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Research Spotlight, Joshua D Lee MD MSc:

Promoting simple and effective addiction treatments

Professor

Department of Population Health | Section on Tobacco, Alcohol and Drug Use (Co-Director)

Medicine | General Internal Medicine and Clinical Innovation

Addiction Medicine Fellowship (Director)

@DrJoshuaDLee | med.nyu.edu/research/lee-lab/

Disclosures, LeeJD

- Grants:
  - NIDA (U01x3, UM1, R01x2, U10 (CTN GNYN), R42)
  - NIAAA (R01-NCE, P01)
  - HRSA (T25)
  - Laura and John Arnold Foundation (x2)
  - Indivior (ISS)
- Study Drug: Alkermes (Vivitrol), Indivior (Suboxone, Sublocade)
- Consulting: Epiodyne (UG3), Nirsum (UG3), Drug Delivery Inc (UG3), U.KY (R01), OHSU (CDC), NYS OPMC

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Lee Lab – An Overview – Grants and Studies

1. OUD and Alcohol treatment in primary care=addiction medicine!
2. Same applies to CJS populations = more treatment during and after incarceration
3. Build knowledge base around newer OUD and AUD treatments:

   -Is XR-Naltrexone any good or is it really killing people?

   -Buprenorphine…does it clearly drive better outcomes in CJS settings?

   -XR formulations vs. generic daily oral or SL medications – sounds great, more expensive, but are they overall any better?

THEMES: criminal justice and drug treatment improvements that hopefully reduce overdose deaths=NIDA funding

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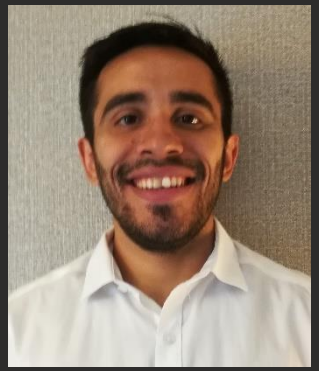
Lee Lab – Our Team

Joshua D. Lee,
Principal Investigator



Kumar Vasudevan,
Addiction Med. Fellow

Wanda Bonilla,
Research Coordinator

Anna Cheng,
Research Coordinator

Nadina Santana-Correa,
Research Coordinator

Ryan McDonald,
Program Manager

Mia Malone,
Project Manager

James Swift,
Participant Tracker

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Long-Acting Medications for Opioid Use Disorders: Most of the newest MOUD formulations

Naltrexone

- Daily tablet 50 mg

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

Buprenorphine

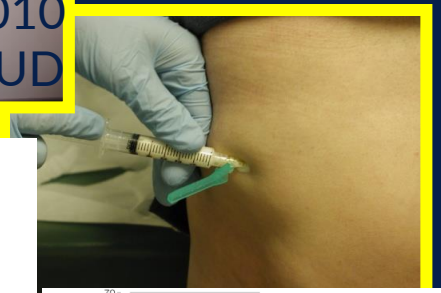
For OUD

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

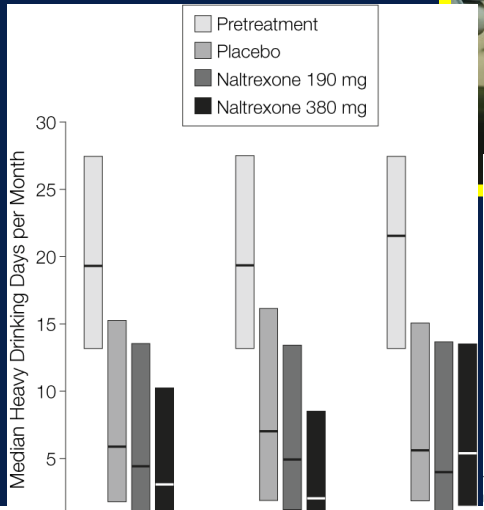
For Pain

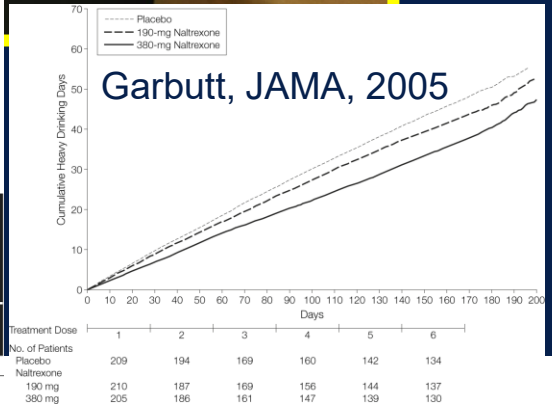
- Injectable BUP
- Buccal and Transdermal BUP

Extended-Release Naltrexone (Vivitrol) for AUD (2006) or OUD (2010)



- Monthly intramuscular injection
- Given by nurse, PA, MD, pharmacist
- Non-narcotic, not a controlled substance
- Must detox off opioids first if OUD
- No detox requirement for AUD
- For AUD, oral naltrexone tablets are cheaper and possibly as effective (COMBINE Trial, 2006)

