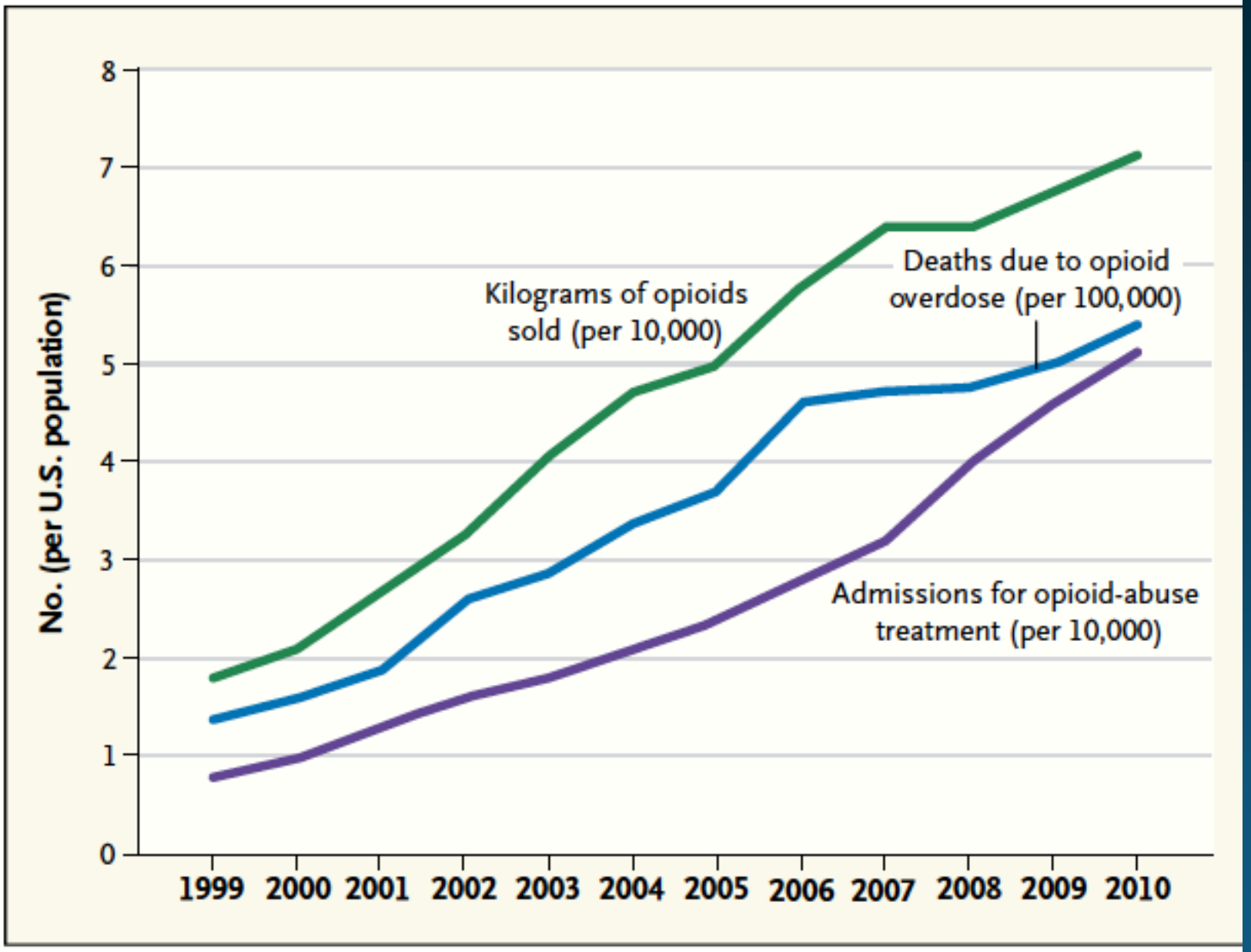
Extended-Release Naltrexone for Opioid Relapse Prevention

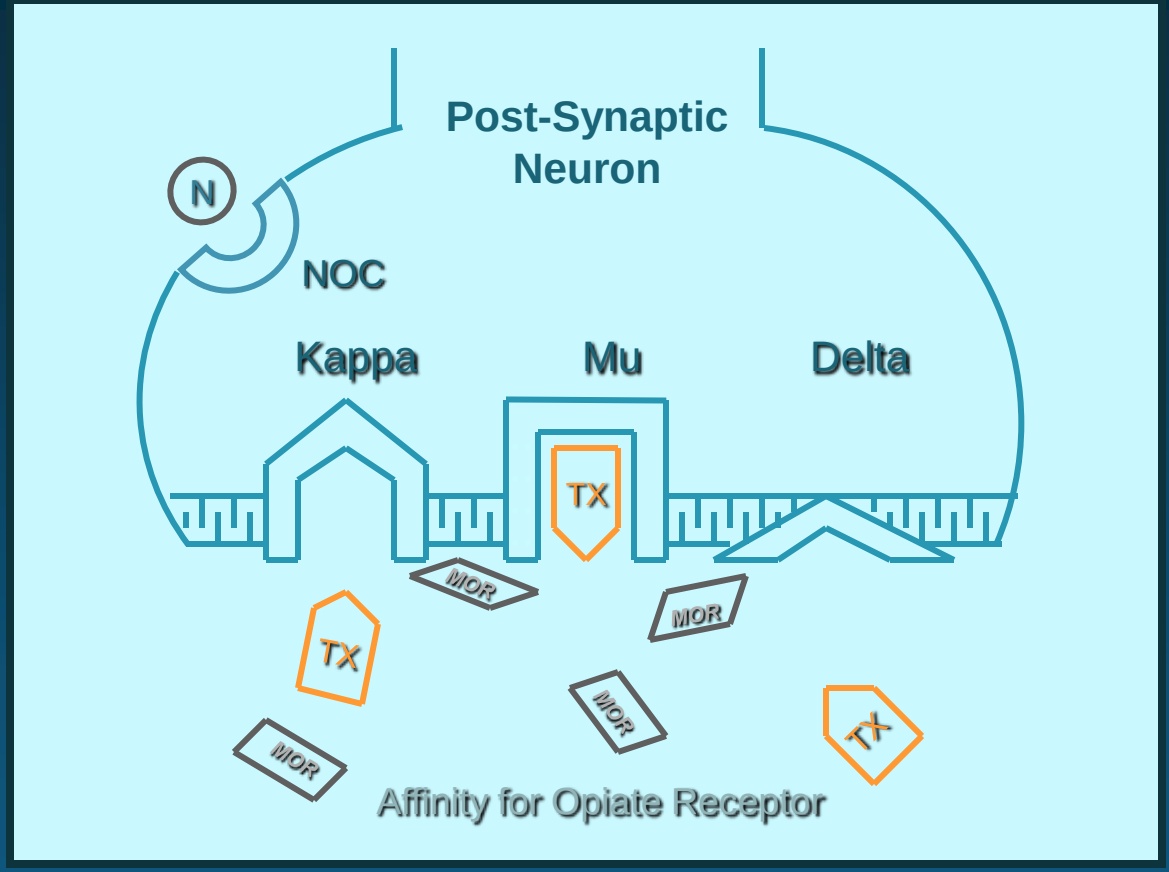
1.NYU SOM; Bellevue Hospital Center 2.Brown Univ. 3. Friends Research Institute
4. Columbia Univ. 5. Univ. Pennsylvania 6. Univ. Virginia

