Rethinking Medication Treatment for Opioid Use Disorder

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Objectives

At the conclusion of this activity, participants will be able to…

1. Describe recent research comparing the effectiveness of buprenorphine/naloxone to injectable naltrexone
2. Explain both the benefits and challenges of novel formulations of medications for opioid use disorder (OUD)
3. Apply information on new and old medications for OUD to treatment decisions for the care of individual patients

Outline

1. Extended-release (XR) Naltrexone
2. Naltrexone-Assisted Detoxification
3. Buprenorphine Implant
4. Buprenorphine Injectables
5. Role of Psychosocial Interventions in MAT
6. Discussion

Disclosures

- JR - Johnson & Johnson (stockholder)
- JR - General Electric (stockholder)

XR-Naltrexone and Buprenorphine/Naloxone

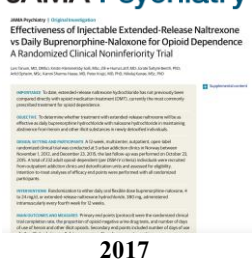
XR-NTX
- Vivitrol®
- Naltrexone - Opioid Antagonist
- Injectable depot
- FDA approval:
  Alcohol use disorder (2006)
  Opioid use disorder (2010)

7-14 **days** abstinence from opioids

BUP-NX
- Suboxone®
- Buprenorphine - Opioid Partial Agonist
- Sublingual tabs or films
- FDA approval:
  Opioid use disorder (2002)

8-36 **hours** abstinence from opioids

JAMA Psychiatry


Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence
A Randomized Clinical Noninferiority Trial

2017

THE LANCET


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

2017

Noninferiority Trial: XR-NTX vs BUP-NX

Design:
12-week, multicenter, open-label, randomized clinical noninferiority trial

Setting:
Norway
5 urban outpatient addiction clinics

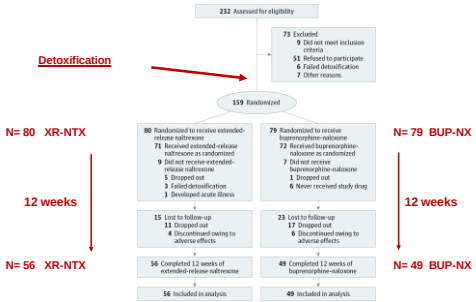
Participants:
DSM-IV Opioid Dependence
Newly detoxified individuals
N=159 randomized

Interventions:
- BUP-NX, flex dosing, 4-24 mg/d
- XR-NTX 380mg q4weeks

Outcome Measures:
Primary - Retention, opioid-neg urines, days of opioid use
Secondary – other substance use, satisfaction, craving, safety, mental health

Funding:
Research Council of Norway, Western Norway Regional Health Authority, and Universities

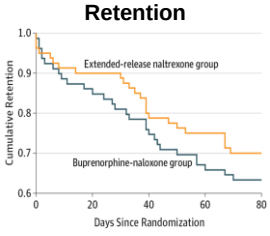
Tanum et al. JAMA Psychiatry. 2017.



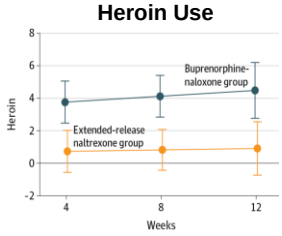
Tanum et al. JAMA Psychiatry. 2017.

Primary Outcome Measures

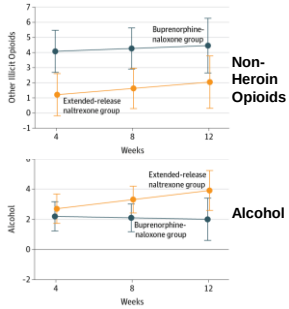
Retention



Heroin Use

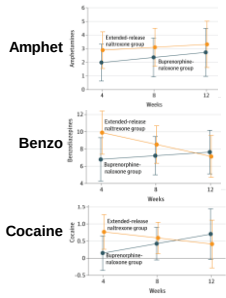


Tanum et al. JAMA Psychiatry. 2017.

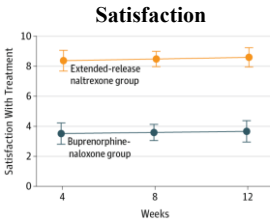


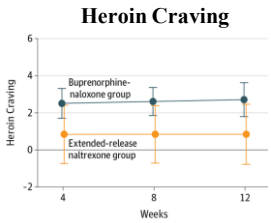
Non-Heroin Opioids

Alcohol



Tanum et al. JAMA Psychiatry. 2017.





