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Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

ANOTHER LOOK AT MAT- OPIOIDS

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SEATTLE, WASHINGTON

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Integrated Care Training Program
UW Psychiatry & Behavioral Sciences

project ECHO

GENERAL DISCLOSURES

The University of Washington School of Medicine also gratefully acknowledges receipt of educational grant support for this activity from the Washington State Legislature through the Safety-Net Hospital Assessment, working to expand access to psychiatric services throughout Washington State.

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SPEAKER DISCLOSURES

- ✓ Any conflicts of interest?

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OBJECTIVES

1. To evaluate potential conflicting research and experience with the role of counseling/therapy in Buprenorphine treatment

2. To consider the focus and types of behavioral therapies which might be included in MAT based opioid addiction treatments

3. To discuss on the web format the pros and cons of long acting forms of buprenorphine treatment which are coming available in the next few months

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FIRST– A QUICK REVIEW----

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FOR THOSE WITH SEVERE OPIOID DEPENDENCE ----- WITHDRAWAL ONLY (DETOX) ---VS. MAINTENANCE VS ----BLOCK ?

- Withdrawal Only—
  - High Relapse (90+ %) whether fast or slow Detox
    - Relapse incurred Morbidity, Mortality, Cost
    - Not only costly, but ethical?
- Maintenance
  - Bup/Ntx- Training certification fits ACO Prim Care
  - Methadone--- only in Federally certified clinics
- Block – Naltrexone
  - Oral– adherence issues, but OK after long term stabilization
  - Injectable– fits in with “abstinence model”, good at inpt DC

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BMJ.

Loss of tolerance and overdose mortality after inpatient opiate detoxification: follow up study.

Strang J McCambridge J Best D Beswick T Bearn J Rees S Gossop M

Med Sci Law.

Mortality following release from prison.

Harding-Pink D

Author information

Abstract

. The mortality rate during the first year after release was about 5 deaths/1000 person years, **a rate over four times the age-adjusted rate in the general population**. **The majority of deaths were due to overdose by opiate drugs among young, frequently imprisoned drug abusers, and occurred within the first few weeks after release**.