Funding: NIDA R01-DA024549-55
Study Drug: Alkermes, Inc. (Vivitrol)
ClinicalTrials.gov NCT01180647



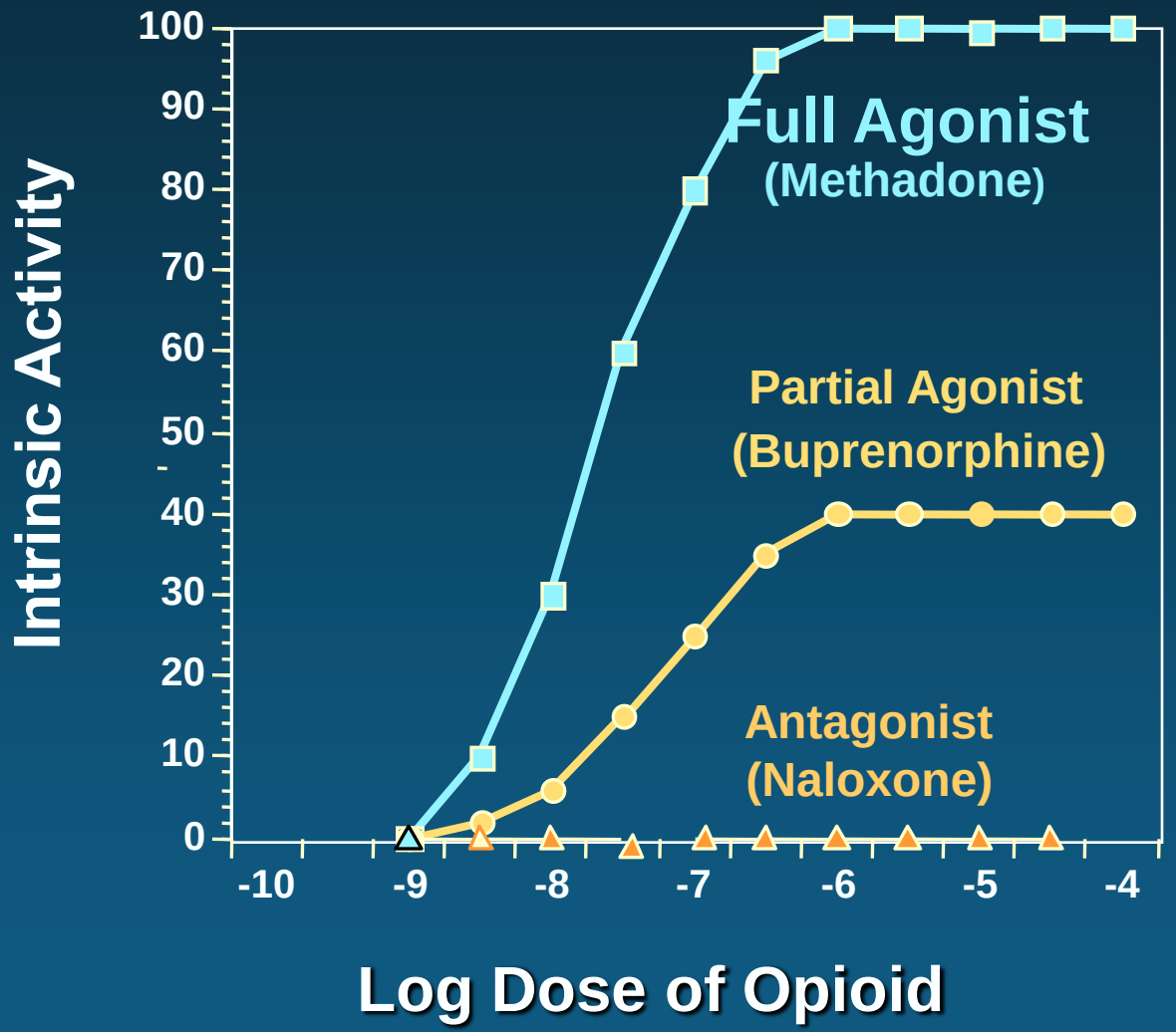
Opioid Sales, Admissions for Opioid-Abuse Treatment, and Deaths Due to Opioid Overdose in the United States, 1999–2010.

