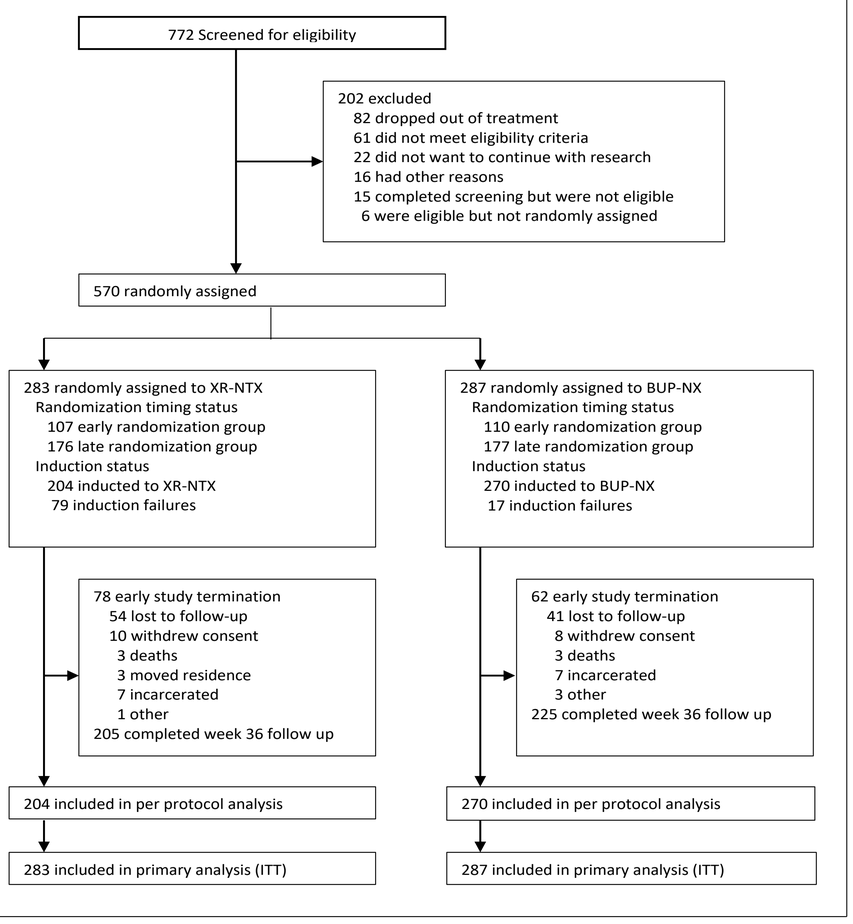
Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicenter, open-label, randomized controlled trial

Patricia Novo[1], Joshua D. Lee[1], Edward V. Nunes, Jr.[2,3], Ken Bachrach[4], Genie L. Bailey[5,6], Snehal Bhatt[7], Sarah Farkas[1], Marc Fishman[8,9], Phoebe Gauthier[1], Candace C. Hodgkins[10], Jacquie King[11], Robert Lindblad[11], David Liu[12], Abigail G. Matthews[11], Jeanine May[11], K. Michelle Peavy[13], Stephen Ross[1], Dagmar Salazar[11], Paul Schkolnik[14], Dikla Shmueli-Blumberg[11], Don Stablein[11], Geetha Subramaniam[12], John Rotrosen[1]

AIMS: Extended-release naltrexone (XR-NTX), an opioid antagonist, and buprenorphine-naloxone (BUP-NX), a partial opioid agonist, are pharmacologically and conceptually distinct opioid relapse prevention interventions. We aimed to estimate the difference in opioid relapse-free survival between XR-NTX and BUP-NX.

METHOD: We initiated this 24 week comparative effectiveness trial at eight community-based inpatient programs and followed participants as outpatients. Participants were 18 years or older, had DSM-5 opioid-use disorder, and non-prescribed opioid use in the past 30 days. Participants were stratified by site and opioid-use severity and randomized (1:1) to receive XR-NTX or BUP-NX. Primary outcome was opioid relapse-free survival (relapse was 4 consecutive weeks of non-study opioid use by urine toxicology or self-report, or 7 consecutive days by self-report).