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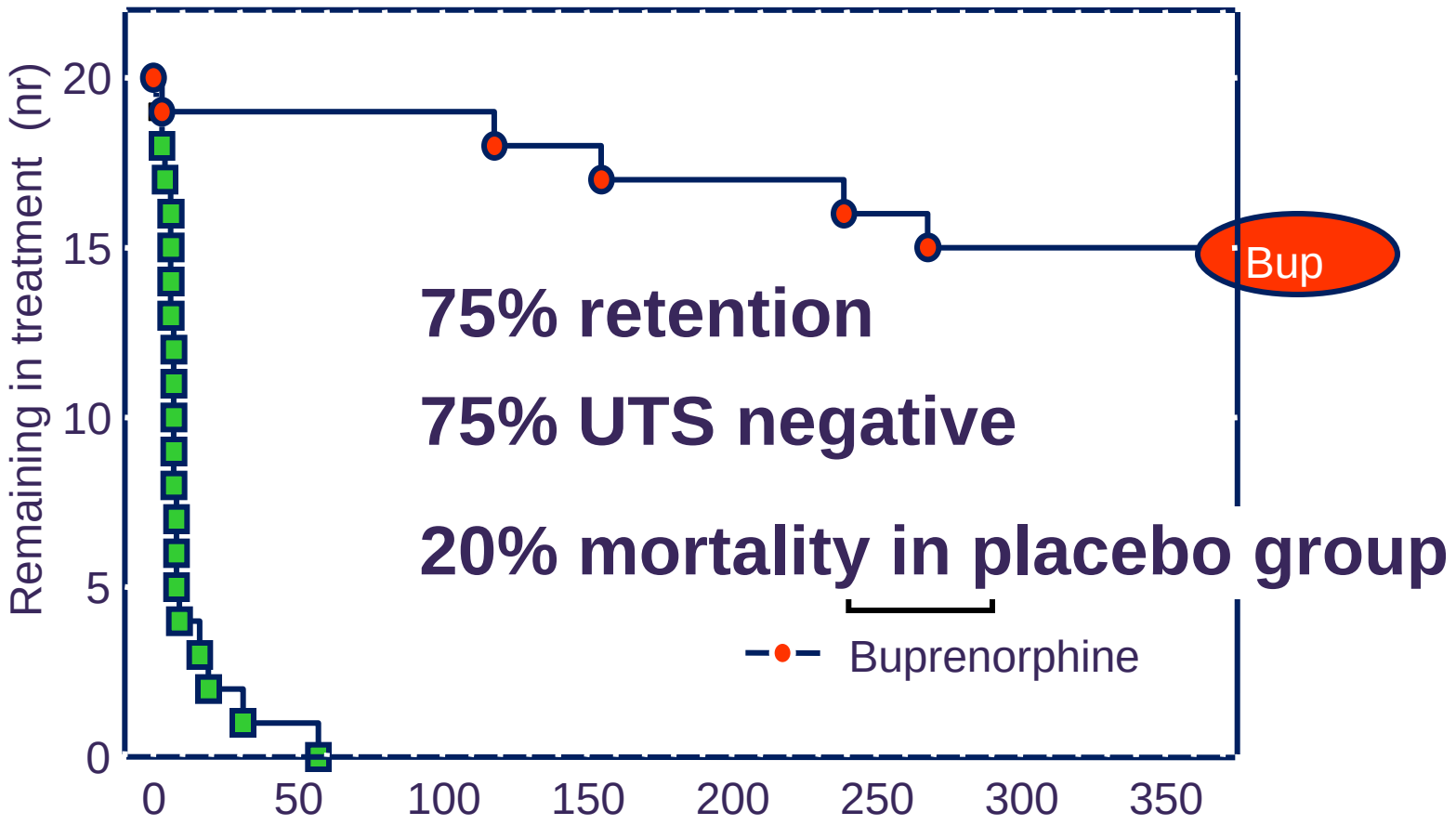
Treatment Retention and Mortality Bup vs Placebo



Kakko J et al. Lancet 2003

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Arch Gen Psychiatry. 2011 Dec;68(12):1238-46. Epub 2011 Nov 7.

Adjunctive Counseling during Brief and Extended Buprenorphine-naloxone Treatment for Prescription Opioid Dependence: a 2-phase Randomized Controlled Trial.

Weiss RD Potter JS Fiellin DA

RESULTS:

Phase 1 (2 week Detox measured at 12 weeks**),**
6.6% (43 of 653) still drug free 10 weeks after detox = 93% Relapse within 2 months off med

Phase 2 (12 week detox) **49.2% successful at end of detox but still on med**
8.6% (31 of 360), still drug free 8 weeks after Detox = 91% Relapse within 2 months off med

No counseling difference in either condition.

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BUT WHAT ABOUT…..

- Are there subsets who do benefit from counseling?
- What types of counseling?
- How to define key Outcomes?
- Does Dose of Bup Matter?
- How effective is Long Acting Injectable Naltrexone?
- What about long acting Injectable Bup ?

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Drug Alcohol Depend. 2014 Jul 1;140:118-22.

Who benefits from additional drug counseling among prescription opioid-dependent patients receiving buprenorphine-naloxone and standard medical management?

Weiss RD, Griffin ML2, Potter JS3, Dodd DR4, Dreifuss JA2, Connery HS2, Carroll KM5.

METHOD:
We conducted a secondary analysis of POATS data to determine whether a subgroup of participants benefited from drug counseling in addition to buprenorphine-naloxone and medical management, **Adequate treatment adherence was defined a priori as attending at least 60% of all offered sessions.**

RESULTS:
Patients who had ever used heroin and received drug counseling were more likely to be successful (i.e., abstinent or nearly abstinent from opioids) than heroin users who received medical management alone, but only if they were adherent to treatment (ie 60% or more sessions) and thus received adequate exposure to counseling **(OR=3.7, p=0.03).**

The association between severity and outcome did not vary by treatment condition for chronic pain or ASI drug severity score.