Opiate Receptors

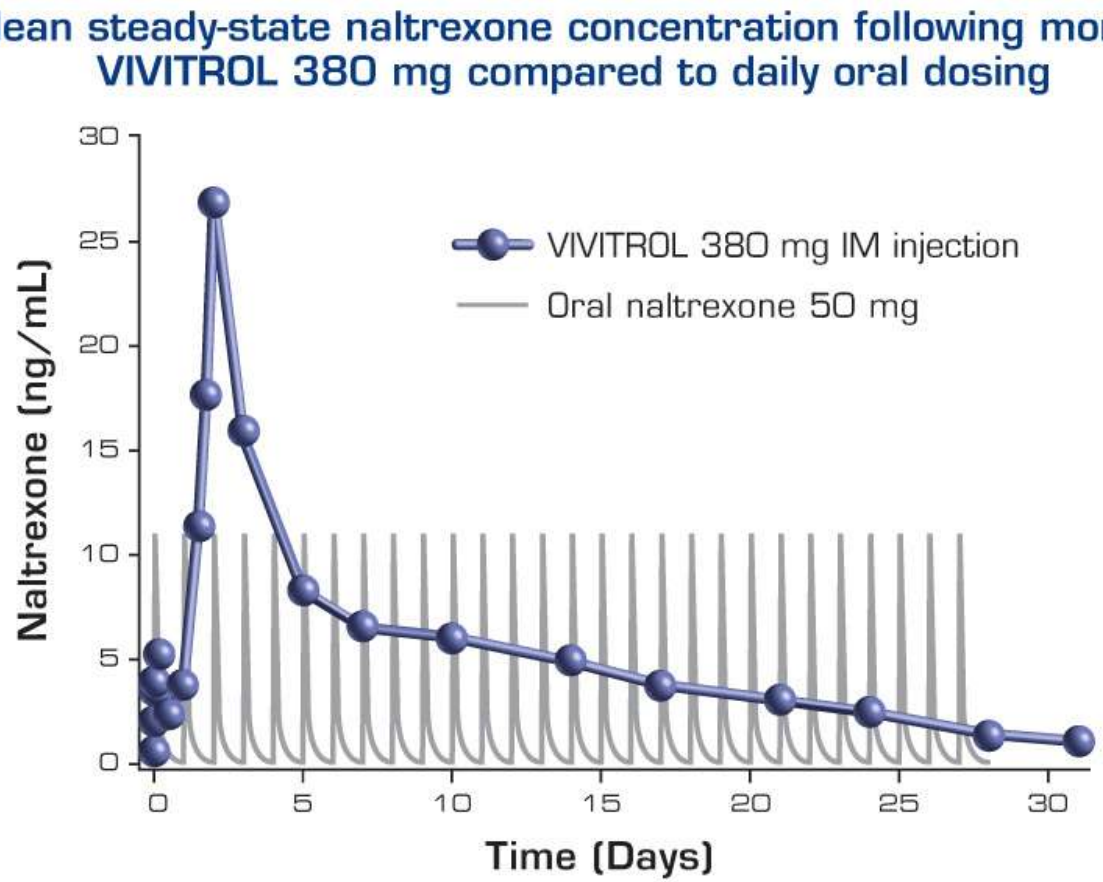


	Kappa	Mu	Delta
Naltrexone	406	108	54
Morphine	1	1	1

Intrinsic Activity: Full Agonist (Methadone), Partial Agonist (Buprenorphine), Antagonist (Naloxone)



Plasma Concentrations



Dean RL. *Front Biosci*. 2005 Jan 1;10:643-655.
Dunbar JL, et al. *Alc Clin Exp Res.* 2006;30:480-490.
Data on File, Alkermes, Inc.

Opioid Disorders: Evidence Base

	Efficacy	Community Effectiveness	CJS Feasibility	CJS Effective	CJS Adoption
Methadone	++++	+++	+++	++	+
BUP	++++	+++	++	+	+
XR-NTX	++	+	?	?	+
O-NTX	+	-	-	-	-