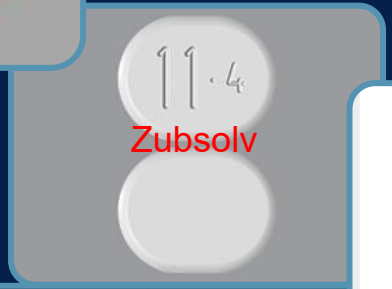


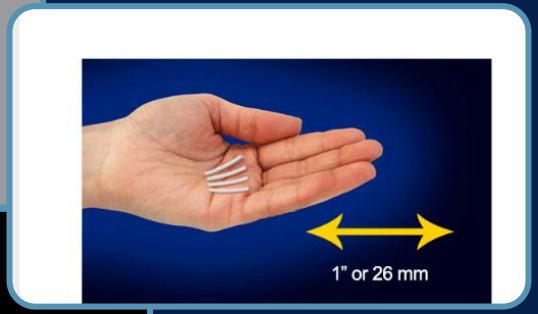


Buprenorphine Products for OUD, 2002-2020

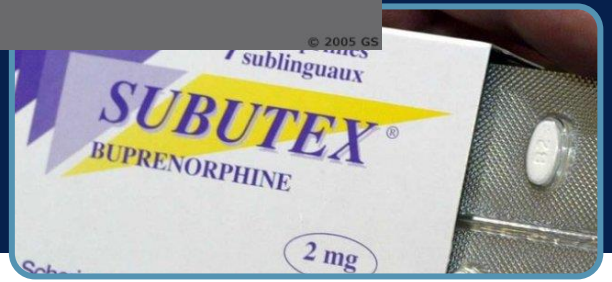
2010

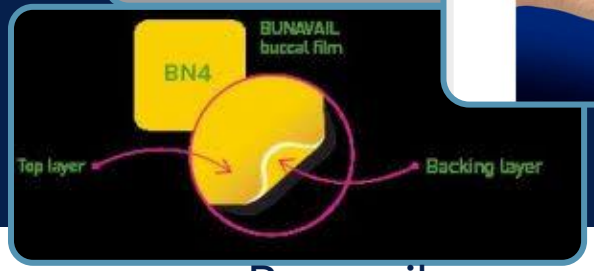
Sublocade 2019





Probuphine Implant 2016





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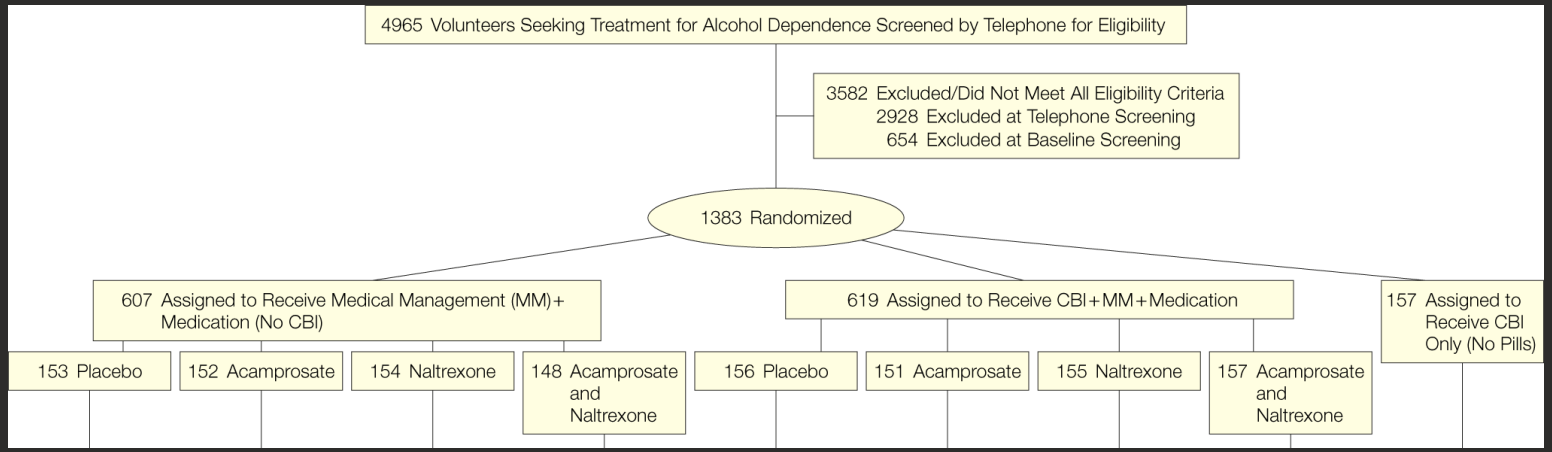
The NIAAA COMBINE Trial (2006) and Naltrexone Med Management in Primary Care

CBI vs. Medical Management PLUS naltrexone vs. acamprostae vs. N+A vs. Placebo

MM is non-specialized: physician, PA, Nurse, pharmacist can all deliver, focuses on adherence, less drinking, getting counseling or 12-step of any kind

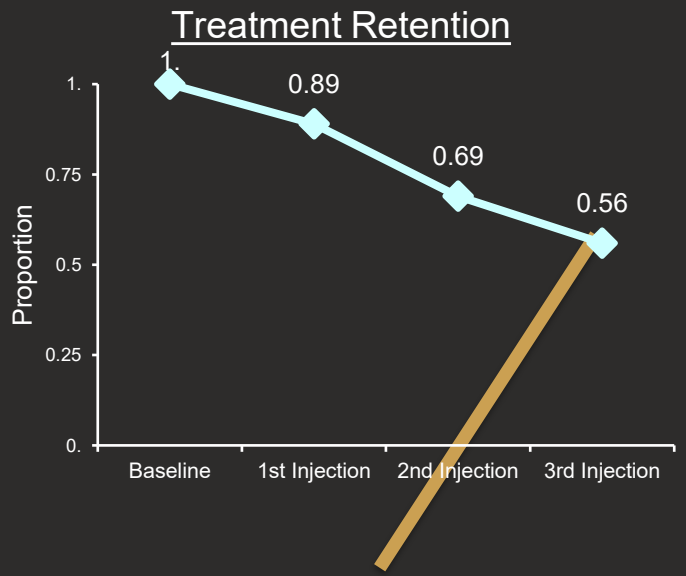
N=1383 RCT, 24-weeks of therapy, fu at 0-24 weeks



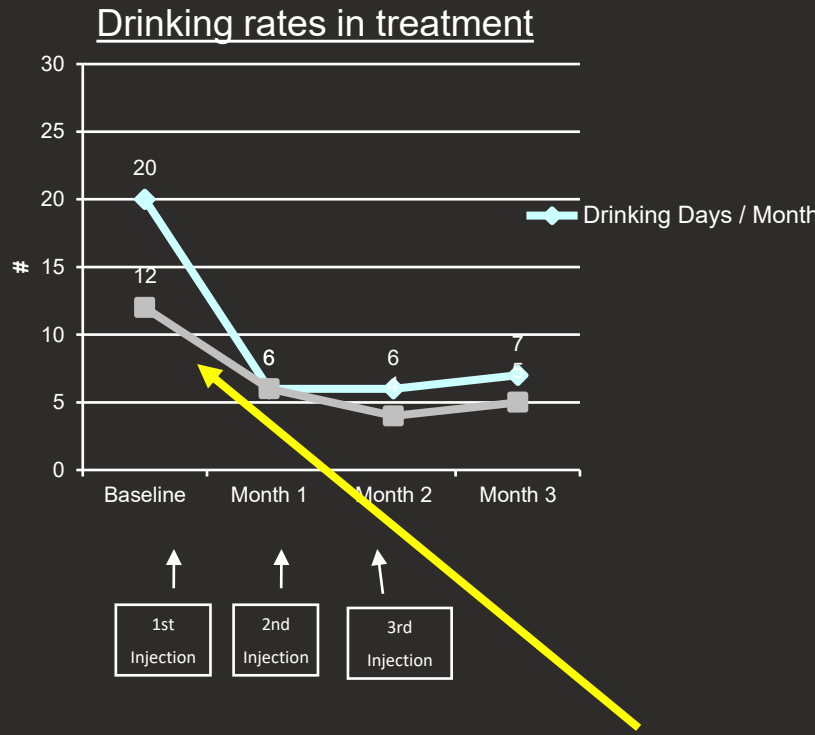
Results: Naltrexone/MM > CBI + placebo/MM > Naltrexone/MM+ CBI > Placebo/MM

COMBINE strongly supported naltrexone in primary care settings

XR-NTX + MM Alcohol Treatment In Primary Care at Bellevue: Acceptable and Feasible, w good outcomes associated w retention



56% of patient stayed in treatment 90 days



Daily drinking reductions were robust and seen within the first month

LeeJD, GourevitchMN, et al, JSAT, 2010, 2013

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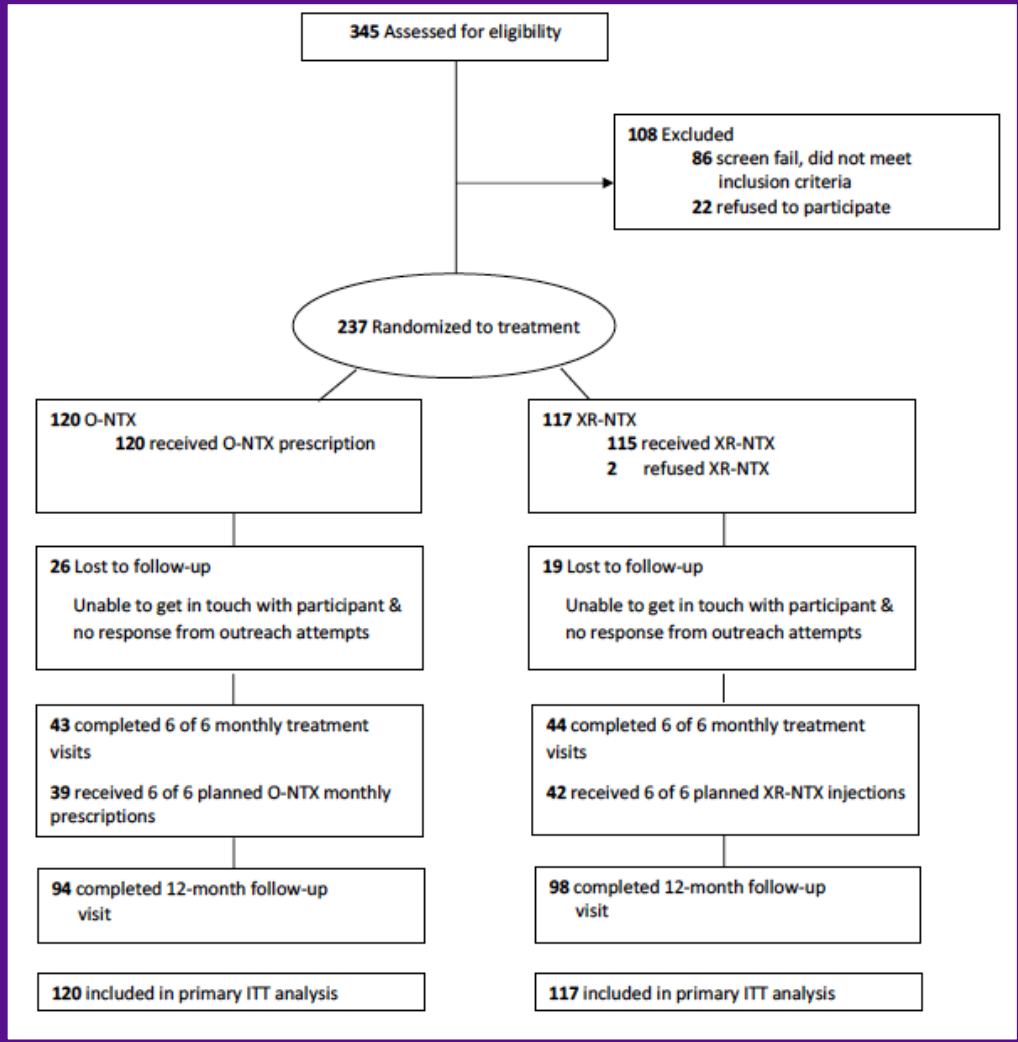
Extended Release vs. Oral Naltrexone for Alcohol Dependence Treatment in Primary Care (NIAAA R01)