OR of 3.7 means a 360 % better outcome…that is HUGE

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J Subst Abuse Treat. 2015 Oct;57:89-95.

Buprenorphine Treatment and 12-step Meeting Attendance: Conflicts, Compatibilities, and Patient Outcomes.

Monico LB[1], **Abstract**

Using quantitative (n = 300) and qualitative (n = 20) data collected during a randomized trial of counseling services in buprenorphine treatment, this mixed-methods analysis of African Americans in BMT finds

1. The number of NA meetings attended in the prior 6 months was associated with a **higher rate of retention in BMT (p < .001)**

2. **Higher rate of Heroin/cocaine abstinence at 6 month follow-up (p = .005).**

3. Twelve-step meeting attendance is associated with better outcomes for BMT patients over the first 6 months of treatment. And clinicians should be aware of potential philosophical conflicts between 12-step and BMT approaches.

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Adm Policy Ment Health. 2017 May;44(3):359-364. doi: 10.1007/s10488-017-0793-2.

Individual Placement and Support (IPS) for Methadone Maintenance Therapy Patients: A Pilot Randomized Controlled Trial.

Lones CE[1,2], Bond GR[3], McGovern MP[4], Carr K[5], Leckron-Myers T[5], Hartnett T[5], Becker DR[3].
Author information

Abstract

Individual Placement and Support (IPS) is an evidence-based employment model for people with severe mental illness, but it has not been evaluated for clients enrolled in substance abuse treatment programs.

This study evaluated the effectiveness of IPS for people with opioid use disorders enrolled in an opioid treatment program. Within a randomized controlled experiment, 45 patients receiving methadone maintenance therapy were assigned to either IPS or a 6-month waitlist. The waitlist group received IPS after 6 months. The primary outcome assessed over 1 year compared the attainment of a job for the IPS condition to the waitlist comparison group.

During the first 6 months after enrollment:
11 (50%) active IPS vs 1 (5%) controls gained employment ($X^2 = 12.0$, $p < 0.001$).

Over 12 months of enrollment:
11 (50%) IPS vs 5 (22%) gained employment ($X^2 = 3.92$, $p = 0.07$).

We conclude that IPS holds promise as an employment intervention for people with opioid use disorders in methadone maintenance treatment, but larger trials with longer follow-up are needed.

HOW TO DEFINE OUTCOMES?

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Drug Alcohol Depend. 2010 Jan 1;106(1):56-60. doi: 10.1016/j.drugalcdep.2009.07.013.

Long-term outcomes of office-based buprenorphine/naloxone maintenance therapy.

Parran TV[1],et al

Evaluation of 18-Month outcome data on the office-based use of buprenorphine/naloxone (bup/nx) and the impact of socioeconomic status and other patient characteristics on the duration and clinical effects of bup/nx are reported.

METHODS:

This retrospective chart review and cross-sectional telephone interview provide treatment retention of opioid-dependent patients receiving bup/nx-OMT in an office-based setting.

RESULTS:

110 subjects (67%) completed the interview, 77% remained on bup/nx with no difference in retention between high and low SES groups.

Those on bup/nx at follow-up were more likely to report abstinence, to be affiliated with 12-step recovery, to be employed and to have improved functional status.

BUT WHAT ABOUT
MEDICAL,
FAMILY,
LEGAL,
HOUSING, ETC ?

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WHAT ABOUT DOSE OF BUPRENORPHINE?

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J Addict Dis. 2012;31(1):8-18. doi: 10.1080/10550887.2011.642758.

Effect of buprenorphine dose on treatment outcome.

Fareed A[1], Vayalapalli S, Casarella J, Drexler K.

The goal of this meta-analysis is to provide evidence based information about proper dosing for buprenorphine maintenance treatment to improve treatment outcome. 21 studies included.