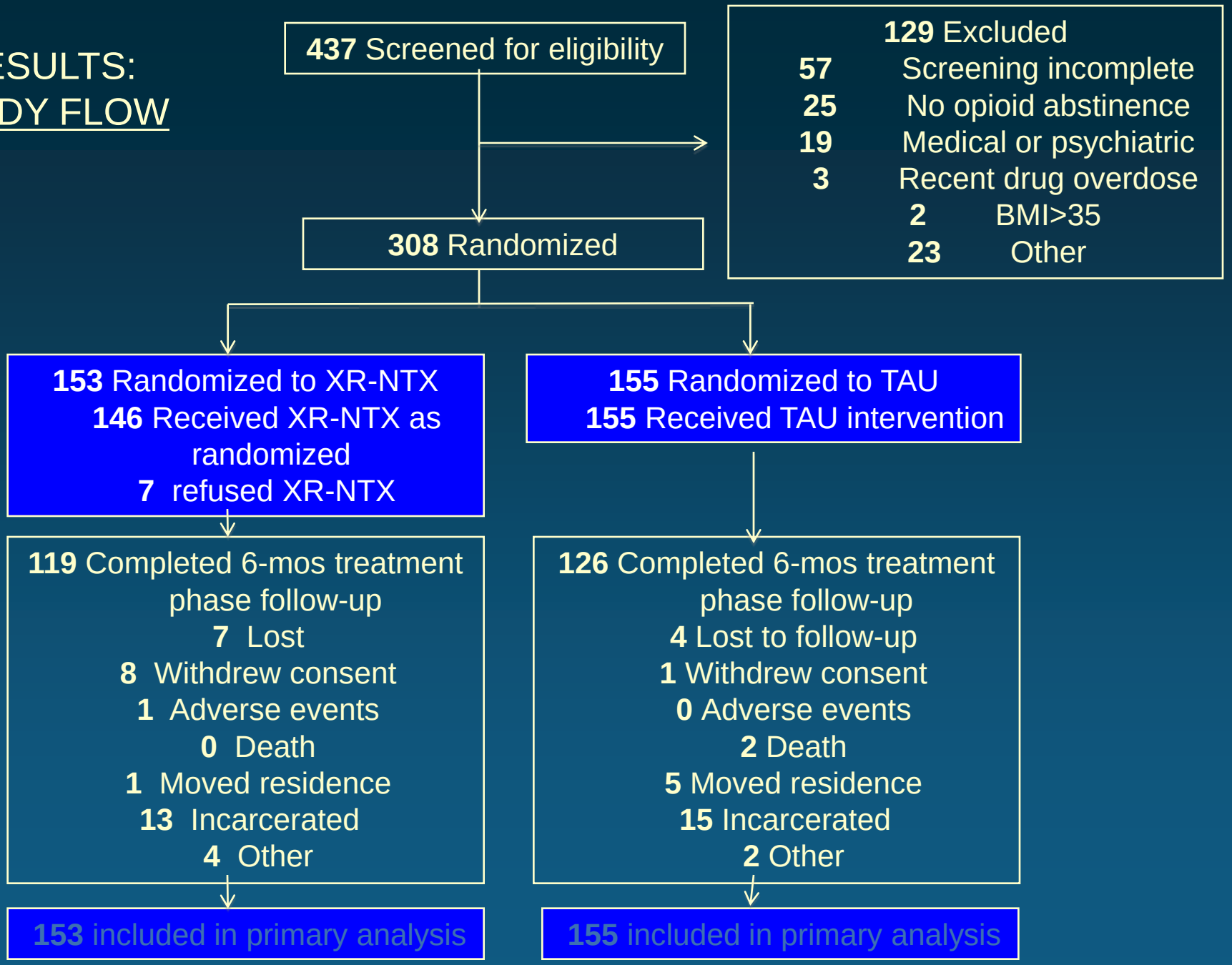
XR-NTX's effectiveness in CJS populations is unknown

Naltrexone Affinity at Opioid Receptor Subtypes

	Receptor Binding Ki (nM)		
	Mu	Delta	Kappa
Antagonist:			
Naltrexone	0.37	9.4	4.8
Agonists:			
Morphine (m)	38	510	1,900
DADL-enke (d)	150	1.8	>10,000
(-)-EKC (k)	2.3	5.2	2.2

Schmidt, W.K., et al., *Drug Alcohol Depend*, 1985;14:339-362.

RESULTS: STUDY FLOW



Study Design

1. Adults w Opioid Dependence (current or lifetime)
2. CJS + (recent parole, probation, jail/prison/arrest)
3. Not seeking agonist rx (methadone, buprenorphine)
4. Opioid negative (urine, self-report) at randomization

Randomization

XR-NTX

TAU

FU every 2 weeks

End of Treatment Phase, 6 months (week 27)
1° outcome: opioid relapse, rates of opioid misuse

Long-term FU @ 12, 18 months

Methods

- **Design**: open-label, non-blinded effectiveness RCT
- **Population**: volunteers only – no CJS agency referrals
- **Population**: Recent release from prison
- **Sites**: Providence, NYC (2x), Baltimore, Philadelphia
- **Intervention**: XR-NTX IM monthly + Med Mgt (MD/RN)
- **TAU**: supportive counseling, referrals to community treatment
- **Assessments** bi-weekly (urine, TLFB), month 6,12,18
- **Primary outcome**: opioid relapse and misuse rates mos. 0-6
  - *No assessment of return to psyiologic opioid dependence*
- **Secondary outcomes**: drug/alcohol rates, HIV risk (IV, sex), SAEs/Overdose, re-incarceration, coercion, cost-effectiveness
- **Power**: target sample N=360

Methods

- **Primay Outcome**: the event of opioid relapse =
  - 10+ days of opioid use by self-report or urine toxicology
    - + or missing urine = 5 days of opioid use
  - Missing = positive: complete primary outcomes

- **Primary Analysis:**
  - Head-to-head intent-to-treat comparison of relapse (yes/no)
    - Cox Proportional Hazard Model w Site Co-variate
  - Time-to-relapse (Wilcox)
  - % 2-weeks abstinent (non-missing, neg. urine, self-report=0) (GEE)
  - % urines negative vs. positive/missing (GEE)
  - % days of self-reported opioid use (GEE)

