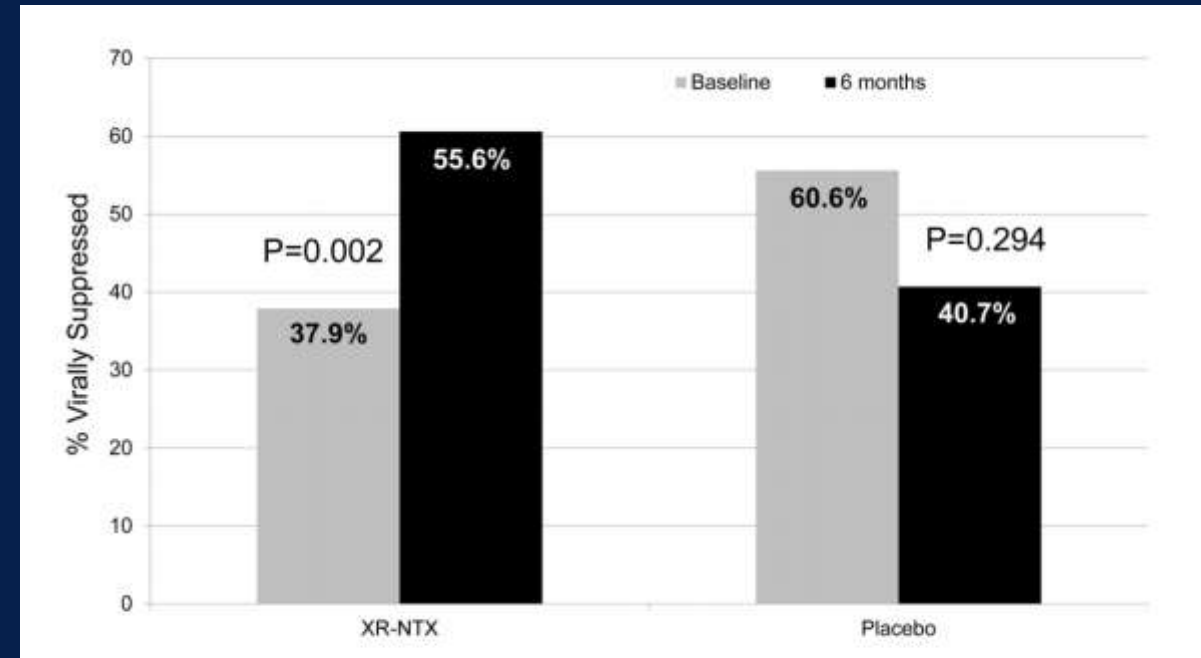


Figure 2. Change in Viral Suppression (<50 copies/mL) from Baseline to 6 months

Extended-Release Naltrexone (XR-NTX): Key Publications

◆ 2011 KrupitskyE

- *The Lancet*; XR-NTX OUD pivotal trial
- Superior relapse prevention vs. placebo, N=250 Russian heroin-dependent adults

◆ 2015 LeeJD

- *Addiction*; XR-NTX jail release RCT
- Superior relapse prevention vs. non-agonist TAU, N=37 NYC jail-released heroin-dependent adults

◆ 2016 LeeJD

- *NEJM*; largest US XR-NTX effectiveness trial to date
- Superior to non-agonist Treatment as Usual, N=306 USA CJS-involved adults with lifetime history of OUD