Tanum et al. JAMA Psychiatry. 2017.

Randomized Comparative Effectiveness Trial: BUP-NX vs XR-NTX

Design:
24-week, multicenter, open-label, randomized comparative effectiveness trial

Setting:
United States
8 inpatient facilities, then followed as outpatients

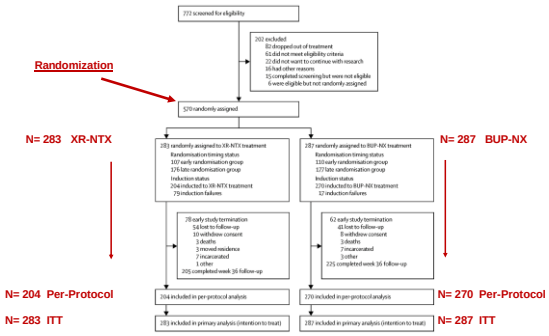
Participants:
DSM-V Opioid Use Disorder
Used non-prescribed opioids in past 30 days
N=570 randomized

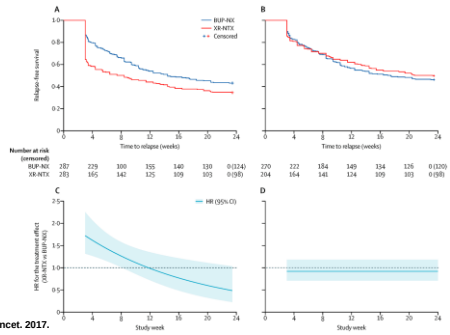
Interventions:
- BUP-NX, 8-24 mg/d
- XR-NTX 380mg q1month

Outcome Measures:
Primary – opioid relapse-free survival
Secondary – proportion inducted onto medication, frequency of opioid use, craving, safety

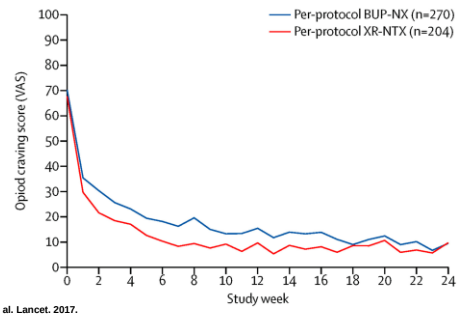
Funding:
NIDA, CTN-0051
Indivior donated Suboxone® (no role in design or manuscript)

Lee et al. Lancet. 2017.



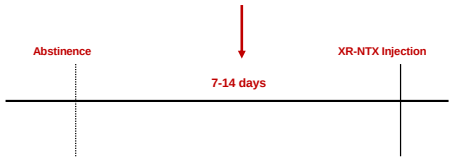


Lee et al. Lancet. 2017.



Lee et al. Lancet. 2017.

The Detox Hurdle



Naltrexone-Assisted Detoxification

Design:
Open-label, RCT, 2:1 randomization

Setting:
United States, outpatient

Participants:
DSM-IV Opioid Dependence for >6 mo
N=150 randomized in 2:1 ratio

Interventions:
- BUP for 1 day, then ascending doses of oral NTX, then XR-NTX
- BUP taper for 7 days, then 7 days abstinent, then XR-NTX

Outcome Measures:
Primary – Successful XR-NTX induction, follow up for 2nd injection
Secondary – Detox completion, opioid withdrawal, depression, abstinence after 1st XR-NTX injection

Funding:
NIH
Lead author is an employee of Alkermes

The American Journal of Psychiatry

TABLE 1. Outpatient Opioid Detoxification Regimen, by Treatment Arm, in a Study of Oral Naltrexone Versus Buprenorphine as Detoxification Strategies for Extended-Release Injectable Naltrexone Induction in Opioid Dependence

Protocol Day	Naltrexone-Assisted Detoxification	Buprenorphine-Assisted Detoxification
1	Ancillary medications[a] to support abstinence	
2	Buprenorphine, 2 mg sublingually every 1–2 hours, up to 8 mg	
3	(Washout)	Buprenorphine, 6 mg
4	Naltrexone, 1 mg	Buprenorphine, 4 mg
5	Naltrexone, 3 mg	Buprenorphine, 4 mg
6	Naltrexone, 12 mg	Buprenorphine, 2 mg
7	Naltrexone, 25 mg	Buprenorphine, 1 mg
8	Extended-release injectable naltrexone, 380 mg i.m.	
15		Extended-release injectable naltrexone, 380 mg i.m.