- **Secondary Outcomes**: same analytic methods

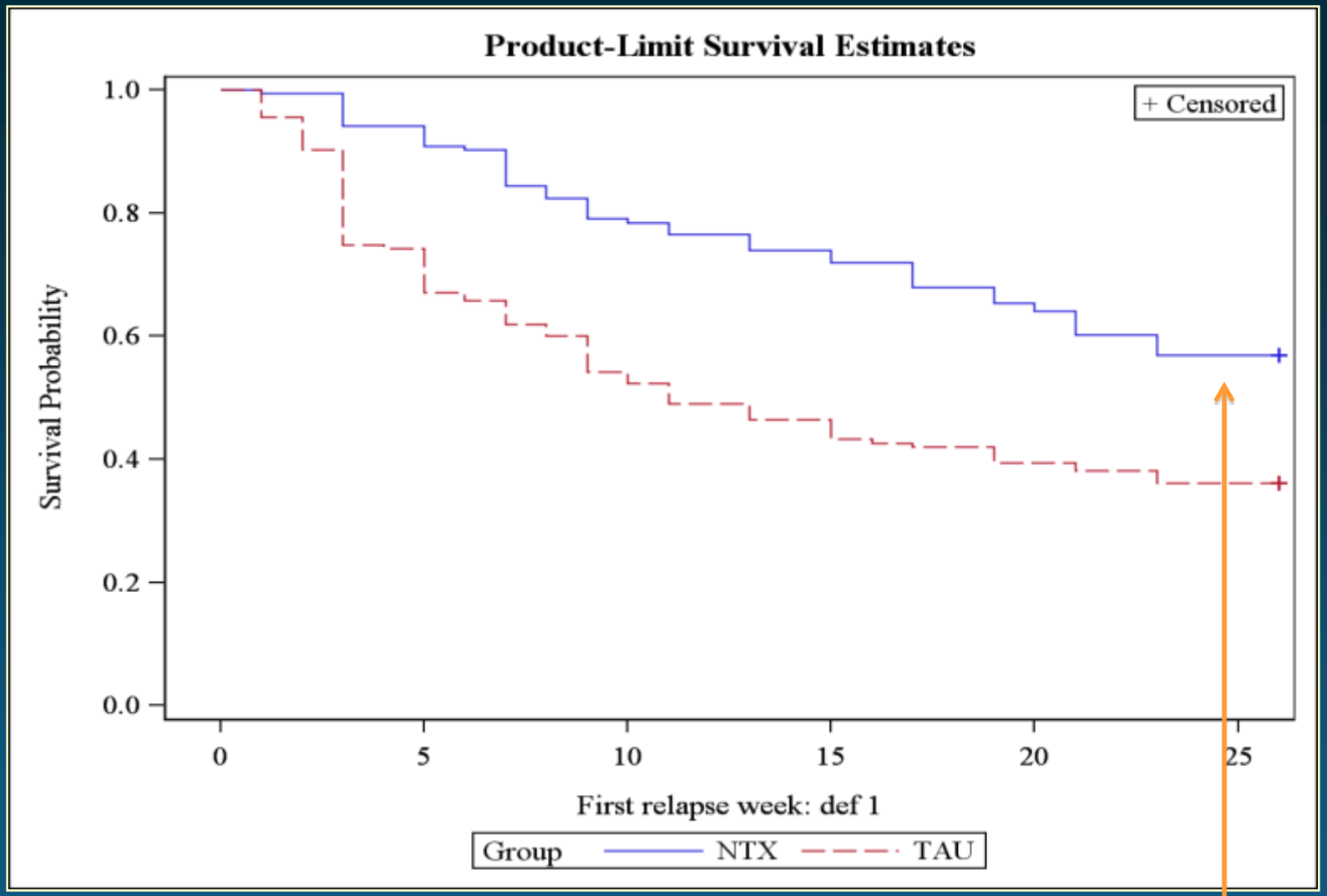
Results at 6 months (week 27): Primary Outcome, Opioid Use, Overdose

	XR-NTX	TAU	P value	RR,95%CI
Primary outcome: Opioid relapse	**66 (43%)**	**99 (64%)**	**<0.001**	**OR 0.43 (0.28,0.65)**
% 2-week abstinent intervals	71%	50%	<0.001	OR 2.50 (1.66, 3.76)
Time–to-relapse (median weeks)	10.5	5.0	<0.001	na
% Urines negative (vs. positive/missing)	74.11%	55.68%	<0.001	OR 2.30 (1.49, 3.56)
% Days of misuse (self-report)*	3.94%	11.30%	<0.02	OR 0.47 (0.24, 0.93)

Cocaine, Alcohol, IVDU, HIV Risk, Recidivism

	XR-NTX	TAU	P	HR (95%CI)
Cocaine misuse % days	3%	4%	0.70	0.89 (0.42, 1.58)
# drinks / week (mean)	1.59	1.23	0.47	na
% IV drug use	6%	9%	0.43	RR 0.69 (0.27, 1.75)
RAB Sex Risk, 6mo (mean)	2.75	2.86	0.68	na
Re-incarceration	23%	29%	0.38	OR 0.71 (0.33, 1.520)

Time to Relapse: Survival Curve



- Retention on XR-NTX was 61% at 6 months
- 711 of 918 (77%) planned injections given