Extended-Release Naltrexone (XR-NTX): Key Publications

◆ 2017 LeeJD

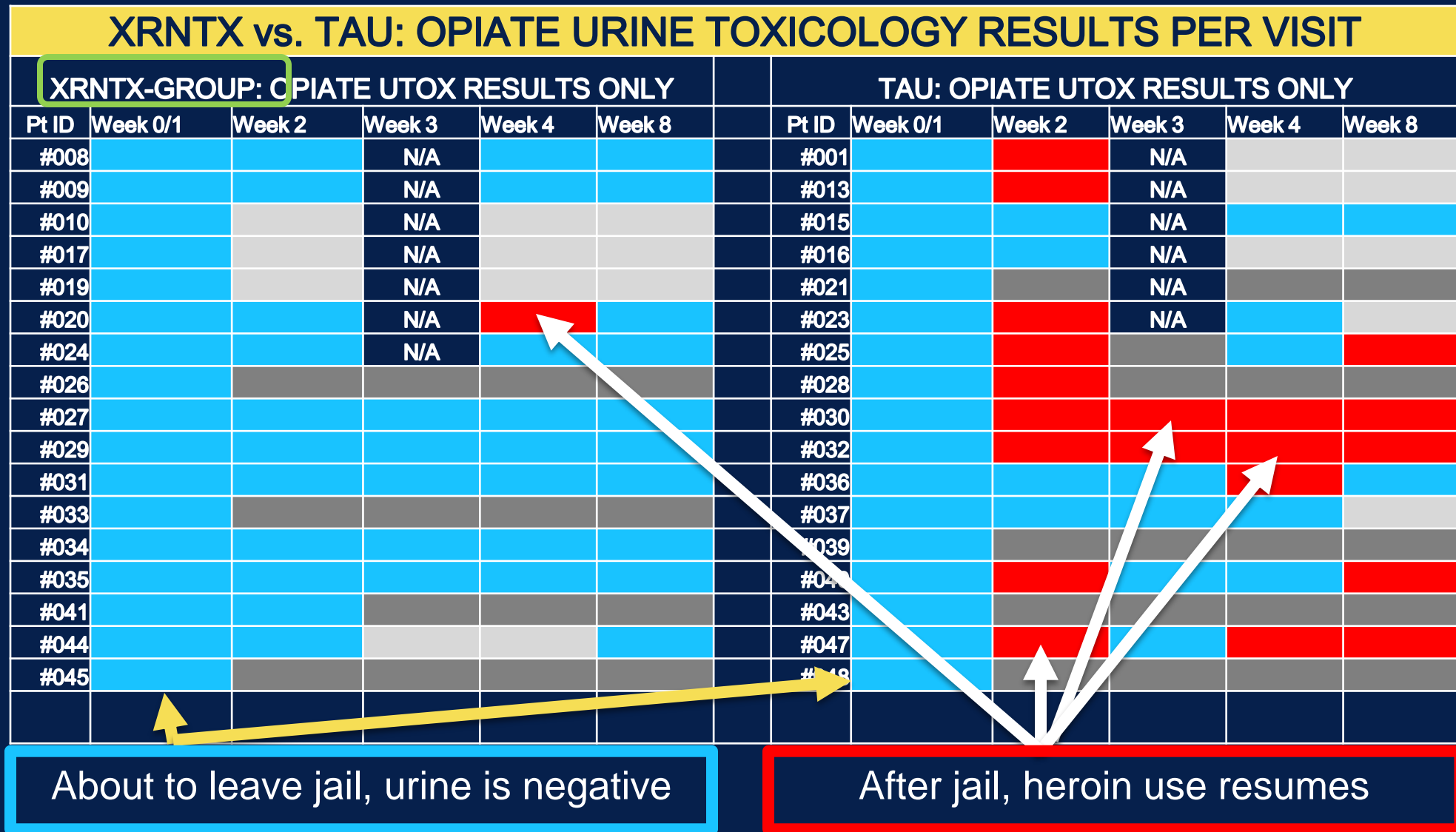
- ***The Lancet*; X:BOT head-to-head vs. Sublingual daily BUP-NX FILM**
- BUP-NX overall superior relapse prevention
- XR-NTX safe and similarly effective once induction is successful
- Harder to induct onto XR-NTX
- N=570 USA heroin-dependent were adults admitted to detox and followed as outpatients