[a] Ancillary medications offered included clonidine (0.1 mg q.i.d., plus every 4 hours as needed; maximum daily dose, 1.2 mg), clonazepam (0.5 mg q.i.d.; maximum daily dose, 2.0 mg), prochlorperazine (10 mg t.i.d.), trazodone (100 mg h.s.), and zolpidem (10 mg h.s.).

Results

Primary Outcome Measures:

XR-NTX Induction:
NTX-assisted detox: **56.1% (N=72)**
BUP detox: **32.7% (N=17)**

2nd XR-NTX Injection:
NTX-assisted detox: **50% (N=49)**
BUP detox: **26.9% (N=14)**

Secondary Outcome Measures:

Proportion of Adverse Events:
No significant differences

8-day Detox Completion:
No significant differences

Opioid Withdrawal:
Mostly comparable

Abstinence at Weeks 4&5 after XR-NTX:
NTX-assisted detox: 78.2% (N=43)
BUP detox: 88.2% (N=15)

Buprenorphine Implant & Injection

Buprenorphine Implant

- Brand: Probuphine®
- Delivery: 4 subdermal implants
- Duration: six months
- FDA approved for opioid use disorder (May 2016)

Buprenorphine Injection

- Brand: Sublocade™
- Delivery: Abdominal subcutaneous injection
- Duration: one month
- FDA approved for opioid use disorder (Nov 2017)

Buprenorphine Implant

Implant:

- Sterile, soft, flexible, ethylene vinyl acetate (EVA) rod
- 26mm in length, 2.5mm in diameter
- Contains 74.2mg buprenorphine (equivalent to 80mg buprenorphine hydrochloride)

Image courtesy of Braeburn Pharmaceuticals

PROBUPHINE® [package insert]. Princeton NJ: Braeburn Pharmaceuticals; 2016

Buprenorphine Implant

Treatment Requirements:

- Sustained prolonged clinical stability on transmucosal buprenorphine, considering:
  - Period free from illicit opioids
  - Living environment
  - Structured activity/job
  - Consistency with therapy, peer support, clinic visits
  - Minimal cravings
  - Period without hospitalizations
- Maintenance dose of 8mg per day or less of a buprenorphine-containing product
- Stable transmucosal dose for three months or longer without supplemental dosing

PROBUPHINE® [package insert]. Princeton NJ: Braeburn Pharmaceuticals; 2016

Buprenorphine Implant

Implantation:

- Each dose consists of four implants
- These are inserted subdermally in the inner aspect of the upper arm
- Must be removed after six months
- Cannot reuse an implant site
- No current research on the safety of using another area on a previously used arm or another part of the body (limits treatment to six months per arm)

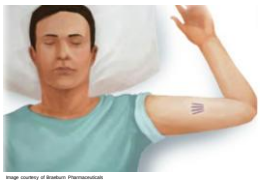


Image courtesy of Braeburn Pharmaceuticals

PROBUPHINE® [package insert]. Princeton NJ: Braeburn Pharmaceuticals; 2016

Buprenorphine Implant

Provider Requirements:

- Must have a buprenorphine waiver
- Must enroll in risk evaluation and mitigation strategy (REMS) program
- Prescribers must participate in a live prescriber training
- Providers who wish to perform implantation/removal must…
  - attend a live training
  - demonstrate procedural competency
  - have performed a qualifying surgical procedure within the past three months
- Product is only distributed to certified prescribers

PROBUPHINE® [package insert]. Princeton NJ: Braeburn Pharmaceuticals; 2016

Randomized Trial: BUP Implant vs BUP-NX vs Placebo

Design:
- 24-week, multicenter, double-blind, randomized clinical noninferiority trial

Setting:
- 20 U.S. addiction treatment centers

Participants:
- 18-65 with DSM-IV Opioid Dependence
- Excluded if other SUD or buprenorphine / methadone treatment in past 90 days
- N=287 randomized

Interventions:
- Open label induction phase of BUP-NX to 12-16mg/d
- Randomized 2:1:2 to four BUP implants, four placebo implants, or open label BUP-NX 12-16mg

Outcome Measures:

Primary - Percentage opioid-neg urines during weeks 1-24

Secondary – opioid neg urines wks 1-16 and 17-24, study completion, withdrawal, craving

Rosenthal RN, et al. Buprenorphine implants for treatment of opioid dependence: randomized comparison to placebo and sublingual buprenorphine/naloxone. Addiction 108:2141-2149, 2013.