The higher buprenorphine dose (16-32 mg per day) predicted better retention in treatment compared with the lower dose (less than 16 mg per day) (P = .009, R(2) adjusted = 0.40), T

The positive urine drug screens for opiates predicted dropping out of treatment (P = .019, R(2) Adjusted = 0.40).

Retention in treatment predicted less illicit opioid use (P = .033, R(2) Adjusted = 0.36), and the

positive urine drug screens for cocaine predicted more illicit opioid use (P = .021, R(2) Adjusted = 0.36).

Strong evidence exists based on 21 randomized clinical trials that the higher buprenorphine dose may improve retention in buprenorphine maintenance treatment.

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Subst Abuse 2017 Oct 4;11:1178221817731320. doi: 10.1177/1178221817731320. eCollection 2017.

Buprenorphine/Naloxone Maintenance Therapy: an Observational Retrospective Report on the Effect of Dose on 18 months Retention in an Office-Based Treatment Program.

Author information

DESIGN SETTING AND PARTICIPANTS:

Case series, at an urban hospital-based primary care clinic providing OBOMT to 157 opiate-dependent, low socioeconomic status, uninsured, nonhomeless patients.

INTERVENTION:

The OBOMT program operated by a comprehensive sobriety treatment program experienced State funding cuts. Thus, after 2 years, the program was required by the State funder to decrease the buprenorphine maintenance dose from 16 to 8 mg/d for all new admissions. We report on patient retention before and after dose reduction.

RESULTS:

No significant differences in patient retention were observed between the 16 and 8 mg/d patient cohorts.

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INJECTABLE NALTREXONE:

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JAMA Psychiatry. 2017 Oct 18. doi: 10.1001/jamapsychiatry.2017.3206. [Epub ahead of print]

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

Tanum L[1,2], Solli KK[1], Latif ZE[2], Benth JŠ[3,4], Opheim A[5,6], Sharma-Haase K[1,7], Krajci P[8], Kunøe N[1].
Author information

Abstract

OBJECTIVE:

- To determine whether treatment with extended-release naltrexone will be as effective as daily buprenorphine hydrochloride with naloxone hydrochloride in maintaining abstinence from heroin and other illicit substances in newly detoxified individuals.

- **DESIGN, SETTING AND PARTICIPANTS:**
- A 12-week, multicenter, outpatient, open-label randomized clinical trial was conducted at 5 urban addiction clinics in Norway between November 1, 2012, and December 23, 2015; the last follow-up was performed on October 23, 2015. A total of 232 adult opioid-dependent (per DSM-IV criteria) individuals were recruited from outpatient addiction clinics and detoxification units and assessed for eligibility. Intention-to-treat analyses of efficacy end points were performed with all randomized participants.

- **Injectable Naltrexone compared to Buprenorphine showed:**
  - **>less Heroin use at 4, 8, and 12 weeks (p<0.001)**
  - **>less other opioid use use at 4, 8, and 12 weeks p<0.05)**

Completion rates were close but favored Inj Naltrex.

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JN The JAM

From: **The Effectiver**
Opioid Dependence

JAMA Psychiatry. Publi

Table 2. Days of Use of Heroin and Other Illegal Substances Assessed at Weeks 4, 8, and 12[a]