◆ 2017 TanumL

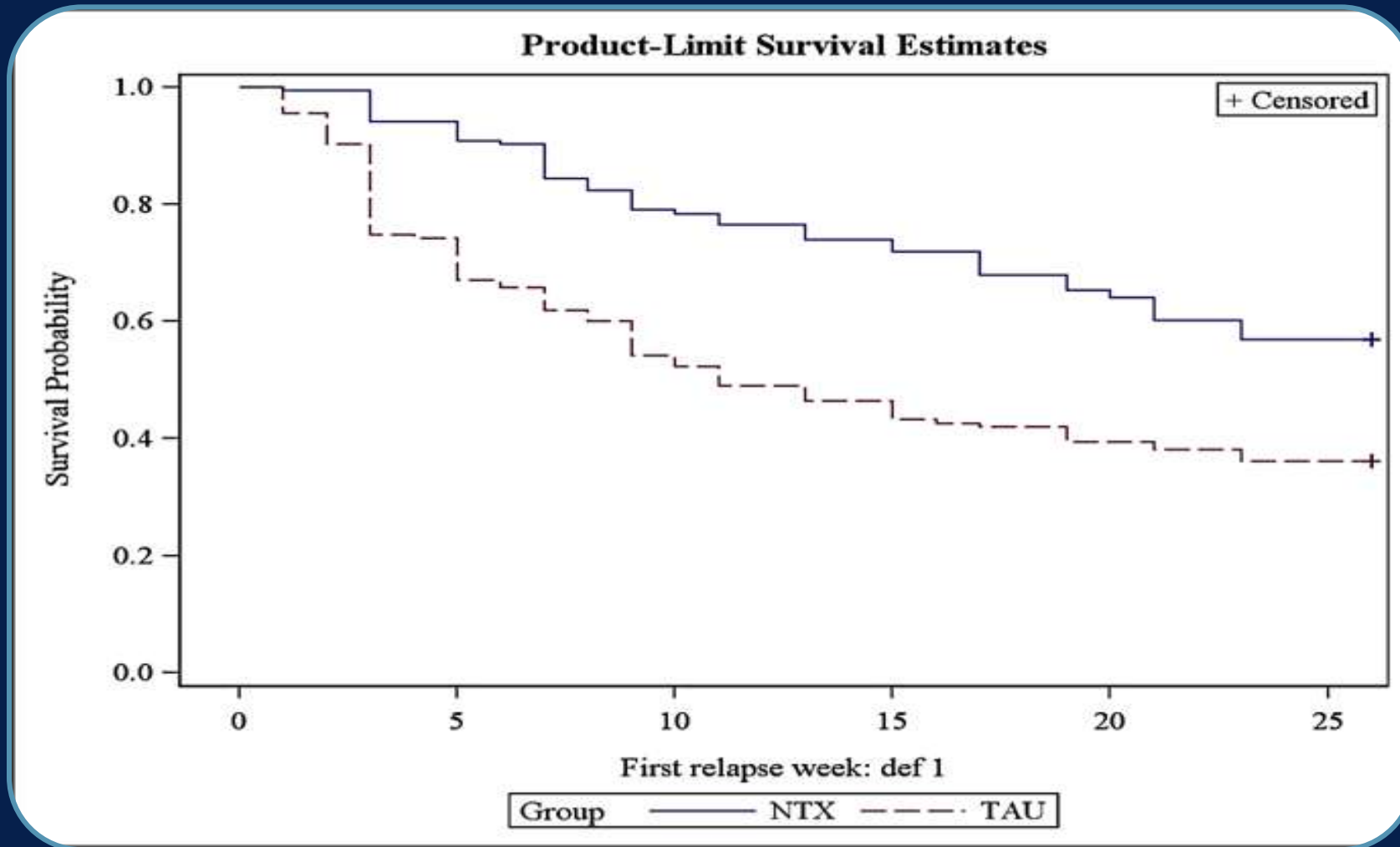
- ***JAMA Psychiatry*; head-to-head vs. BUP-NX in Norway**
- XR-NTX non-inferior to BUP-NX
- N=159 heroin-dependent Norwegian adults
- 12-week study followed by 48-week extension phase