Trial Profile



Baseline Characteristics

	Intention to Treat		Per Protocol	
	BUP-NX (N=287)	XR-NTX (N=283)	BUP-NX (N=270)	XR-NTX (N=204)
Demographics				
Female Gender	81 (28·2%)	88 (31·1%)	77 (28·5%)	66 (32·4%)
Age, Mean Years (SD)	33·7 (9·80)	34·0 (9·46)	33·7 (9·81)	33·7 (9·31)
Hispanic or Latino	54 (18·8%)	45 (15·9%)	53 (19·6%)	27 (13·2%)
Black or African American	28 (9·8%)	29 (10·2%)	27 (10·0%)	20 (9·8%)
White	215 (74·9%)	206 (72·8%)	201 (74·4%)	157 (77·0%)
Education Completed				
Less than high school diploma	69 (24·0%)	63 (22·3%)	65 (24·1%)	49 (24·0%)
High school graduate	58 (20·2%)	51 (18·0%)	55 (20·4%)	35 (17·2%)
GED or equivalent	38 (13·2%)	43 (15·2%)	38 (14·1%)	28 (13·7%)
Some college, no degree	77 (26·8%)	80 (28·3%)	70 (25·9%)	62 (30·4%)
Marital Status				
Married	22 (7·7%)	30 (10·6%)	21 (7·8%)	20 (9·8%)
Widowed	8 (2·8%)	5 (1·8%)	7 (2·6%)	3 (1·5%)
Divorced	39 (13·6%)	29 (10·2%)	35 (13·0%)	25 (12·3%)
Separated	18 (6·3%)	20 (7·1%)	17 (6·3%)	12 (5·9%)
Never married	189 (65·9%)	187 (66·1%)	180 (66·7%)	134 (65·7%)
Employment				
Working now	57 (19·9%)	48 (17·0%)	50 (18·5%)	34 (16·7%)
Temporarily laid off or leave	20 (7·0%)	28 (9·9%)	19 (7·0%)	22 (10·8%)
Looking for work, unemployed	181 (63·1%)	179 (63·3%)	172 (63·7%)	125 (61·3%)
Disabled permanently or temporarily	15 (5·2%)	11 (3·9%)	15 (5·6%)	10 (4·9%)
Clinical Characteristics				
IV Use	183 (63·8%)	177 (62·5%)	171 (63·3%)	131 (64·2%)
Primary Opioid Used in the 7 Days Prior to Detox Admission				
Buprenorphine	2 (0·7%)	6 (2·1%)	2 (0·7%)	4 (2·0%)
Opioid analgesics	47 (16·4%)	43 (15·2%)	45 (16·7%)	36 (17·6%)
Methadone	4 (1·4%)	3 (1·1%)	4 (1·5%)	3 (1·5%)
Heroin	233 (81·2%)	230 (81·3%)	218 (80·7%)	160 (78·4%)
Cost per Day for Primary Opioid, Mean (SD)	$96·3 (74·50)	$90·7 (76·74)	$94·1 (73·92)	$91·0 (84·27)
Age at Onset of Any Opioid Use, Mean (SD)	21·4 (7·56)	21·2 (6·54)	21·4 (7·57)	20·8 (6·48)
Duration of Opioid Use, years, Mean (SD)	12·2 (9·03)	12·8 (8·94)	12·3 (9·06)	12·9 (9·06)
Index Admission is First Opioid Treatment Episode	109 (38·0%)	100 (35·3%)	105 (38·9%)	75 (36·8%)
Stimulant Use (past 30 days)	164 (57·1%)	133 (47·0%)	155 (57·4%)	99 (48·5%)
Sedative Use (past 30 days)	93 (32·4%)	72 (25·4%)	86 (31·9%)	53 (26·0%)
Heavy Alcohol Use (past 30 days)	77 (26·8%)	71 (25·1%)	74 (27·4%)	56 (27·5%)
Cannabis Use (past 30 days)	133 (46·3%)	122 (43·1%)	130 (48·1%)	86 (42·2%)
Hamilton Depression Scale, Mean (SD)	9·3 (6·63)	8·6 (6·45)	9·5 (6·72)	8·5 (6·41)
History of Psychiatric Disorders, Self-report	191 (66·6%)	190 (67·1%)	183 (67·8%)	141 (69·1%)
Subjective Opioid Withdrawal Scale (0-64), Mean (SD)	15·6 (13·15)	15·6 (13·38)	15·9 (13·16)	15·3 (13·51)

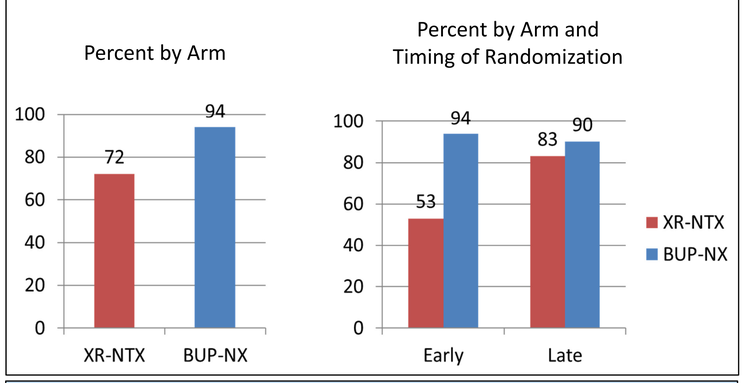
Note: SD=standard deviation.