Randomized Trial: BUP Implant vs BUP-NX vs Placebo

Results:
- Percentage of opioid neg urines was similar for BUP implant (31.2%) and BUP-NX (33.5%), both superior to placebo (13.4%)
- Study completion similar for BUP implant (64%) and BUP-NX (64%)
- Subjective withdrawal symptoms greater for BUP implant vs BUP-NX.
- Supplemental BUP-NX was used by 39.5% of subjects in the implant group

Conclusions:
- BUP implant superior to placebo in reducing illicit use and retention
- Non-inferior to sublingual BUP-NX

Limitations:
- Open-label BUP-NX group, so not fully blinded
- Excluded other substance use disorders, recent methadone / BUP, chronic pain requiring opioid analgesics
- Rescue BUP-NX was used across all groups making comparisons difficult

Rosenthal RN, et al. Buprenorphine implants for treatment of opioid dependence: randomized comparison to placebo and sublingual buprenorphine/naloxone. Addiction 108:2141-2149, 2013.

Randomized Trial: BUP Implant vs BUP-NX

Design:
- 26-week, multicenter, double-blind, double-dummy randomized clinical trial

Setting:
- 21 U.S. addiction treatment centers

Participants:
- 18-65 with DSM-IV Opioid Dependence
- SL BUP 8mg or less for 24 weeks with no withdrawal or positive urines x90 days
- Excluded if other SUD
- N=177 randomized

Interventions:
- Randomized 1:1 to SL BUP with placebo implants or BUP implants with placebo SL tablets

Outcome Measures:

Primary - 4 of 6 months without opioid positive urine

Secondary – percentage opioid neg urines, abstinence, time to first illicit opioid

Rosenthal RN, et al. Effects of buprenorphine implants on illicit opioid use among abstinent adults with opioid dependence treated with sublingual buprenorphine. JAMA 316(3)282-290, 2016.

Randomized Trial: BUP Implant vs BUP-NX

Results:

- BUP implant was non-inferior to SL BUP in treatment response (4/6 months without opioid positive urine) with 96.4% and 87.6% respectively
- Greater abstinence in BUP implant (85.7%) compared with SL BUP (71.9%)
- No difference in craving or withdrawal

Conclusions:

- BUP implant was non-inferior to SL BUP among adults with OUD on a stable dose of sublingual buprenorphine
- BUP implant resulted in greater abstinence from illicit opioids

Limitations:

- Excluded other substance use disorders
- Rescue SL BUP was used across both groups making comparisons difficult
- Population was highly selective

Rosenthal RN, et al. Effects of buprenorphine implants on illicit opioid use among abstinent adults with opioid dependence treated with sublingual buprenorphine. JAMA 316(3)282-290, 2016.

Buprenorphine Injection

Indications:

- Moderate to severe opioid use disorder
- Have initiated treatment with transmucosal buprenorphine product with dose adjustment for minimum of 7 days

Image courtesy of Indivior Pharmaceuticals

SUBLOCADE™ [package insert]. North, Chesterfield VA: Indivior Inc; 2017

Buprenorphine Injection

Dosing / Administration:

- For abdominal subcutaneous injection only
- Minimum 26 days between doses
- 300mg monthly x2 months, then 100mg monthly
- Maintenance dose can be increased to 300mg for patients without a satisfactory response

Image courtesy of Indivior Pharmaceuticals

SUBLOCADE™ [package insert]. North, Chesterfield VA: Indivior Inc; 2017

Buprenorphine Injection

Provider Requirements:

- Must have a buprenorphine waiver
- Healthcare settings and pharmacies must be certified in Sublocade™ REMS Program
- Healthcare settings and pharmacies must ensure that buprenorphine extended-release is not dispensed to the patient

Image courtesy of Indivior Pharmaceuticals

SUBLOCADE™ [package insert]. North, Chesterfield VA: Indivior Inc; 2017

Buprenorphine Injection

FDA Approval Efficacy Trial:

- NCT02357901
- 24-week randomized, double-blind, placebo-controlled trial of patients with OUD
- 504 pts randomized to:
  - 6 once-monthly 300mg doses
  - 2 once-monthly 300mg doses then 4 once-monthly 100mg doses
  - 6 once-monthly placebo injections
- Prior to first dose, pts initiated on BUP-NX 8-2mg adjusted to 24-6mg over 7-14 days
- Supplemental BUP-NX not allowed after randomization