- 2018: **Springer et al x 2...see above**

Less Post-Jail Heroin Use if XR-NTX: NYC Jail RCT

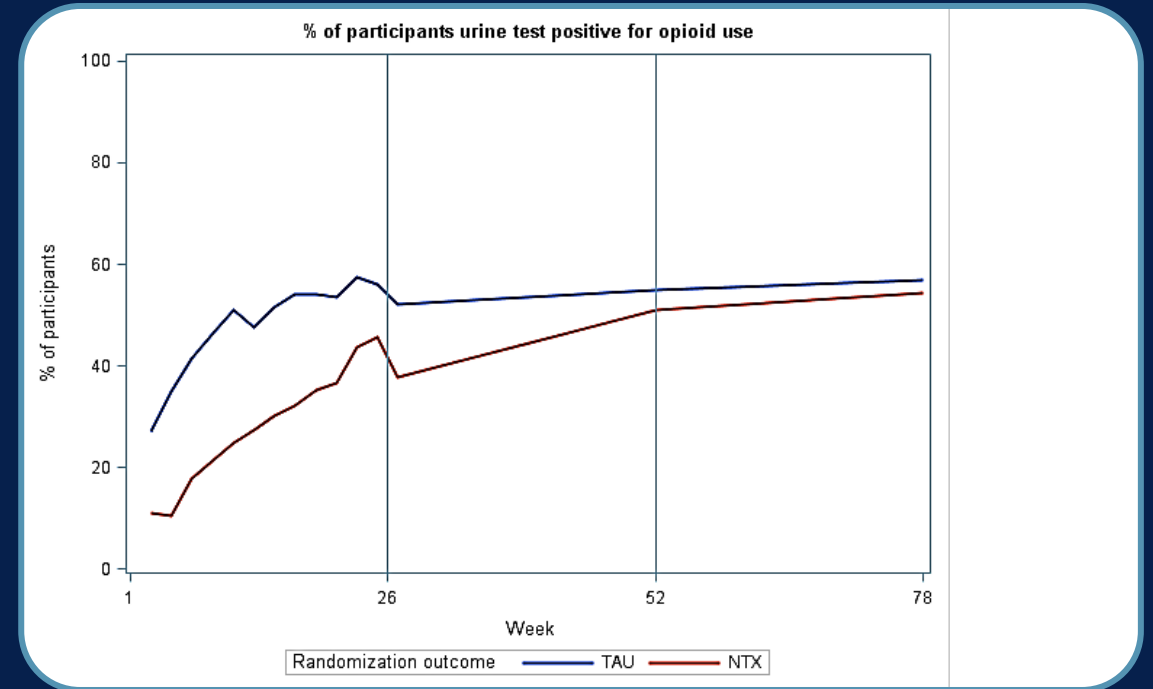
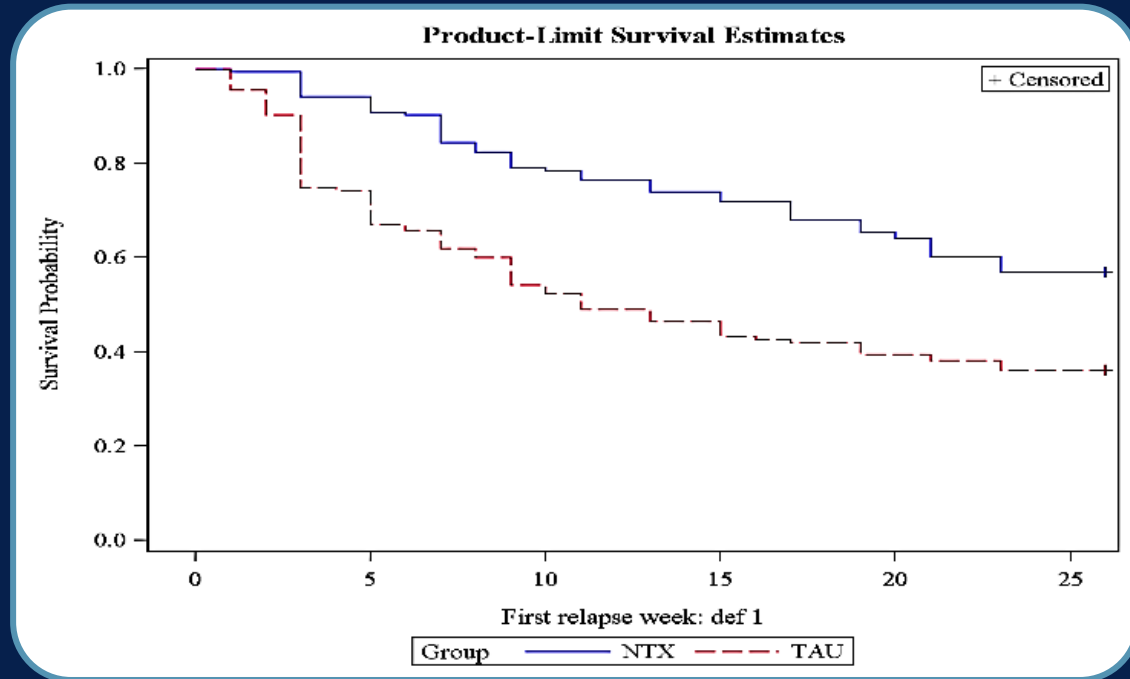


Less Heroin Relapse Among Parolees and Probationers: XR-NTX vs. Treatment as Usual, N=308, 5 US Sites



XR-NTX vs. TAU in CJS-Involved Outpatients

Long-Term Urine Positive rates at 12- and 18-Months catch up...but OD rates do not



24-week treatment trial, 75% XR-NTX doses given

- No participants known to continue XR-NTX after 24-weeks
- 12- and 18-month urine positive rates similar to TAU

XR-NTX vs. TAU in CJS-Involved Outpatients

Long-Term Urine Positive Rates at 12- and 18-Months Catch up, but OD Rates do not