OUTCOMES:
See adjacent statistical analysis

570 participants were randomly assigned to receive XR-NTX (Vivitrol® , 4cc, ~380mg naloxone base) (n=283) or BUP-NX (Suboxone® sublingual film, 4mg/1mg and 8mg/2mg strengths, doses were flexible up to 32 mg per day) (n=287).

As expected, XR-NTX had a substantial induction hurdle: fewer initiated XR-NTX (72%) than BUP-NX (94%). Among the intention-to-treat (ITT) population (n=570) 24-week relapse events were greater for XR-NTX (65%) than for BUP-NX (57%); most of this difference is accounted for by early relapse in nearly all (89%) XR-NTX induction failures. Among participants successfully inducted (per-protocol population, n=474), 24-week relapse events were similar across arms. Opioid-negative urines and opioid-abstinent days favored BUP-NX among the ITT population, but were similar across arms among the per-protocol population. Opioid craving was initially less with XR-NTX than BUP-NX, converging by week-24. Except for XR-NTX injection site reactions, treatment-emergent adverse events did not differ between treatment groups. Five fatal overdoses occurred (two in the XR-NTX group, three in the BUP-NX group).

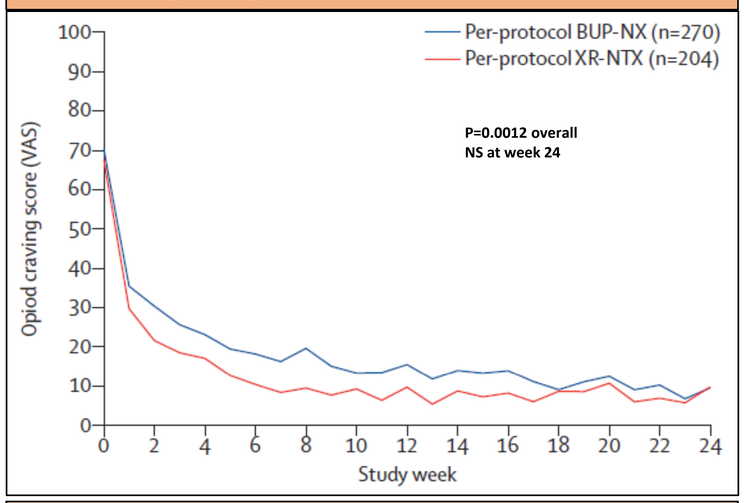
Induction Success



Early randomizers were those who were randomized within 72 hours of last opioid use (including opioids use for detoxification.

Induction Failures:
Randomized to XR-NTX = 79
*70 met relapse criteria at Day 21
Randomized to BUP-NX = 17
*10 met relapse criteria at Day 21

Opioid craving during treatment



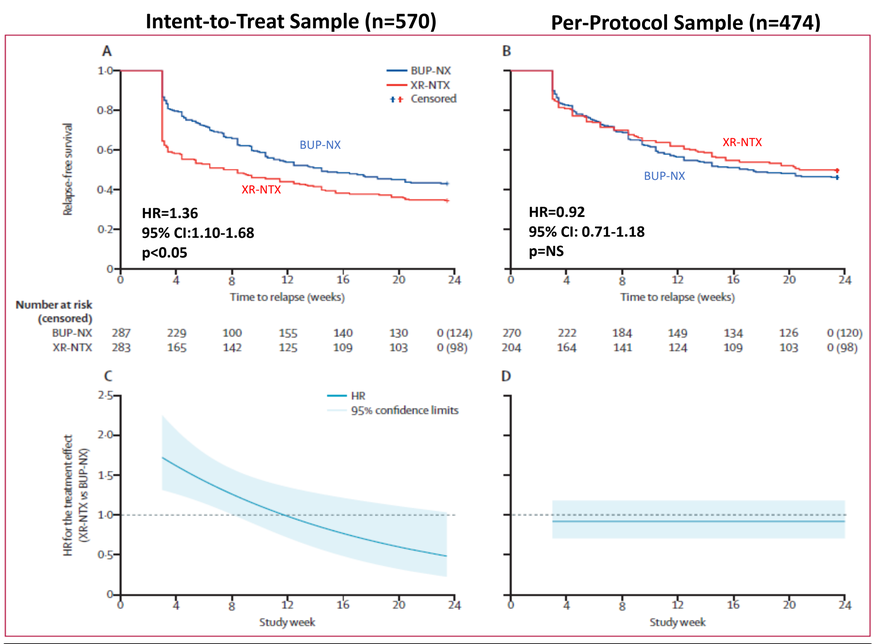
Craving was self-reported with an opioid craving VAS, range 0–100. VAS=Visual Analogue Scale.