Time Point	Extended-Release Naltrexone		Buprenorphine-Naloxone		Extended-Release Naltrexone vs Buprenorphine-Naloxone	
	No. of Participants	Mean (SD)[b]	No. of Participants	Mean (SD)[b]	Mean Difference (95% CI)[c]	*P* Value[c]
Heroin Use						
Week 4	63	0.8 (1.5)	65	3.7 (7.4)	−3.0 (−4.9 to −1.2)	.001
Week 8	59	0.8 (1.9)	55	4.4 (9.1)	−3.3 (−5.1 to −1.5)	<.001
Week 12	57	1.1 (2.3)	50	4.1 (8.4)	−3.6 (−6.0 to −1.2)	.003
Other Illicit Opioids Use						
Week 4	63	1.2 (2.2)	65	4.2 (7.9)	−2.9 (−4.8 to −0.9)	.004
Week 8	59	1.8 (4.7)	55	4.0 (8.5)	−2.6 (−4.6 to −0.7)	.007
Week 12	57	2.0 (5.0)	50	4.4 (8.7)	−2.4 (−4.9 to 0.1)	.06
Cannabis Use						
Week 4	63	6.7 (9.8)	65	5.3 (9.4)	1.4 (−1.8 to 4.7)	.38
Week 8	59	6.4 (8.9)	55	4.8 (8.5)	1.6 (−1.3 to 4.6)	.28
Week 12	57	7.5 (9.7)	50	5.1 (9.6)	1.8 (−1.5 to 5.1)	.27
Amphetamine Use						
Week 4	63	2.9 (6.0)	65	2.0 (5.3)	9 (−1.0 to 2.8)	.35
Week 8	59	3.4 (7.0)	55	1.9 (5.4)	8 (−1.2 to 2.7)	.46
Week 12	57	3.4 (7.5)	50	2.1 (5.7)	0.6 (−1.9 to 3.0)	.64
Cocaine Use						
Week 4	63	0.8 (3.2)	65	0.1 (0.3)	0.6 (−0.1 to 1.3)	.09
Week 8	59	0.5 (1.8)	55	0.7 (3.4)	0.2 (−0.5 to 0.8)	.62
Week 12	57	0.5 (1.8)	50	0.6 (2.9)	−0.3 (−1.3 to 0.7)	.58
Benzodiazepine Use						
Week 4	63	1.1 (11.2)	65	6.9 (1.3)	3.1 (−0.5 to 6.7)	.09
Week 8	59	8.0 (11.3)	55	6.6 (9.4)	1.3 (−1.8 to 4.4)	.41
Week 12	57	6.7 (9.5)	50	7.3 (1.4)	−0.5 (−4.0 to 3.0)	.78
Alcohol Use for Intoxication						
Week 4	63	3.0 (4.4)	65	2.3 (3.8)	0.5 (−0.9 to 1.9)	.47
Week 8	59	2.9 (4.6)	55	1.9 (3.1)	1.2 (−0.1 to 2.5)	.06
Week 12	57	4.4 (7.3)	50	2.1 (3.6)	1.9 (−0.02 to 3.8)	.05

[a] Hallucinogens were used once or twice by 5 participants receiving extended-release naltrexone hydrochloride and 4 receiving buprenorphine-naloxone hydrochloride.

[b] Means and SDs are descriptive numbers, not adjusted for repeated measurements or for site effects.

[c] Results of linear mixed model for difference between groups; adjusted for repeated measurements and site effect; random effect for time included.

Table Title:

Days of Use of Heroin and Other Illegal Substances Ass

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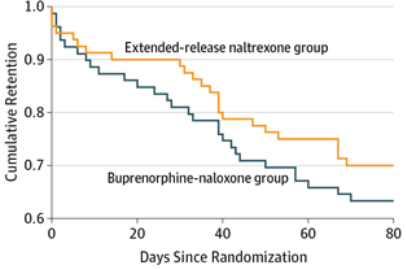
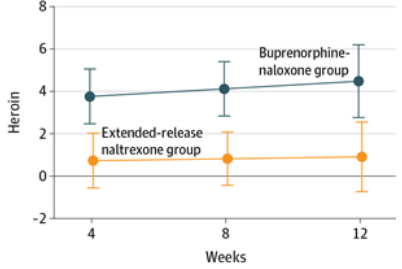
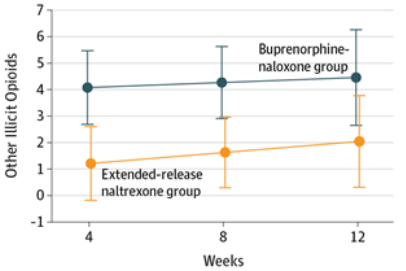
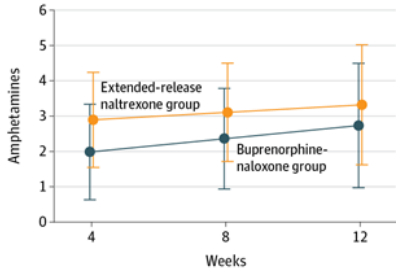