Mia Malone[1], Ryan McDonald, MA[1], Alex Vittitow[1], Babak Tofighi, MD[1], Anne Garment, MD[1], Daniel Schatz, MD[1], Keith Goldfeld, DrPH[1], Eugene Laska, PhD[2], John Rotrosen, MD[2], Joshua Lee, MD, MSc[1]

- Randomized, open-label, comparative effectiveness trial of N=237 adults evaluating 24 weeks of XR-NTX vs. O-NTX for AUD in primary care at Bellevue, NYC
- Adults (>18yo) with AUD randomized to XR-NTX (380mg/month) vs. O-NTX (50-100mg/day) MM
- The primary outcome is a continuous Good Clinical Outcome (GCO) across weeks 5-24: abstinence or moderate drinking and 0-2 days of heavy drinking per month.

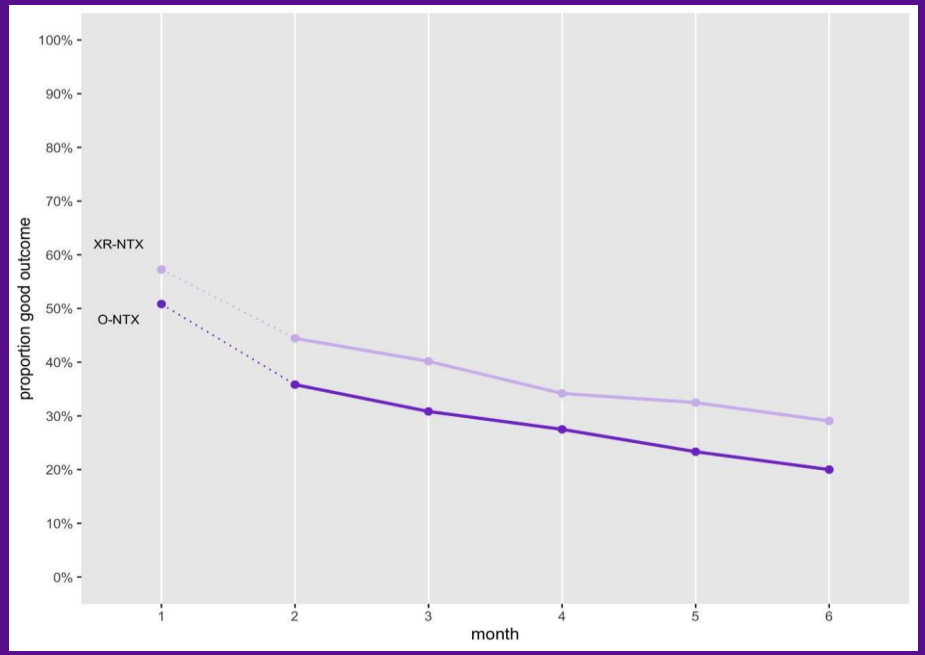


Extended Release vs. Oral Naltrexone for Alcohol Dependence Treatment in Primary Care

BASELINES	XR-NTX (n=117) # (%)	O-NTX (n=120) # (%)
Male	82 (70%)	84 (70%)
Age, mean (SD)	48 (10.6)	49 (10.7)
Hispanic	24 (21%)	27 (23%)
Non-Hispanic Black	67 (57%)	62 (52%)
Non-Hispanic White	30 (26%)	44 (37%)
High School Graduate or Higher	100 (85%)	99 (83%)
Employed (Full or Part-Time)	64 (55%)	72 (60%)
Alcohol Use, mean (SD) AUDIT* scores	24.6 (8.3)	23.6 (7.8)
Current Drinking, average drinks per day in the last 28 days** (SD)	10.3 (12.5)	9.1 (10.7)

DRINKING RATES, 1-24 WKS	XR-NTX (n=74) # (SD)	O-NTX (n=82) # (SD)
Days Abstinent	12 (8.4)	12 (9.6)
% Days Abstinent	63% (33.4)	61% (37.2)
Days Heavy Drinking	4 (5.9)	4 (6.7)
% Days Heavy Drinking	21% (29.3)	22% (32.2)
Average drinks per day in the last 28 days	3 (6.1)	2 (4.0)

Primary Outcome	XR-NTX (n=117) # (%)	O-NTX (n=120) # (%)
Good Clinical Outcome	29%	23%



Bottom Line: ***few if any differences***

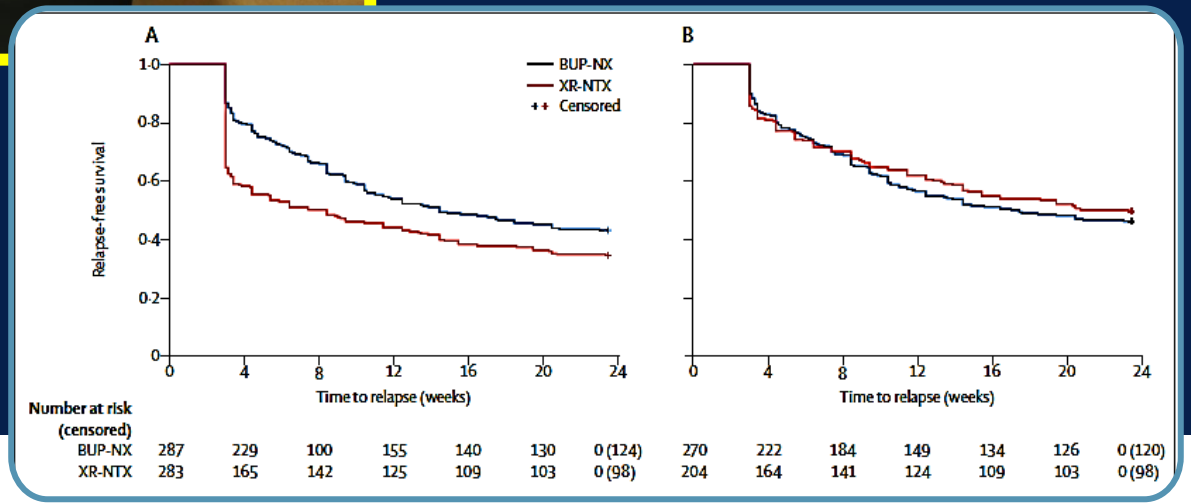
Extended Release vs. Oral Naltrexone for Alcohol Dependence Treatment in Primary Care (NIAAA R01, 2013-2019)