CONCLUSIONS:

1. In these settings, it was more difficult for participants to initiate XR-NTX
2. Nearly all those who failed induction quickly relapsed
3. Better overall opioid outcomes for the BUP-NX group in Intention-to-Treat population were directly related to differential induction failure
4. Essentially equivalent safety and effectiveness for XR-NTX and BUP-NX in the Per-Protocol sample
5. No differences in AEs, SAEs, ODs and fatal ODs

Future work should focus on facilitating induction to XR-NTX and on improving treatment retention on both medications.

Relapse-free survival and treatment effect over time



Survival (A) and HRs and corresponding 95% CIs from the non-proportional hazards Cox model (time by treatment interaction included in the model); (C) assessed in the intention-to-treat population (n=570). Survival (B) and HRs by time (D) in the per-protocol population (n=474).

Opioid Treatment Outcomes

	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). OR=odds ratio. HR=hazard ratio. CI=confidence interval.

Treatment-emergent reportable events

	XR-NTX group (n=283)	BUP-NX group (n=287)
Treatment-emergent adverse events		
Participants with one or more treatment-emergent adverse event*	111	141
Number of treatment-emergent adverse events	247	334
Study medication discontinued due to adverse event	6	8
Type of treatment-emergent adverse event		
Injection site reaction, mild or moderate	46	NA
Gastrointestinal	34	59
Psychiatric disorders	30	29
Injury, poisoning, and procedural complications	23	25
Infections and infestations	22	27
Nervous system disorders	22	28
Treatment-emergent serious adverse events		
Participants with one or more serious adverse event	29	29
Number of treatment-emergent serious adverse events	39	35
Type of treatment-emergent serious adverse event		
Psychiatric disorders	9	11
Infections and infestations	5	6
Death	3	4
Pregnancy	3	4
Overdose events		
Participants with one or more overdose event (all)†	15	8
Participants with one or more overdose event (per protocol)‡	9	7
Number of overdose events (all)§	18	10
Number of overdose events (per protocol)	10	9
Fatal overdose events		
Number of fatal overdose events (all)	2	3
Number of fatal overdose events (per protocol)	2	3

Data are n (%) or N. NA=not applicable. *Treatment emergent is defined as any adverse events that occurred after the study day of induction for those participants inducted onto study medication. †p=0·14 (Fisher's exact). ‡p=0·31 (Fisher's exact). §Four participants reported more than one overdose event. Three of the four participants were randomly assigned to XR-NTX (two of these induction failures, one successfully inducted); each reported two overdose events. One of the four was randomly assigned to BUP-NX (successfully inducted) and reported three overdose events. None of these nine overdoses were fatal.

NCT02032433
This research was supported by grants from the NIDA National Drug Abuse Treatment Clinical Trials Network (CTN): HHSN271201500065C, HHSN271201200017C, U10DA013046, UG1/U10DA013035, UG1/U10DA013034, U10DA013045, UG1/U10DA013720, UG1/U10DA013732, UG1/U10DA013714, UG1/U10DA015831, U10DA015833 – and K24DA022412.

[1]New York University School of Medicine, [2]New York State Psychiatric Institute, [3]Columbia University Medical Center, [4]Tarzana Treatment Centers, [5]Warren Alpert Medical School, Brown University, [6]Stanley Street Treatment and Resources, [7]University of New Mexico School of Medicine, [8]Johns Hopkins University School of Medicine, [9]Maryland Treatment Centers, [10]Gateway Community Services, [11]The Emmes Corporation, [12]National Institute on Drug Abuse, [13]Evergreen Treatment Services, [14]Maryhaven, Inc.