RESULTS:
Visit retention

105 (69%) **12 month** urine data

116 (75%) **12 month** urine data

247 (80%) 12 month self-report data

112 (73%) **18 month** urine data

120 (77%) **18 month** urine data

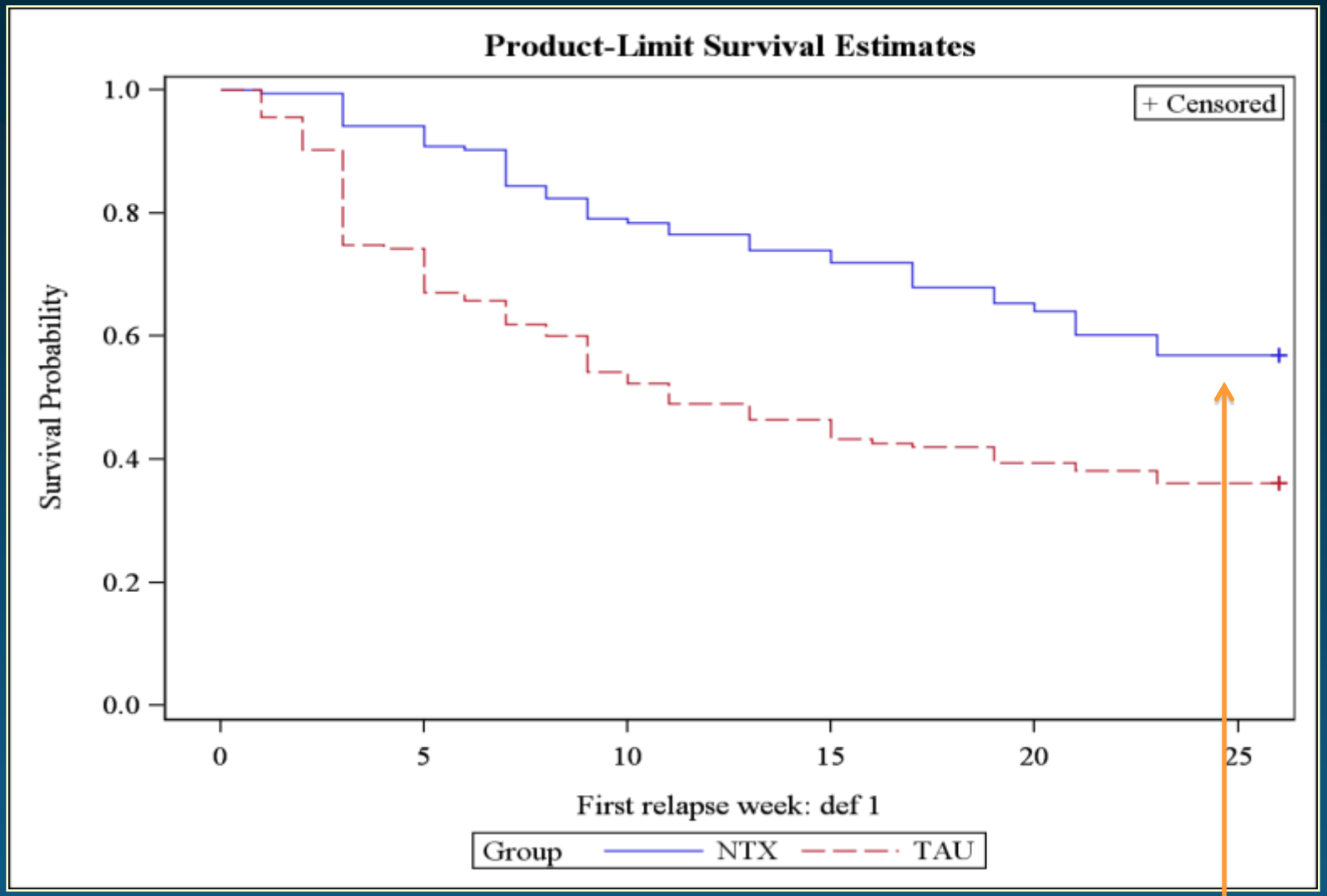
120 (77%) **18 month** self-report data

Baseline characteristics

	XR-NTX	TAU
Male, Age (mean)	84%, 44yo	85%, 43yo
Parole	37%	34%
Probation	36%	40%
No CJS supervision	20%	20%
Heroin use, every	88.8%	88.4%
Other opioid use, ever	50.7%	47.7%
Injection drug use, ever	42.1%	40.0%
Opioid use, current*	**20.4%**	**16.8%**
Cocaine use, current	19.7%	18.7%
Heavy drinking, current	11.8%	12.3%

*Current = last 30 days

Time to Relapse: Survival Curve



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Results at 6 months (week 2
Primary Outcome, Opioid Use, Overdo

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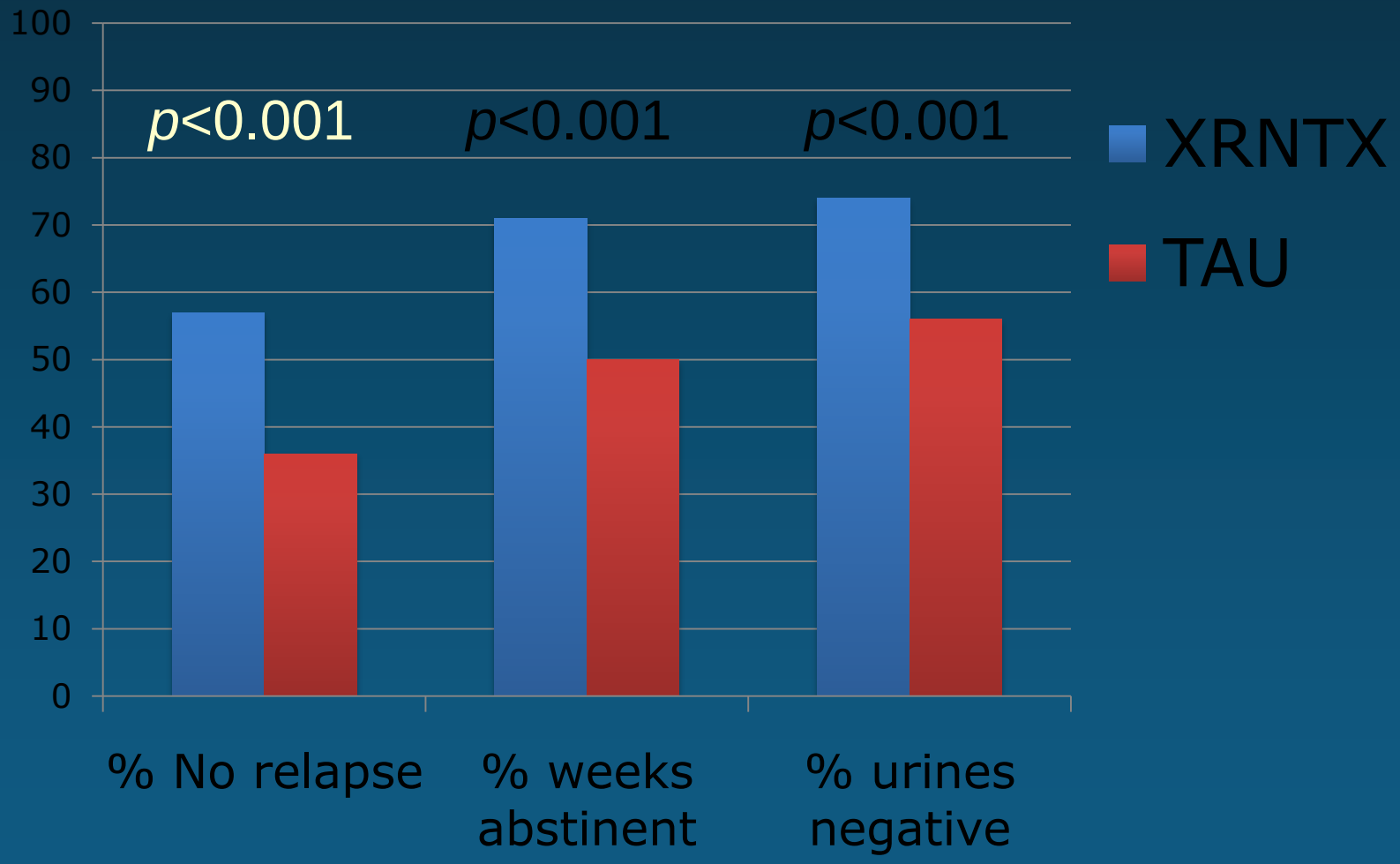
Primary Opioid Outcome:
No relapse, weeks abstinent, urines negative