Mia Malone[1], Ryan McDonald, MA[1], Alex Vittitow[1], Babak Tofighi, MD[1], Anne Garment, MD[1], Daniel Schatz, MD[1], Keith Goldfeld, DrPH[1], Eugene Laska, PhD[2], John Rotrosen, MD[2], Joshua Lee, MD, MSc[1]

- Insufficient evidence of major differences between monthly XR-Naltrexone and daily oral NTX in terms of self-reported retention and drinking rates over time
- Rates of improved drinking from baseline were broadly observed in both arms: 10 drinks/day on average down to 2.5 drinks/day during treatment
- Also no differences in LFTs, SBP, BMI, or SAEs by arm
- These are two safe, effective and easy to use naltrexone formulations that are appropriate for use in primary care among underserved patients with moderate-to-severe AUD.
- Limitations: AUD trials largely rely on self-report, some response bias is expected, no TAU or placebo control arm and placebo effect in AUD trials is substantial, majority black patient sample which some have theorized is less responsive to NTX based on genetics (no evidence of that in this trial)

Extended-Release Naltrexone (Vivitrol) for ~~AUD (2006) or~~ OUD (2010)

- Monthly intramuscular injection
- Given by nurse, PA, MD, pharmacist
- Non-narcotic, not a controlled substance
- Must detox off opioids first if OUD
- Recent NIDA CTN X:BOT trial show it is comparable to BUP for OUD but harder to start in hospital or outpatient



XR-Naltrexone (XR-NTX) pre/post jail and prison: the 'XOR' study

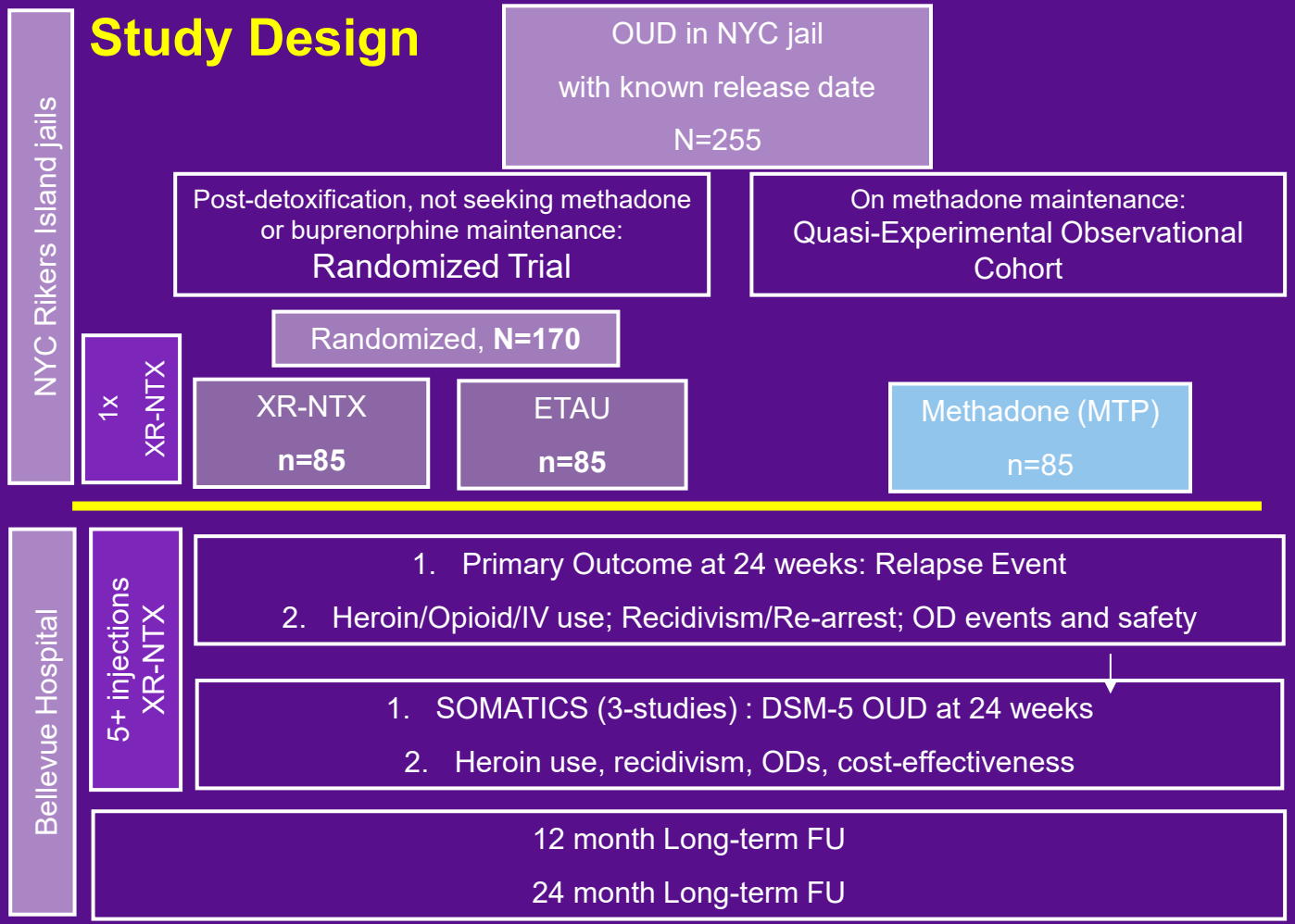
- The use of XR-NTX seems to have expanded in US jails…per media and public announcements
  - Alkermes' XR-NTX+CJS marketing widely covered in press
  - 'Empty space w high needs' … lots of OUD in CJS but historically no MOUD
  - Concerns re: controlled substances and diversion

2 peer-reviewed studies have evaluated this model to date:

- NYU/NYC Jail pilot RCT
- (*LeeJD, Addiction 2015*):
  - XR-NTX more effective short-term vs. TAU
  - 50% retention at week 4 (2nd shot)

- Massachusetts jail, single-arm observational study
- (*LincolnT, JSAT, 2018*):
  - 55% retention at week 4, declining to 21% at week 24

Study Design



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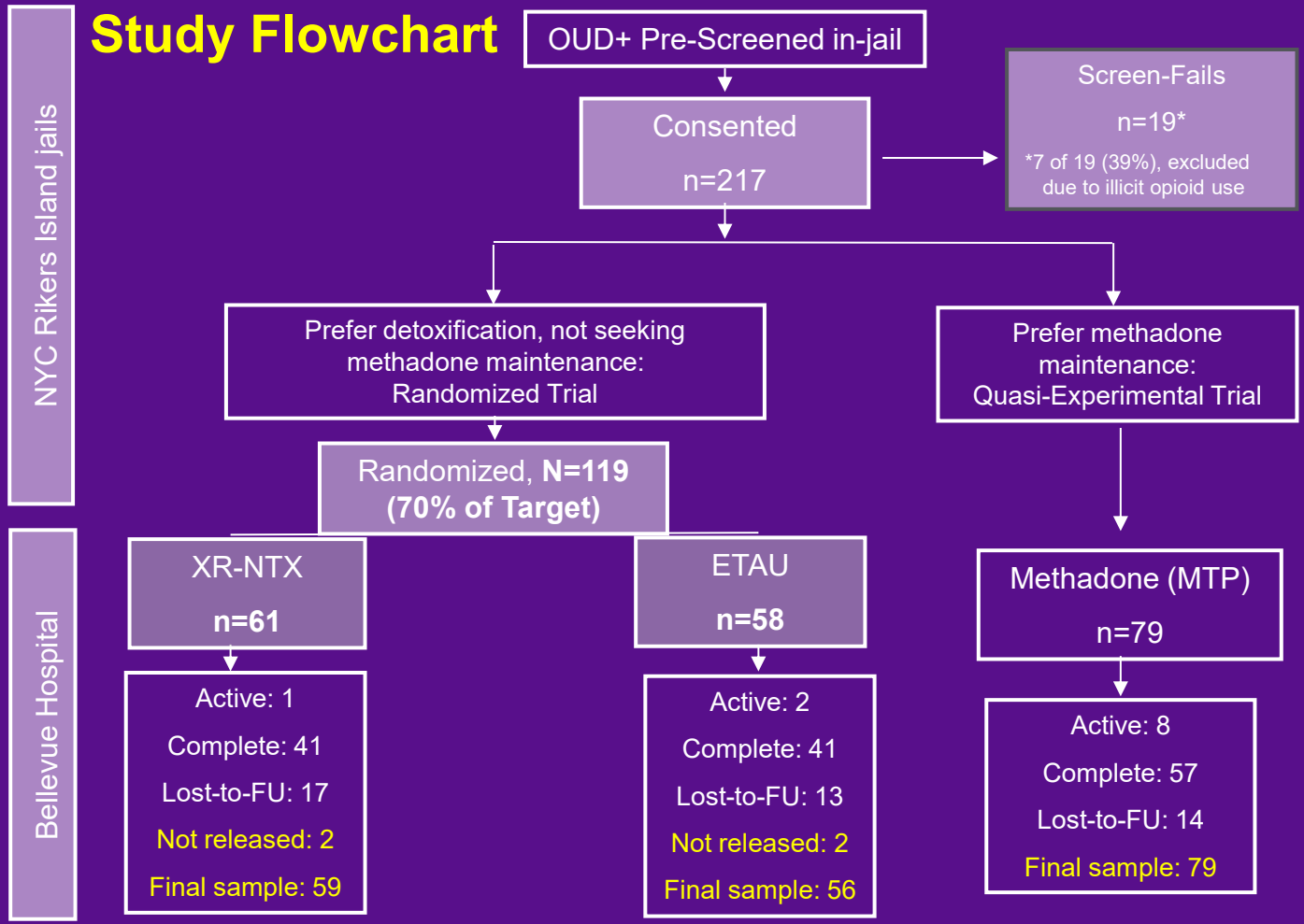
Study Flowchart