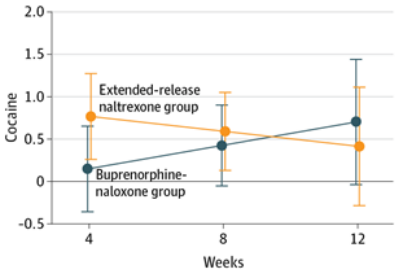
No. at risk

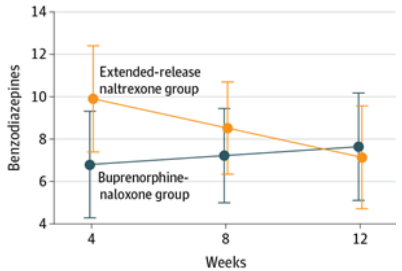
Buprenorphine-naloxone group	78	67	59	52	50
Extended-release naltrexone group	78	73	64	60	56

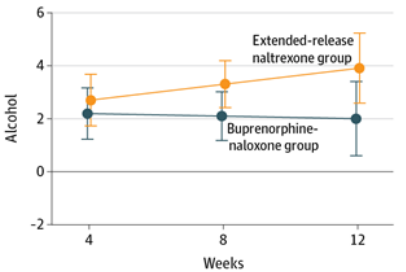


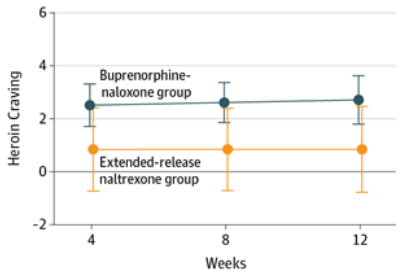


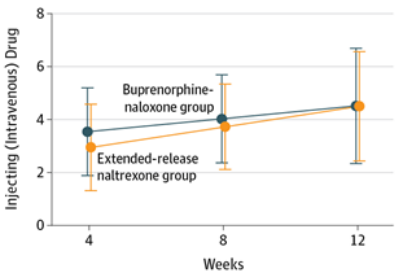


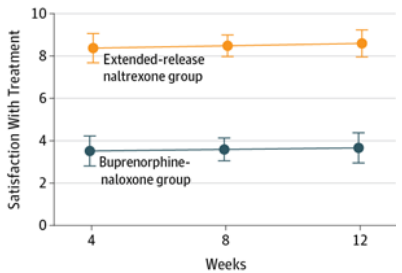












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AM J PSYCHIATRY. 2017 MAY 1;174(5):459-467.

LONG-ACTING INJECTABLE NALTREXONE INDUCTION: A RANDOMIZED TRIAL OF OUTPATIENT OPIOID DETOXIFICATION WITH NALTREXONE VERSUS BUPRENORPHINE.

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:**
- participants assigned to naltrexone-assisted detoxification were significantly more likely to be
  - successfully inducted to XR-naltrexone (56.1% compared with 32.7%)
  - to receive the second injection at week 5 (50.0% compared with 26.9%).

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AM J PSYCHIATRY. 2017 MAY 1;174(5):459-467.

LONG-ACTING INJECTABLE NALTREXONE INDUCTION: A RANDOMIZED TRIAL OF OUTPATIENT OPIOID DETOXIFICATION WITH NALTREXONE VERSUS BUPRENORPHINE.

SULLIVAN M[1], BISAGA A[1]

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.

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JAMA Psychiatry. 2017 Sep 1;74(9):885-893. doi: 10.1001/jamapsychiatry.2017.1838.

Efficacy of Tramadol Extended-Release for Opioid Withdrawal: A Randomized Clinical Trial.

Dunn KE[1], Tompkins DA[1], Bigelow GE[1], Strain EC[1].
Author information

RESULTS:

- Of the 103 participants, 88 (85.4%) were men and 43 (41.7%) were white; mean (SD) age was 28.9 (10.4) years.