Preliminary Results at 6 months: Other Community Treatment

	XR-NTX (%)	TAU (%)	P value	HR (95%CI)
Outpatient treatment	62	65	0.63	0.96 (0.81, 1.14)
Detox Episode	3	2	0.73	1.30 (0.30, 5.69)
Residential	9	11	0.63	0.84 (0.42, 1.71)
Bup-Nx	8	25	<0.001	0.30 (0.16, 0.56)
Methadone	3	11	0.01	0.30 (0.11, 0.81)

Cocaine, Alcohol, IVDU, HIV Risk, Recidivism

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Re-incarceration	23%	29%	0.38	OR 0.71 (0.33, 1.520)

AE/SAE	XR-NTX (n=153)	TAU (n=155)	*p*
Reporting ≥1 AE	119 (77.8%)	90 (58.1%)	0.0002
AE, study drug related	59 (38.6%)	-	na
Study drug discontinued due to AE	5 (3.3%)	-	na
Headache	29 (19.0%)	13 (8.4%)	0.07
GI upset	28 (18.3%)	3 (1.9%)	<0.001
Flu-like symptoms	6 (3.9%)	2 (1.3%)	0.15
Depression/suicidality	2 (1.3%)	11 (7.1%)	0.02
Insomnia	11 (7.2%)	8 (5.2%)	0.46
Nasopharyngitis	15 (9.8%)	17 (11.0%)	0.74
SAE	16 (10.5%)	45 (29.0%)	0.006
SAE, study drug related	1 (0.7%)	-	na
Overdose, any	0	5 (3.2%)	0.06
Overdose, fatal	0	2 (1.3%)	0.50

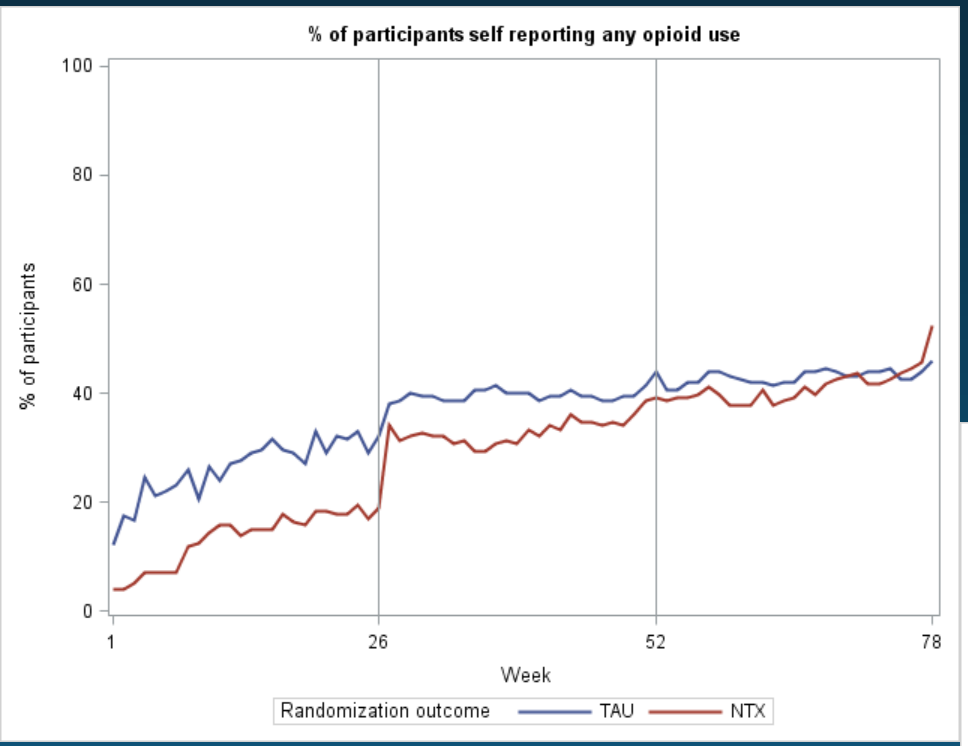
Results at 6 months

- **XR-NTX prevented opioid misuse, relapse, and prolonged time-to-relapse.**
  - % of weeks abstinent: 71% vs. 49%
  - Krupitsky RCT: @75% vs. @50% (=AOC, Fig 2)
- No differences in secondary outcomes: cocaine and alcohol use, HIV risk, re-incarceration (self-report)
- XR-NTX retention was substantial: 61% at 24 weeks
  - high rates of community outpatient treatment in both arms