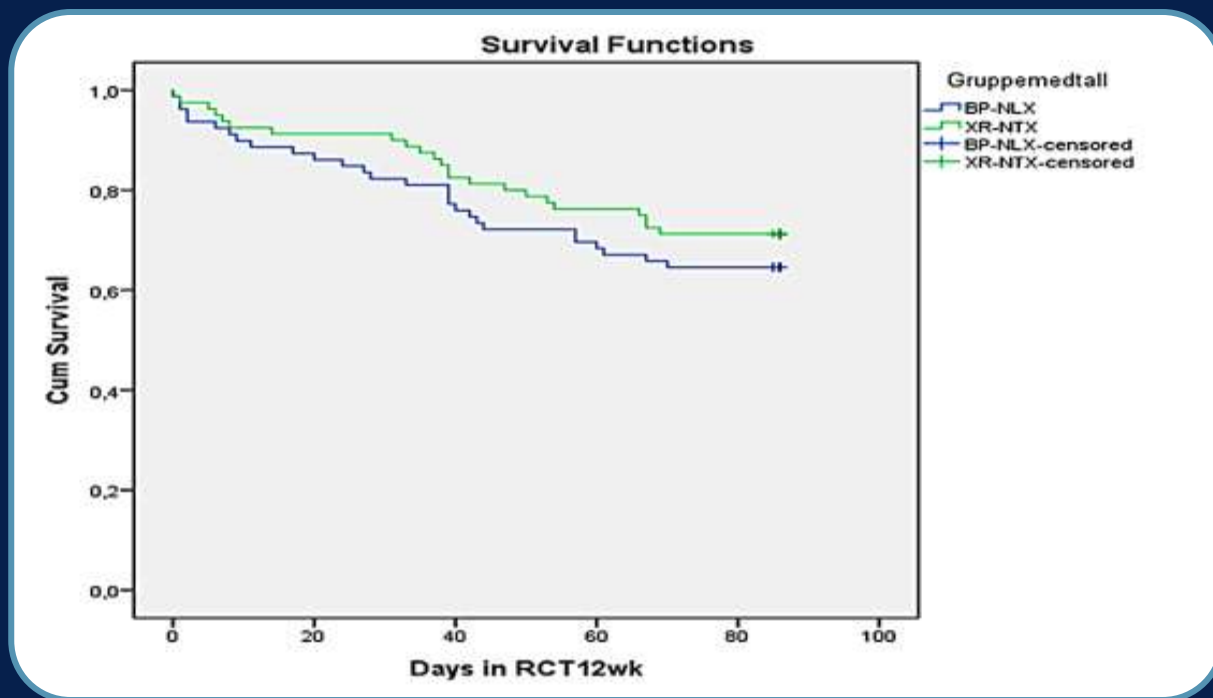
◆ Despite 'catch up' relapse post-XR-NTX, OD events favored XR-NTX at 18-months

◆ No signal of post-XR-NTX OD risk

Urines, 12 & 18 mos	XR-NTX	TAU	p
% opioid negative urine, 12 months	49%	45%	ns
% opioid negative urine, 18 months	46%	43%	ns
SAEs, 1-18 mos			
Overdose, any	0	7	0.02
Overdose, fatal	0	3	0.25
All-case mortality	2	5	0.45

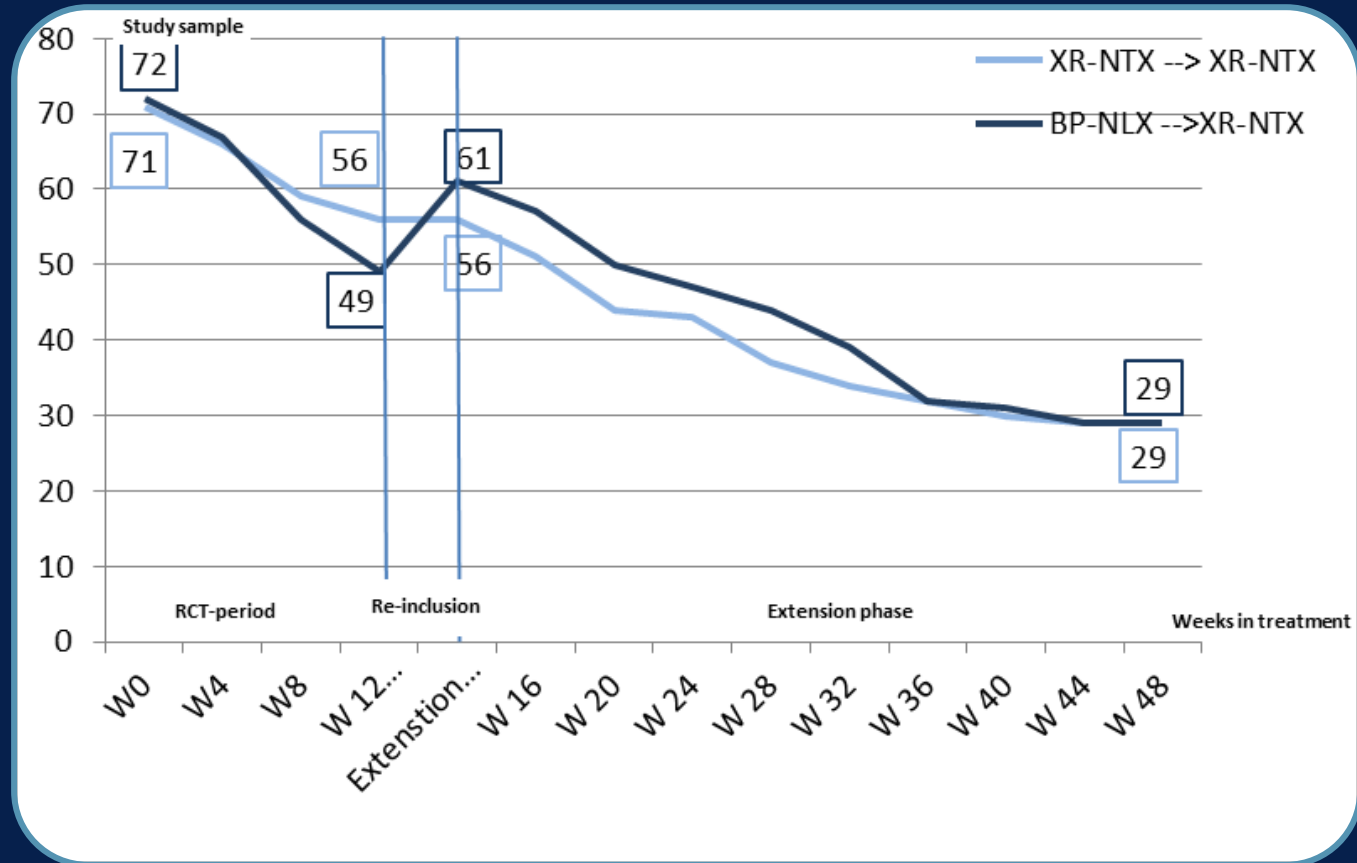
TanumL 2017 JAMA Psyche: XR-NTX vs. BUP-NX in Norway