Image courtesy of Indivior Pharmaceuticals

SUBLOCADE™ [package insert]. North, Chesterfield VA: Indivior Inc; 2017

Buprenorphine Injection

FDA Approval Efficacy Trial:

- Primary outcome was at least 80% opioid-free weeks
- Buprenorphine extended-release groups showed superiority over placebo
- Treatment success:
  - **28.4%** (300mg/100mg)
  - **29.1%** (300mg/300mg)
  - **2%** (placebo)

Image courtesy of Indivior Pharmaceuticals

SUBLOCADE™ [package insert]. North, Chesterfield VA: Indivior Inc; 2017

Medical Management

Most sessions 15-25 minutes, weekly to monthly:

- Monitoring adherence, response to treatment and adverse effects
- Education about AUD/OUD, health consequences and treatments
- Encouragement to abstain from illicit opioids and other addictive substances
- Encouragement to attend and referral to community supports for recovery
- Encouragement to make lifestyle changes that support recovery

VA/DoD SUD Practice Guidelines 2015, pg 23. www.healthquality.va.gov

Research on Medical Management

Four buprenorphine trials suggest that brief, frequent physician medication monitoring visits are equal to, if not more effective than, more intensive drug counseling –

- Fiellin DA, Pantalon M. N Engl J Med 2006; 355(4):365-371
- Weiss RD, Potter JS, Fiellin DA. Arch Gen Psych 2011; 68(12):1268-1246
- Ling W, Hillhouse M, Jenkins J. Addiction 2013; 108(10):1788-1798
- Fiellin DA, Barry D, Sullivan L. Am J Med 2013; Jan 126(1)

Randomized Trials of Medical Management

Study	Site	Time	Inclusion	Exclusion	Results
Fiellin 2006	Primary Care	24 week	8 yr history 15-20% prescription drug use; 30-34% IV use	No serious problems with alc., benzos or sedatives; no serious psych or med problems	Extended counseling no better than MM
Weiss 2011	Psychiatry Clinic	Up to 36 week	Prescription opioid dependence; psychiatrically stable	No IV Heroin; No serious problems with alc., benzos or other drugs	No difference between MM and MM plus opioid counseling
Ling 2013	Research Clinic	18 week	Good medical & psych. health	No serious problems with alc., benzos or other drugs	Adding CBT or CM no better than BUP + MM
Fiellin 2013	Primary Care	24 week	30-35 % IV use; 33-39% prescription drug use	No dependence on alc., benzos or cocaine No serious psychiatric problems	Adding CBT no better than MM

Comments Regarding Medical Management

- Relevant in context of research where patients are also monitored weekly with urine toxicology and study visits
- Patients with severe medical and psychiatric comorbidity were excluded
- Positive outcomes favored patients with no IV drug use and minimal use of alcohol and other substances

Discussion

Modes of Evidence-Based of Counseling Approaches

- Cognitive-Behavioral Therapy
- Motivational Interviewing
- Mutual Support Groups (e.g. AA, NA, Smart Recovery)
- Medication Management

Cognitive-Behavioral Therapy

- Evidence-based on social learning theories and principles of operant conditioning.
- Key Features:
  - An emphasis on functional analysis of drug use, i.e., understanding drug use within the context of its antecedents, behaviors and consequences
  - Skills training, that help the individual recognize:
    - States/ situations of vulnerability to drug use;
    - Strategies to avoid high-risk situations whenever possible
    - Utilize skills to cope effectively with those situations if they are unavoidable

Carrol, 1998, 2005

Motivational Interviewing

- Developed by William Miller and Stephen Rollnick in the 1980's
  - Clinical tool conceptualized for individuals "less ready" for change
- 200 Randomized Controlled Trials & 25,000 citations in literature
- Effectiveness of MI varies widely across counselors, studies, and sites within studies
- Fidelity of delivery affects outcomes

Mutual Support Groups

- Alcoholics Anonymous
  - Founded in 1935
  - Based on a 12-step model of sobriety with a fundamental evoking of God or a Higher Power
- Narcotics Anonymous
  - Founded in 1947
  - Also based on a 12-step model of sobriety with a fundamental evoking of God or a Higher Power
- Self Management and Recovery Training (SMART) Recovery
  - Founded in 1994
  - Is based on Secular principles and uses Stages of change, MI, CBT
  - Recognized by the National Institute on Drug Abuse (NIDA) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as evidence based