Long-term Follow-Up (18 Months)

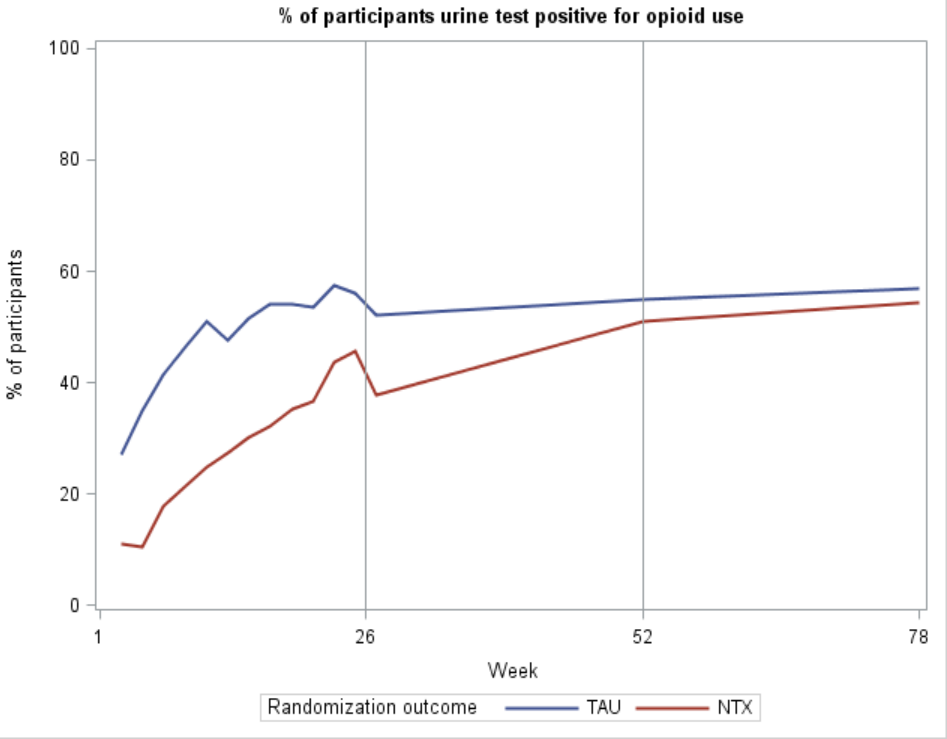
Urines, 12 & 18 mos	**XR-NTX**	**TAU**	***p***
% opioid negative urine, 12 months	49%	45%	ns
% opioid negative urine, 18 months	46%	43%	ns
SAEs, 1-18 mos			
Overdose, any	**0**	**7**	**0.02**
Overdose, fatal	0	3	0.25
All-case mortality	2	5	0.45

Opioid Use at 12 and 18 Months



Self-report: any opioid use

Opioid urines: missing|positive



Results at 18 months

- Post-XR-NTX, treatment effects fade and decay
  - Gradual decline in % urines negative at 12 and 18 months
  - No difference in % urines negative at 18 months

- In-treatment and post-XR-NTX = fewer overdoses
  - 0 vs. 5 in treatment, 0 vs. 7 total at 18 months
  - ***There was no increase in overdose risk post-XR-NTX***

Conclusions

- **XR-NTX prevented opioid misuse and relapse, and it prolonged time-to-relapse.**
  - 71% vs. 49% weeks abstinent
  - Similar to Russian pivotal RCT:

    Krupitsky RCT: @75% vs. @50% (=AOC, Fig 2)
  - Effects were not long-lasting post-treatment
- **Overdose data favored XR-NTX**
  - 0 vs. 7 ODs, p=0.01, over 18 months
  - No overdoses among post-XR-NTX participants
- **12 months after treatment rates of opioid use were similar**

Preliminary cost effectiveness

- XR-NTX was more expensive:
  - 6 months: $2,569 (p=0.03, taxpayer perspective) and $1,983 (p<0.001, third-party payer)
  - 18 months: $2,192 (p=0.33) and $1,808 (p=0.002)

- This increased spend bought increased QALYs and Opioid Free Years (OFY)
  - 6 months: taxpayer costs per QALY $128,436; OFY $42,812
  - third-party payer QALY $99,140 and OFY $33,047.
  - 18 month: cost/QALY was $73,056 (taxpayer) and $60,267 (payer).

- Using an 18 month horizon and a (WTP) threshold of $200,000 per QALY, acceptability curves indicate XR-NTX has a 79% (taxpayer) and 82% (payer) chance of being considered cost-effective.

- XR-NTX has a 100% chance of being considered a “good value” at 6 months using a WTP threshold of $200,000 per OFY.

Methods

- **Advantages**
- Only one injection per month
- Decreased drug craving
- No reward if opiate injected
- No overdose in this study
-

Inconvenients

Detox necessary

Limitations

- Open-label, non-placebo, non-blinded
  - community effectiveness vs. efficacy trial
- No head-to-head comparison to agonists
  - Participants generally selected bup-nx or methadone after or during other opioid misuse (data not shown)
- Cost-effectiveness and CJS data (recidivism) *preliminary/pending*

Implications

- XR-NTX was well-tolerated and feasible as a 6-month intervention in a US CJS outpatient population
- XR-NTX provided effective relapse prevention vs. treatement-as-usual
- XR-NTX may have prevented overodose events
- Post-treatment, relapse prevention effects faded; long-term (>6 month) treatment may be warrented