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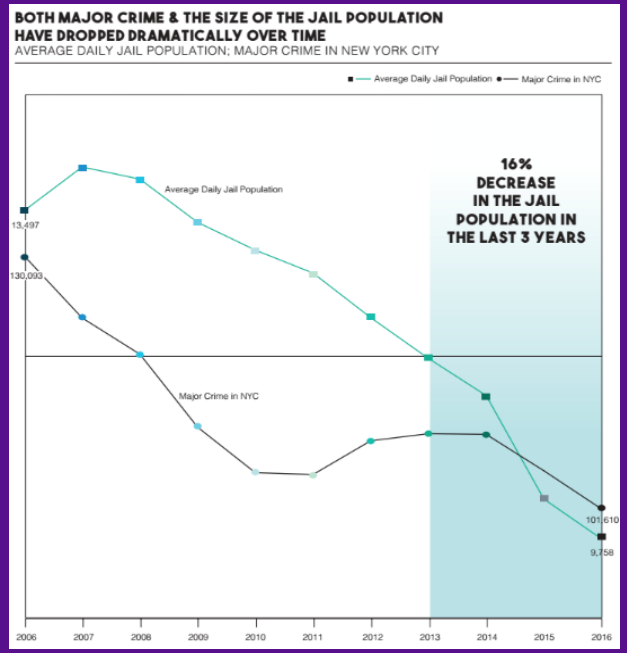
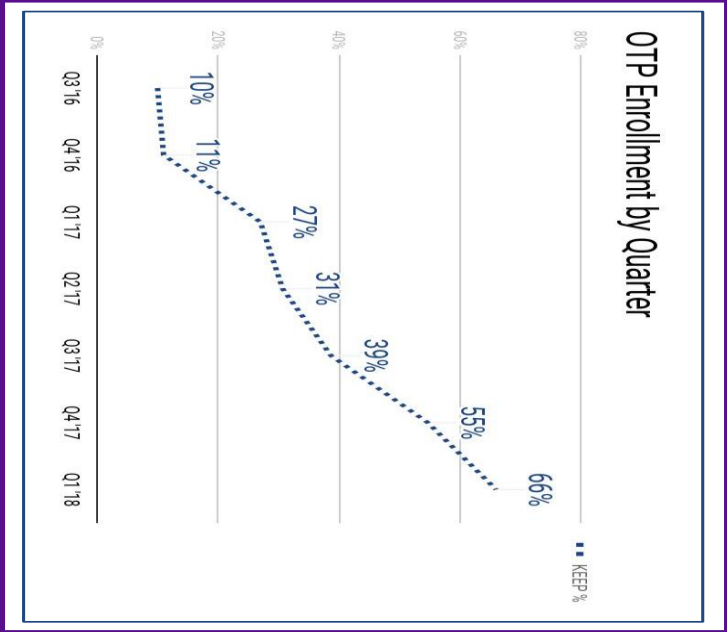
NYC JAIL & OUD TRENDS: 2010-2019



1. Declining jail population



2. Increases in # and % of OUD on opioid agonists

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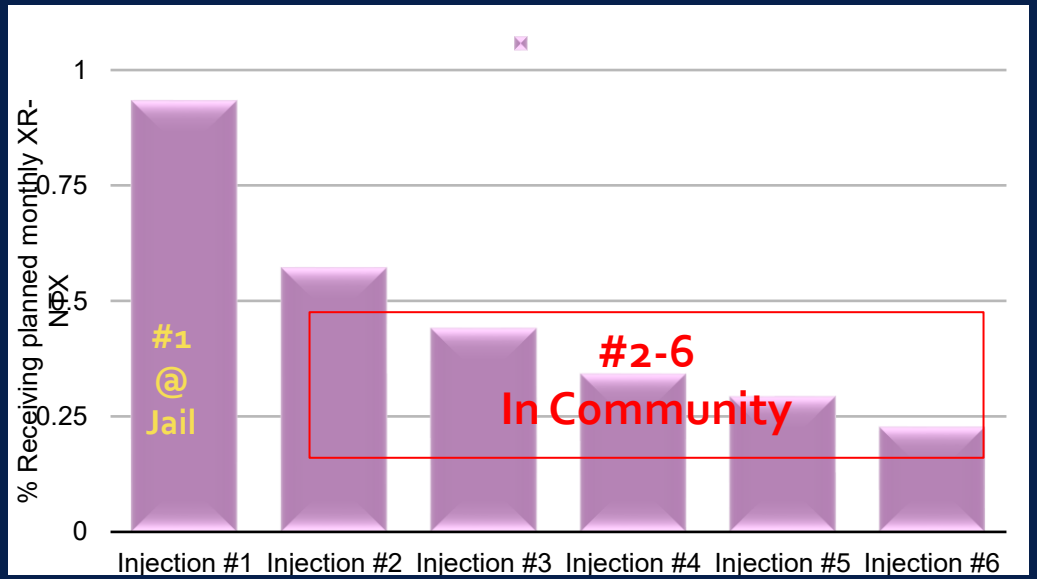
Table 1: X:OR Baseline Demographics

Characteristic	XR-NTX (59)	ETAU (56)	MTP (79)
Male- no. (%)	52 (88%)	50 (89%)	60 (76%)
Age- mean (SD)	42.9 (10.9)	43.7 (9.8)	42.5 (9.7)
Hispanic- no. (%)	25 (42%)	22 (39%)	35 (44%)
Black- no. (%)	29 (49%)	30 (54%)	34 (43%)
Full or parttime employment- no. (%)	29 (49%)	24 (43%)	**20 (25%)**
Homelessness- no. (%)	24 (41%)	21 (38%)	**43 (54%)**
Days heroin use 30 days PTI*- mean (SD)	25.8 (7.6)	25.3 (8.3)	28.1 (6.3)
IV injection drug use 30 days PTI*- no. (%)	17 (29%)	17 (30%)	**42 (53%)**
Heroin use bags/day 30 days PTI*- mean (SD)	10.0 (7.2)	10.4 (11.8)	13.2 (9.4)
Cocaine use (any) 30 days PTI*- no. (%)	27 (46%)	28 (50%)	**51 (65%)**
HIV-Positive- no. (%)	5 (9%)	4 (7%)	**9 (11%)**
Hepatitis C- no. (%)	12 (20%)	12 (21%)	**31 (39%)**