- ◆ Primary Outcome: Retention in Treatment
- ◆ Non-inferior retention in treatment
- ◆ 89% of participants inducted onto both study medications
- ◆ BUP-NX was dispensed daily at OTP
- ◆ Higher satisfaction, lower rates of opioid use if XR-NTX
- ◆ 0 deaths total; 0 ODs observed in either arm



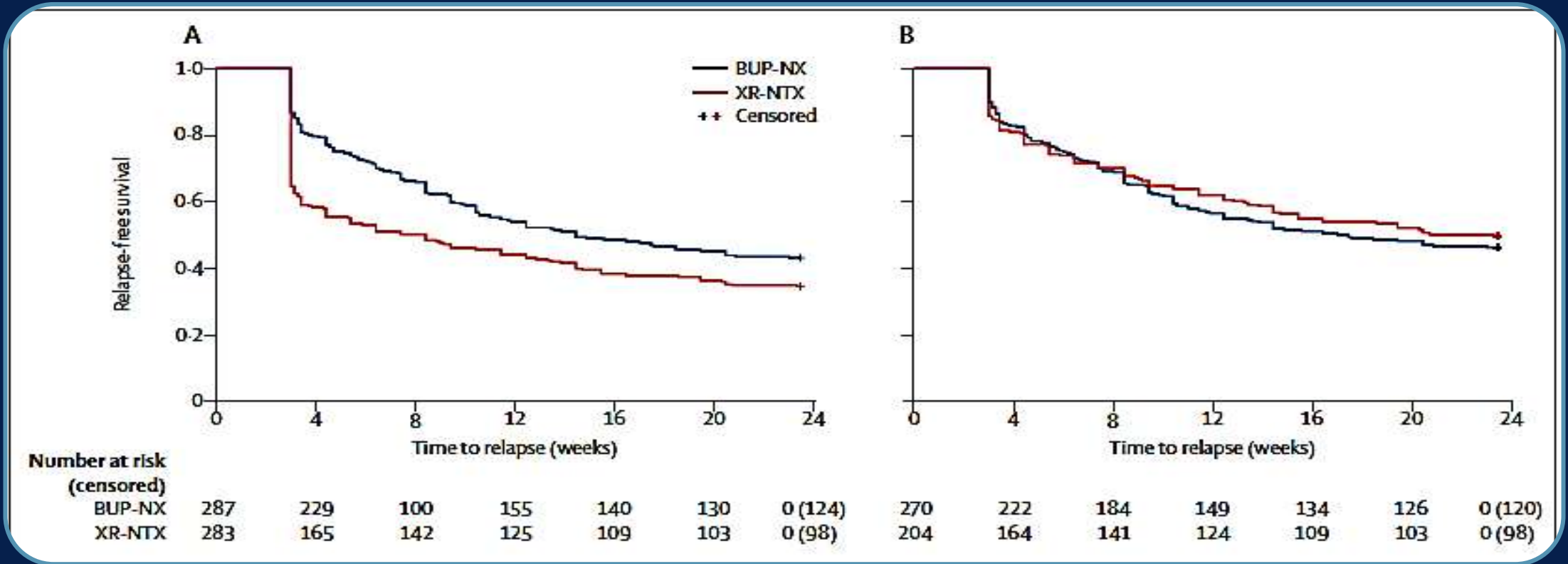
SolliKK 2018 Addiction: 9-Month Extension Study, Norway