- Buprenorphine participants (28 [90.3%]) were significantly more likely to be retained at the end of the taper compared with clonidine participants (22 [61.1%]);

- Tramadol ER retention was intermediate and did not differ significantly from that of the other groups (26 [72.2%]; $\chi 2 = 8.5$, $P = .01$).

CONCLUSIONS AND RELEVANCE:

- The results of this trial suggest that tramadol ER is more effective than clonidine and comparable to buprenorphine in reducing opioid withdrawal symptoms during a residential tapering program.

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The JAMA Network

From: Efficacy of Tramadol Extended-Release for Opioid Withdrawal: A Randomized Clinical Trial

JAMA Psychiatry. 2017;74(9):885-893. doi:10.1001/jamapsychiatry.2017.1838

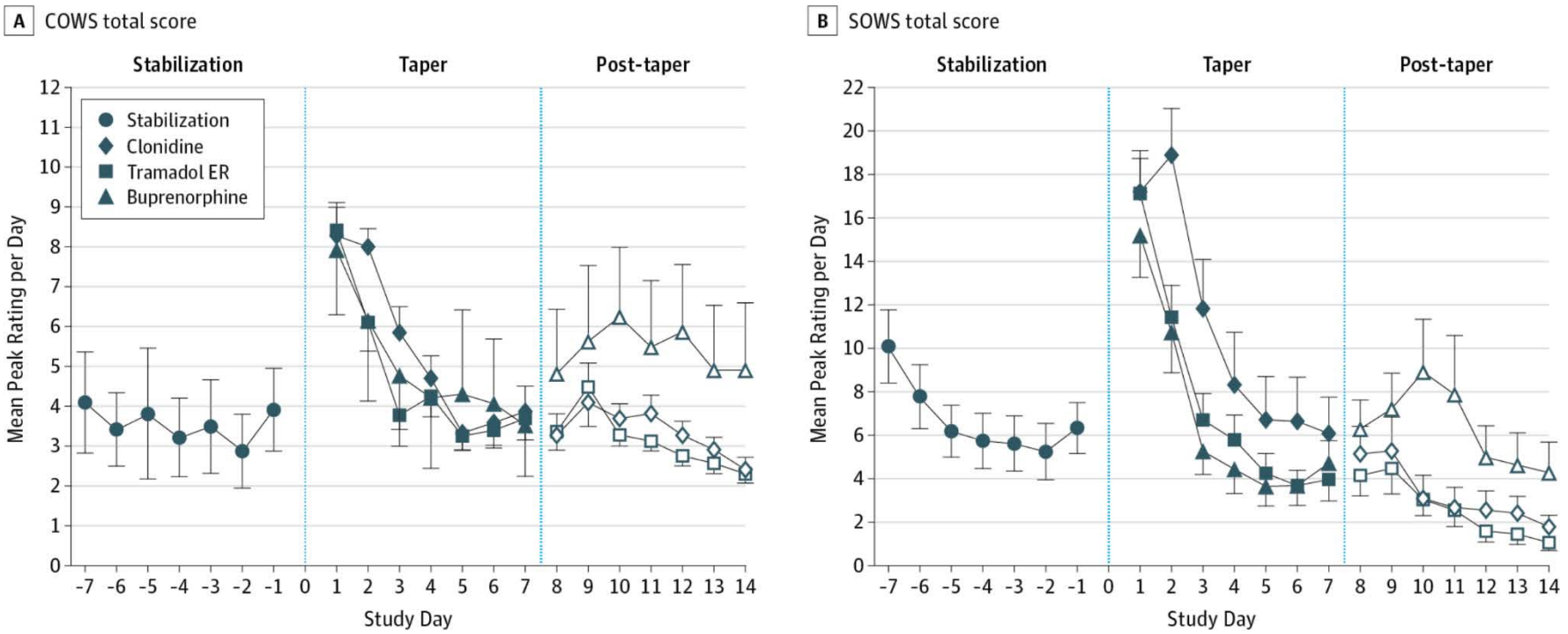

Figure Legend:

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JAMA Pediatr. 2017 Aug 1;171(8):747-755. doi: 10.1001/jamapediatrics.2017.0745.