NYC Jail RCT: MOUD retention 0 – 24 weeks post-release

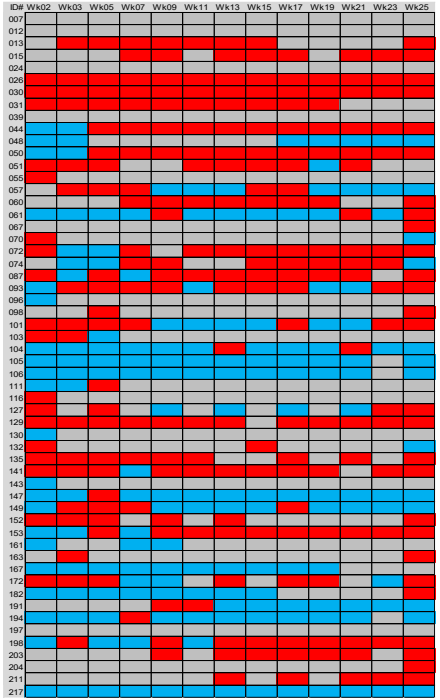
MOUD Treatment during 24-Week treatment phase	XR-NTX (n=59)	ETAU (n=56)	MTP (n=79)
Any MOUD Treatment	*59%	29%	42%
Outpatient Buprenorphine	0%	18%	1%
Methadone Maintenance	0%	9%	41%
Extended-Release Naltrexone	*59%	2%	0%

Injection (#) Received	XR-N Injection Rate(%)
≥ 1 XR-N Injection	93%
≥ 2 XR-N Injections	59%
≥ 3 XR-N Injections	46%
≥ 4 XR-N Injections	36%
≥ 5 XR-N Injections	31%
All 6 XR-N Injections	24%

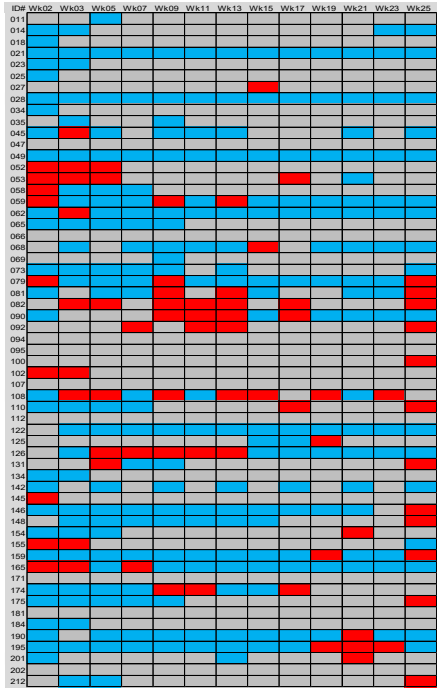


Urine Toxicology Plots by Study Arm

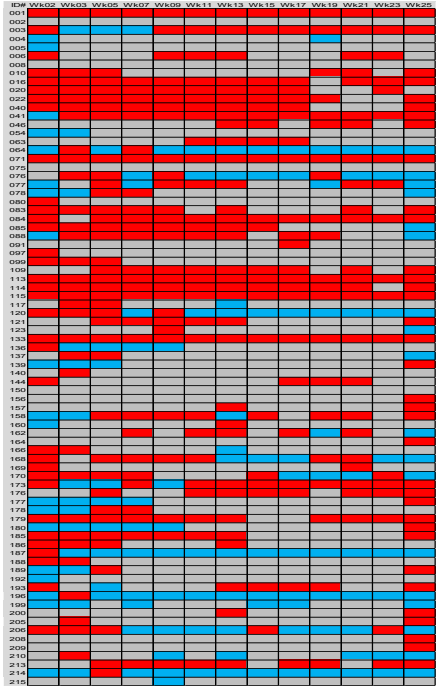
ETAU (n=56) UTOX Results



XR-NTX (n=59) UTOX Results



MTP (n=79) UTOX Results



	NEGATIVE
	OPI+POSITIVE
	MISSED

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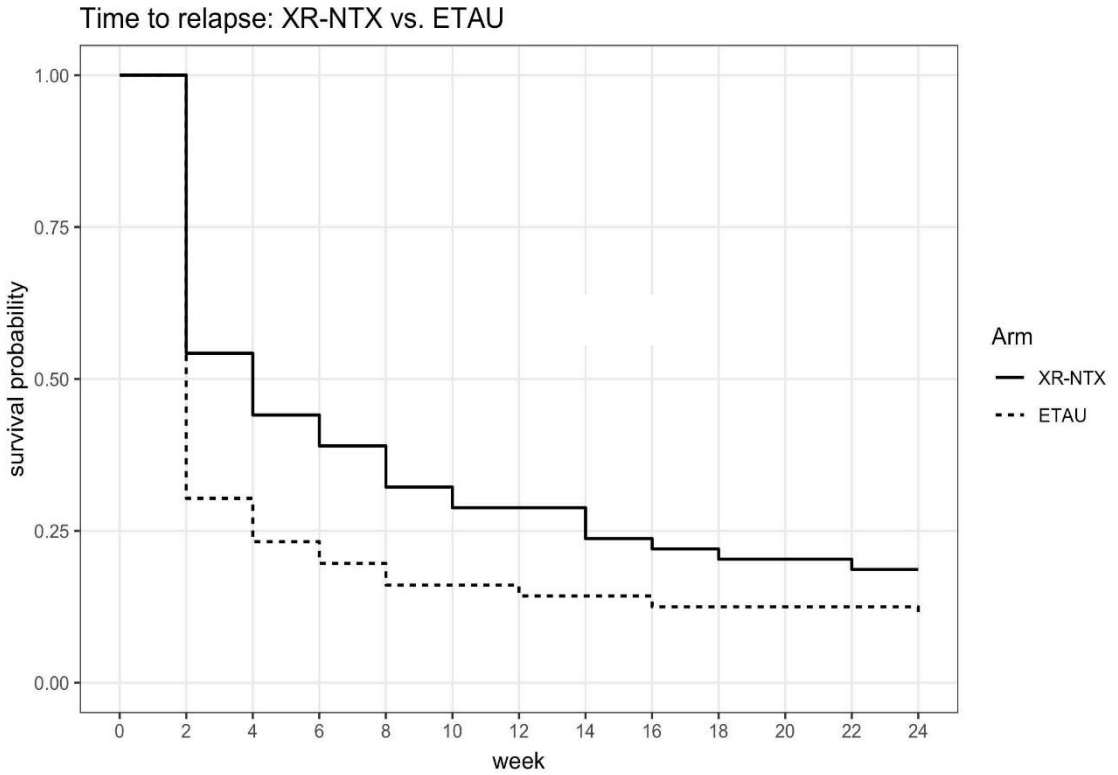
Opioid Relapse Outcome, 0-24 weeks



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XOR: Serious Adverse Events (SAEs) 0-6 months & Jail Recidivism

SAEs = 27	XR-NTX (59)	ETAU (56)	MTP (79)
Death (non-fatal opioid OD)	0	1	0
Fatal Opioid Overdose	1	1	0
Non-fatal Opioid Overdose	1	5	2
Prolonged Hospitalization	0	0	3
Important medical event/procedure	6	2	5

Recidivism	XR-NTX (59)	ETAU (56)	MTP (79)
Participants w 1+ Re-arrest, # (%)	8 (14%)	7 (13%)	**28 (35%)**
Total Arrests	9	12	44
Participant's Reincarcerated, # (%)	8 (14%)	7 (13%)	**21 (27%)**
Total Days Reincarcerated	139	168	**744**

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XOR Results and Conclusions: Primary Outcome: Time-to-Relapse, XR-NTX vs. ETA