- ◆ 117 of 159 enrolled
- ◆ 36% retention on XR-NTX at 48 weeks among 80 participants randomized to XR-NTX
- ◆ No participants chose to continue on BUP-NX (!)
- ◆ High satisfaction and minimal heroin use during XR-NTX
- ◆ 1 death, not an OD



XR-NTX vs. BUP-NX Opioid Treatment

LeeJD 2017 Lancet: X:BOT Study



◆ 570 US adults admitted to 8 detox units

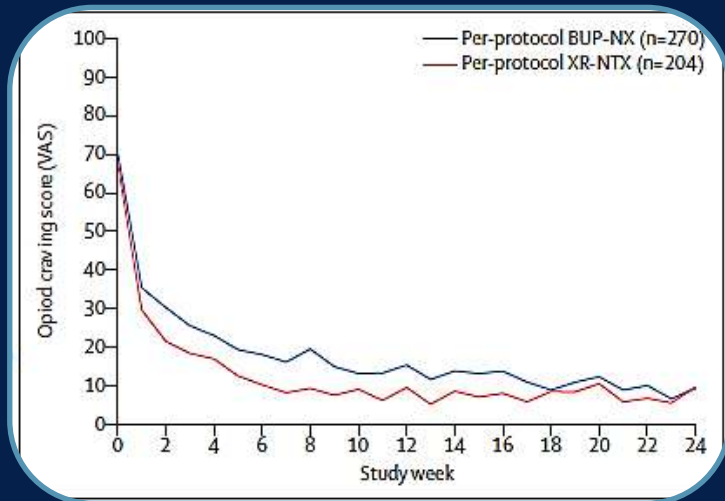
◆ Table 1:
 ◆ male, white, unemployed,
 ◆ IV heroin

◆ Lower induction rates for XR-NTX (72% vs. 94%)

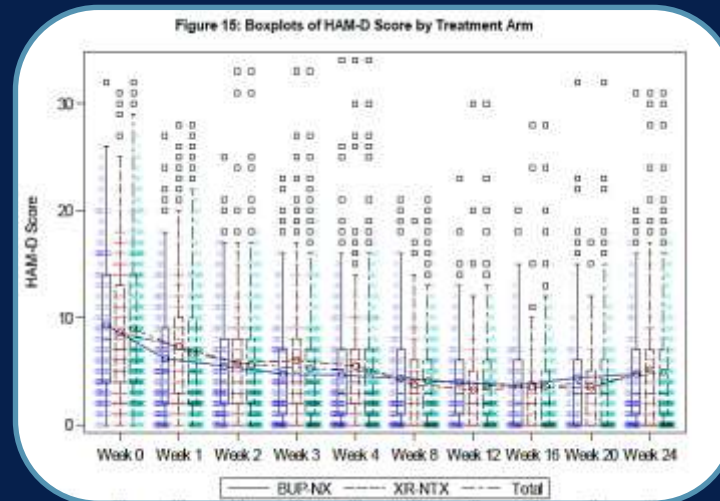
◆ Higher early relapse rates if induction failed

◆ Similar opioid relapse rates if induction was successful

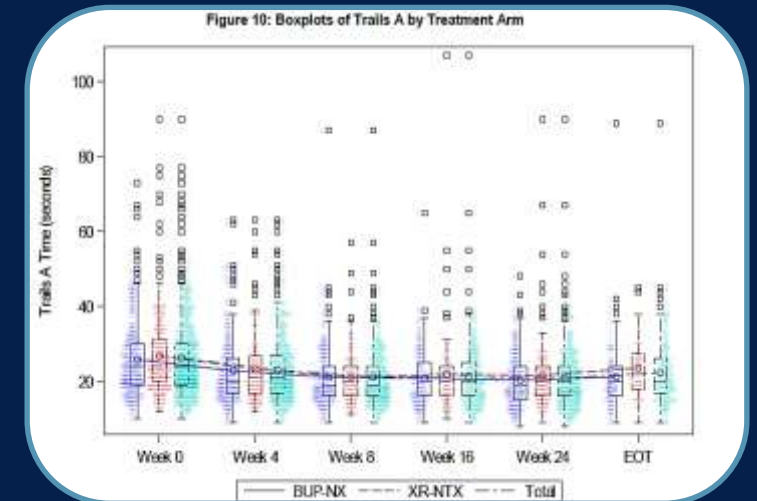
X:BOT Secondary Outcomes: Cravings, Depressive Symptoms, Cognition: all similar



- ◆ Opioid craving:
 - ◆ similar



- ◆ Depressive symptoms:
 - ◆ similar



- ◆ Cognitive function:
 - ◆ similar

X:BOT Secondary Outcomes:

Overdose rates: similar overall, favor staying on Rx.