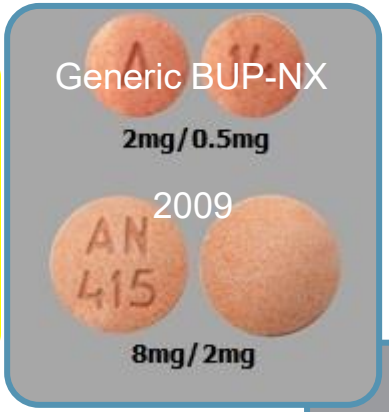
Outcomes	XR-NTX (n=59)	ETAU (n=56)	p-value	HR/OR (95% CI)
Mean time-to-relapse (SD)	**8.6 (8.7)**	**5.9 (7.7)**	**0.02**	**HR 0.77 (0.52 - 1.16)**
Mean time-to-relapse, if relapse occurred - weeks (SD)	5.1 (5.0)	3.3 (3.6)	0.02	HR 1.78 (0.03 - 3.52)
Relapse free- no. (%)	11 (18.6)	7 (12.5)	0.44	OR 1.59 (0.51 - 5.30)
Percentage of opioid-negative urine samples	32%	21%	0.12	na

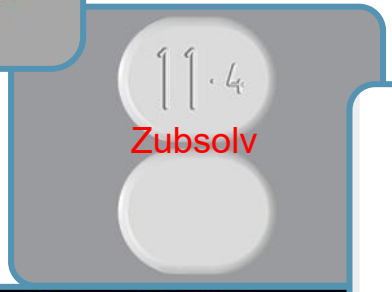
XR-NTX was marginally effective as opioid relapse prevention in terms of time-to-relapse (8.6 vs. 5.9 weeks, p=0.02), but no different in terms of the overall probability of relapse-free-survival (HR 0.77, 0.52-1.16) or % relapse-free at Week 24 (18.6% vs. 12.5%, p=0.44).

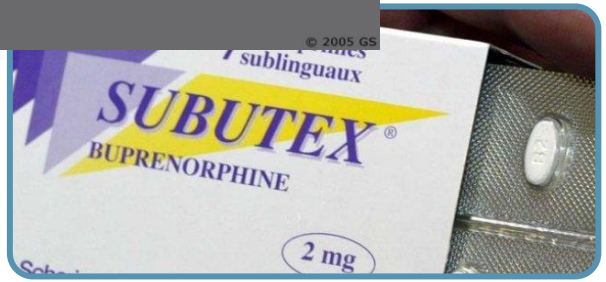
There was insufficient evidence of a large, clinically significant relapse prevention effect, counter to the main a priori hypothesis of XR-NTX's effectiveness.

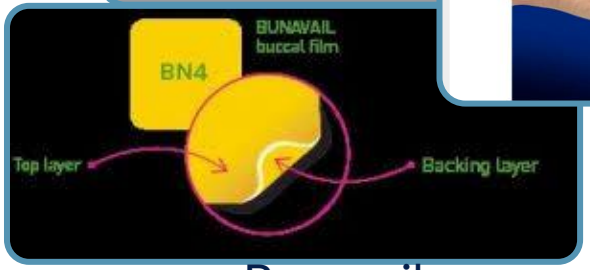
Limitation: lack of power (70% of target randomized sample) and high rates of missing urine data.

Buprenorphine Products for OUD, 2002-2020









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Sublocade (XR-B) at Rikers, Pilot RCT

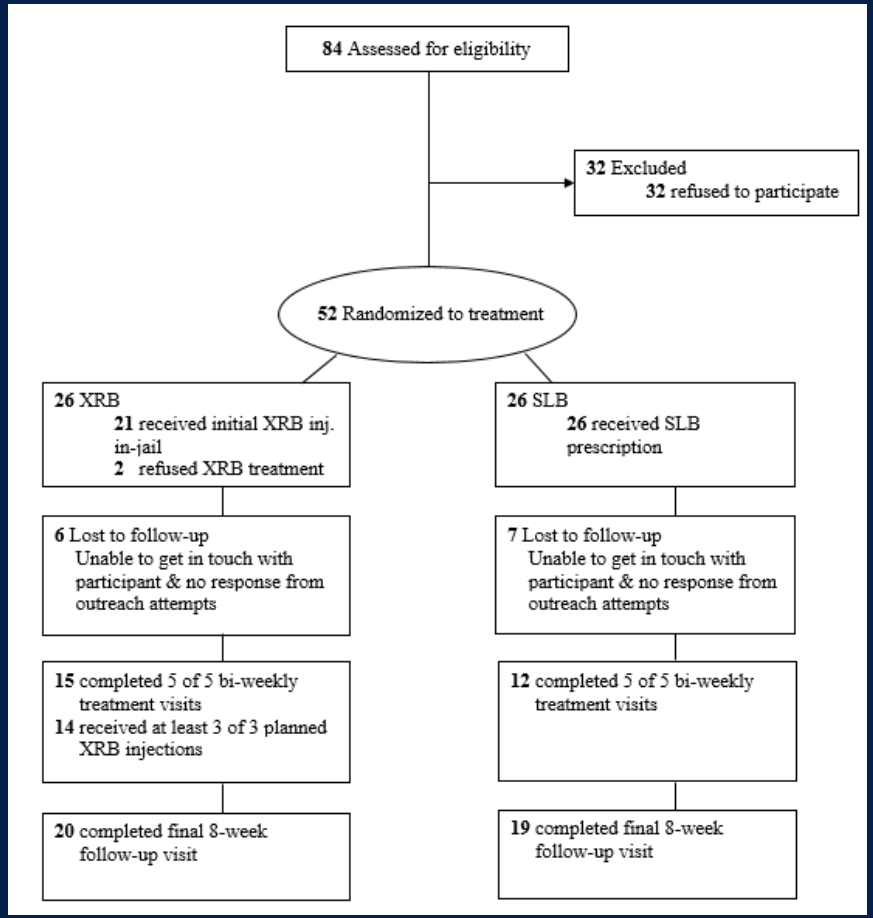
- Randomized, unblinded, pilot proof-of-concept RCT evaluating 8 weeks of XR-B vs. SL-B in N=52 adults with OUD currently incarcerated in NYC jails.

- Adults (>18yo) currently incarcerated with known release date and OUD randomized to XR-B (300mg/month) vs. SL-B (8-24mg/day) treatment-as-usual

- The primary clinical outcome is treatment retention during weeks 1-8

Of 26 assigned to XR-B:
- 21 received 1st injection in jail
- 5 refused 1st in. in-jail
- 3 of these 5 subsequently received XR-B in community

Of 26 assigned to SL-B:
- All were released with 7-day supply of SL-B from jail



XR-BUP at release from NYC jails RCT

Table 1: Demographics

	XR-B (n=26) # (%)	SL-B (n=26) # (%)
Male	22 (85%)	22 (89%)
Age, mean (SD)	43 (9.2)	42 (10.7)
Hispanic	14 (54%)	9 (35%)
Non-Hispanic Black	6 (23%)	9 (35%)
Non-Hispanic White	6 (23%)	9 (35%)
High School Graduate or Higher	14 (54%)	17 (65%)
Employed (Full or Part-Time)	12 (46%)	13 (50%)
Heroin/ opiate use 30 days prior to incarceration	19 (73%)	21 (81%)
IV use 30 days prior to incarceration	8 (31%)	6 (23%)
Mean lifetime treatment intake episodes, mean (SD)	3.3 (2.9)	3.2 (2.5)
Tried buprenorphine treatment prior to in-jail program participation	15 (58%)	15 (58%)

Table 2: Treatment Retention

	XR-B (n=26) # (%)	SL-B (n=26) # (%)
Retained in treatment (Weeks 1-8)*	15 (58%)	10 (38%)
Days Covered by Active XR-B inj. or SL-B Rx, mean (SD)	44 (24.1)	18.1 (22.6)
Number of XR-B participants who switched to SL-B	7 (27%)	N/A
Achieved 5/5 opioid/opiate free urine toxicology	4 (15.3%)	3 (11.5%)
# Re-Arrested	2 (7.6%)	4 (15.3%)
SAEs**	2	0

**No overdoses reported

28-week therapeutic treatment extension study

- Offered to both XR-B & SL-B arms
- 6 XR-B enrolled, 0 SL-B
- 16 injections administered

Sublocade (XR-BUP) at Rikers, Pilot RCT

Perceptions and experiences toward extended-release buprenorphine among criminal justice system involved people who use opioids: an in-depth qualitative study

- 16 XR-B participants interviewed (13 stayed on XR-B, 3 switched to SL-B after 1st injection)
- Interviewed at an average of 9 weeks since release (1 in-jail injection and 2 community injections)

Facilitators of XR-BUP

"I didn't have to go every single day, you know. I wouldn't have to get up and wait for escorts and be locked in a cage waiting for hours for my medication." [49]

Barriers to XR-BUP

"And then actually getting the shot was painful. It's like a real, real bad stinging pain. You know, and after, you know, it's like a lump. You know, with time it goes down. I'm guessing as the medication releases, it goes down. But it's pretty annoying. Like when you are putting on your clothes, it's painful. Anything that touches, it's like you know, it bothers. And then you get a real bad bruising around the area. That's the only part, it's bad." [19]

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Testing the blockade

"This time I was controlled. Like I said, you know, it's really a block. You cannot get high no matter how much you try. No matter how much you do, it's not gonna work. Your body rejects it...You can't do too much on that at all. That's actually a great thing, if you ask me."[19]

Monthly schedule reduces decision points

"For the shot, you gotta take it as prescribed because you got no choice. This is what it is. You can't take more one day if you want, you can't skip days… Sometimes I'll make the wrong choice. If I had someone to make a better choice for me, I'll let them make the decision. That's how it is with the shot…" [01]

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Reasons for switching from XR-B to SL-B:

- XR-B not fitting with lifestyle or recovery preferences
  "Especially in early recovery... complete abstinence is very difficult, for myself. I saw it as the lesser of two evils, in a sense... Meaning I would rather look forward to getting a little boost off of suboxone than sniffing heroin and having a habit and committing a crime to get it… It's like taking alcohol away from an alcoholic. You're going to be miserable for a little while." [08]
- *Injection site pain*
- Appearance of residual lump at injection site

Overall:

- Participants' familiarity with SL-B granted a level of comfort and willingness to try XR-B that may not be present for other novel forms of MOUD
- Participants expressed the feeling of safety they experienced upon release, with significantly reduced pressure to obtain a prescription for SL-B after reentry to their community.
- Monthly dosing of XRB reduced interactions with CJS staff and allowed them to avoid the time-consuming daily routine of obtaining treatment. Some also felt that XRB changed peer dynamics while incarcerated, preventing the diversion or misuse of their MOUD.
- Potential to alleviate the burden of crowded treatment systems in jail

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Impacts of COVID-19 pandemic

- **Reduced access to outpatient care resources**

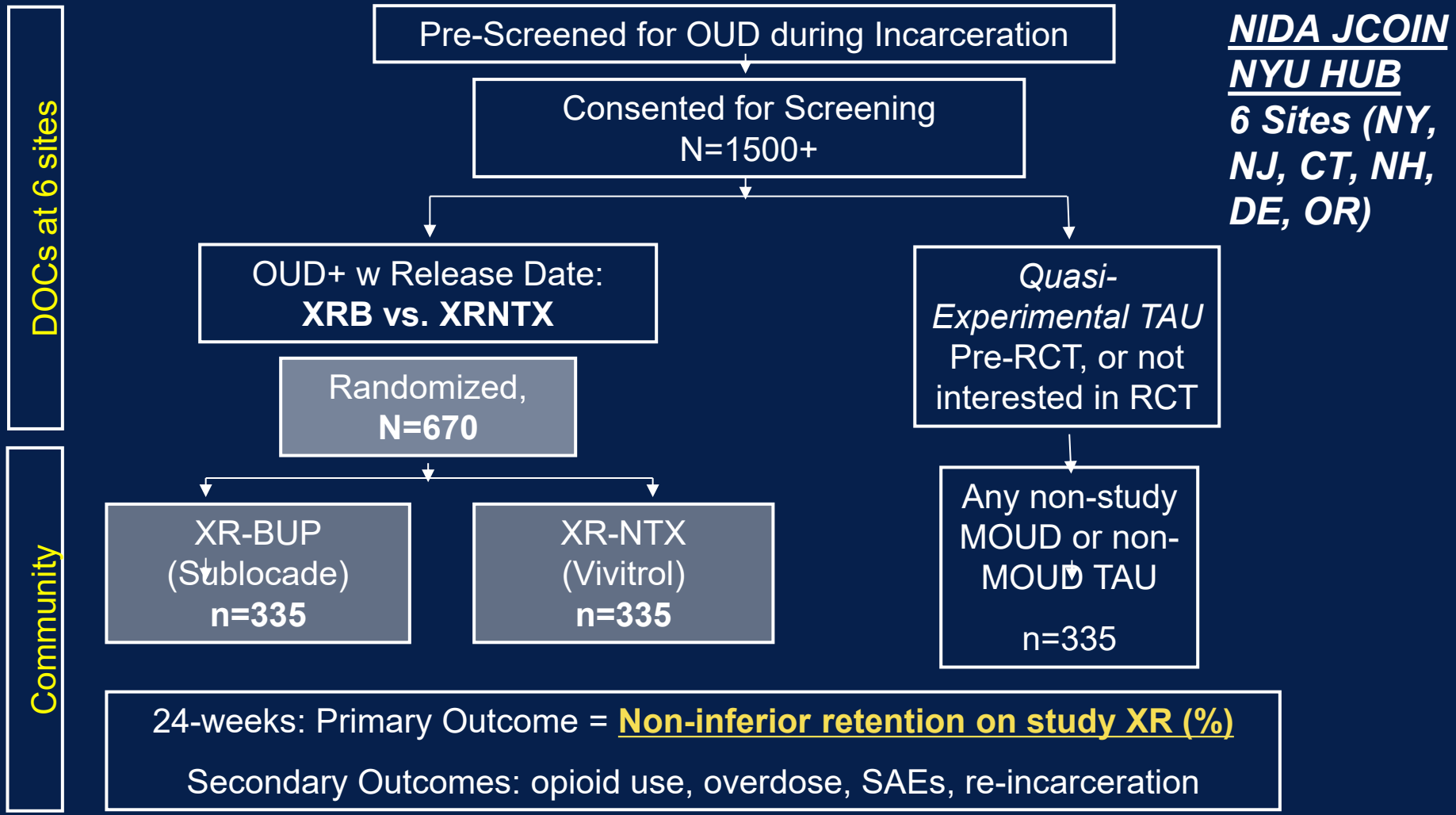
  "Well everything is messed up because you don't got access to a lot of things no more. the hospitals… everything is so difficult right now. Dealing with this coronavirus. It's very hard" [27]

- **Insight into taper experience from forced XR-B to SL-B transition**

  "Y'all told me it would last 4-5 weeks...I'm at 5 weeks. I ain't had nothing else." [41]

- **Perceptions regarding the effects of quarantine/isolation on treatment**

  "'I believe that if I get sick I can stay home for fourteen days' as long as I have my medication, my pill, my shot, I can stay in the house as long as I want." [33]


DOCs at 6 sites
Community
Pre-Screened for OUD during Incarceration
Consented for Screening
N=1500+
OUD+ w Release Date:
XRB vs. XRNTX
Randomized,
N=670
XR-BUP
(Sublocade)
n=335
XR-NTX
(Vivitrol)
n=335
Quasi-
Experimental TAU
Pre-RCT, or not
interested in RCT
Any non-study
MOUD or non-
MOUD TAU
n=335
24-weeks: Primary Outcome = Non-inferior retention on study XR (%)
Secondary Outcomes: opioid use, overdose, SAEs, re-incarceration
NIDA JCOIN
NYU HUB
6 Sites (NY,
NJ, CT, NH,
DE, OR)

NYU Langone Health

Thank You
@DrJoshuaDLee