OVERDOSE EVENTS	XR-NTX	BUP-NX	P Value
Overdose Events			
Participants with ≥1 Overdose Event	15	8	p=0.15
Number of Overdose Events (overall)	18	10	
Number of Overdose Events (per-protocol)	10	9	
Fatal Overdose Events			
Number of Fatal Overdose Events (overall)	2	3	p>0.99
Number of Fatal Overdose Events (per-protocol)	2	3	

OD Rates	# ODs	Weeks-at-Risk	Ods / Weeks-at-Risk
Total Sample	28	18,779	0.0015
Not Inducted	9	2,730	0.0033
On Study XR-NTX	1 or 2	3,471	0.0003 - 0.0006
On Study BUP-NX	0	5,532	0.0000
On Study Medication	1 or 2	9,003	0.0001 - 0.0002
Not On Study Medication	26 or 27	9,776	0.0027

Press - 2010-2017: XR-NTX is Bad/Evil

**The
New York
Times**

*Seizing on Opioid Crisis, a Drug
Maker Lobbies Hard for Its Product*



- ◆ XR-NTX is not effective and too few studies
- ◆ XR-NTX is inferior to BUP or methadone
- ◆ XR-NTX causes overdoses
- ◆ XR-NTX causes depression and anhedonia
- ◆ Alkermes' marketing to Gov't, States and CJS is unethical

Evidence - 2010-2018:

XR-NTX is actually quite effective and safe

JAMA Network

JAMA Psychiatry Journals Enter Search Term

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Original Investigation
December 2017

Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence

A Randomized Clinical Noninferiority Trial

Lars Tanum, MD, DMSc^{1,2}; Kristin Klemmetsby Solli, MSc¹; Zill-e-Huma Latif, MD²; [et al](#)

[Author Affiliations](#)

JAMA Psychiatry. 2017;74(12):1197-1205. doi:10.1001/jamapsychiatry.2017.3206

- ◆ XR-NTX is efficacious vs. placebo (2010)
- ◆ XR-NTX is effective vs. TAU post-jail (2015)
- ◆ XR-NTX is effective vs. TAU in community CJS (2016)
- ◆ XR-NTX is not associated with depression/anhedonia (2010, 2016, 2017)
- ◆ XR-NTX is similarly effective as BUP-NX (Norway 2017)
- ◆ XR-NTX is less effective vs. BUP-NX due to more difficult induction (US 2017)
- ◆ XR-NTX is safe and not associated with excessive ODs (2010, 2016, 2017)
- ◆ XR-NTX is not associated with increased depression or cravings (2010, 2016, 2017)
- ◆ XR-NTX induction is a big limitation
- ◆ Retention is OK, similar to BUP-NX, could be improved

Practical Issues, XR-NTX for OUD

- **Awareness**
 - Many patients and providers are unfamiliar with XR-NTX
- **Induction**
 - 2nd Line Treatment: patient has to detox beforehand or already be detoxed off opioids
- **Sustained Engagement**
 - Keeping persons interested and in touch for monthly injection visits

XR-NTX for OUD, Practical Issues: Induction Procedures

- **Induction onto XR-NTX**
 - Patient should be opioid-free 3+ days and willing to give urine and undergo a naloxone challenge
 - Test urine using point-of-care dip cards for most common opioids, including buprenorphine
 - Naloxone 0.4-1.2mg IM/SC/IV or oral naltrexone 12.5-50mg oral tablet
- **Detox prior to XR-NTX Induction**
 - Likely most successful if completed in a controlled environment (hospital, treatment center, CJS)
 - Non-opioid detox using clonidine and comfort meds has clear advantages
 - Brief buprenorphine taper over 1-3 days is standard, plus comfort meds
 - Drop-out and incomplete detox is more common with outpatients vs. inpatients
 - XR-Induction in long-term residential settings is ideal (28-day rehab, extended hospital stay, jail/prison)

XR-NTX for OUD, Practical Issues: Medication Maintenance

- **First month**
 - Side effects more likely : prolonged withdrawal, headache, nausea
 - 'Testing' the naltrexone mu opioid receptor antagonist blockade is common
 - The most positive experience is one of relief and confidence and abstinence from all opioids
 - **Cravings generally decrease substantially from pre-treatment**
 - All patients will experience an effective naltrexone blockade



QUESTIONS?

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