Trends in Receipt of Buprenorphine and Naltrexone for Opioid Use Disorder Among Adolescents and Young Adults, 2001-2014.

Hadland SE[1,2,3]**DESIGN, SETTING, AND PARTICIPANTS:**
was conducted using deidentified **data** from a national commercial insurance database

RESULTS:

Among 20 822 youth diagnosed with OUD (0.2% of the 9.7 million sample),

13 698 (65.8%) were male and 17 119 (82.2%) were non-Hispanic white. Mean (SD) age was 21.0 (2.5) years at the first observed diagnosis.

The diagnosis rate of OUD increased nearly 6-fold from 2001 to 2014 (from 0.26 per 100 000 person-years to 1.51 per 100 000 person-years).

Overall, 5580 (26.8%) youth were dispensed a medication within 6 months of diagnosis, with 4976 (89.2%) of medication-treated youth receiving buprenorphine and 604 (10.8%) receiving naltrexone.

Medication receipt increased more than 10-fold, from 3.0% in 2002 (when buprenorphine was introduced) to 31.8% in 2009, but declined in subsequent years (27.5% in 2014).

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LONG ACTING BUPRENORPHINE

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JAMA. 2016 Jul 19;316(3):282-90. doi: 10.1001/jama.2016.9382.

Effect of Buprenorphine Implants on Illicit Opioid Use Among Abstinent Adults With Opioid Dependence Treated With Sublingual Buprenorphine: A Randomized Clinical Trial.

Rosenthal RN[1],et al

DESIGN, SETTING, AND PARTICIPANTS:

Of 177 participants (mean age, 39 years; 40.9% female), 90 were randomized to sublingual buprenorphine with placebo implants and 87 to buprenorphine implants with sublingual placebo; 165 of 177 (93.2%) completed the trial.

Eighty-one of 84 (96.4%) receiving buprenorphine implants and 78 of 89 (87.6%) receiving sublingual buprenorphine were responders, an 8.8% difference (1-sided 97.5% CI, 0.009 to ∞; P < .001 for noninferiority).

This study showed that IMPLANT was not inferior but also not substantially superior to oral Bup in highly motivated already stable patients

Over 6 months, 72 of 84 (85.7%) receiving buprenorphine implants and 64 of 89 (71.9%) receiving sublingual buprenorphine maintained opioid abstinence (hazard ratio, 13.8; 95% CI, 0.018-0.258; P = .03).

Non-implant-related and implant-related adverse events occurred in 48.3% and 23% of the buprenorphine implant group and in 52.8% and 13.5% of participants in the sublingual buprenorphine group, respectively.

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JAMA Psychiatry. 2017 Sep 1;74(9):894-902. doi: 10.1001/jamapsychiatry.2017.1874.

Effect of Buprenorphine Weekly Depot (CAM2038) and Hydromorphone Blockade in Individuals With Opioid Use Disorder: A Randomized Clinical Trial.

Walsh SL[1], et a;

Buprenorphine is an efficacious, widely used treatment for opioid use disorder (OUD). Daily oral transmucosal formulations can be associated with misuse, diversion, and nonadherence; these limitations may be obviated by a sustained release formulation.

INTERVENTIONS:

A total of five 3-day test sessions evaluated the response to hydromorphone (0, 6, and 18 mg intramuscular in random order; 1 dose/session/day). After the first 3-day session (ie, qualification phase), participants were randomized to either CAM2038 weekly at 24 mg (n = 22) or 32 mg (n = 25); the assigned CAM2038 dose was given twice, 1 week apart (day 0 and 7). Four sets of sessions were conducted after randomization (days 1-3, 4-6, 8-10, and 11-13).

MAIN OUTCOMES AND MEASURES:

The primary end point was maximum rating on the visual analog scale for drug liking. Secondary end points included other visual analog scale (eg, high and desire to use), opioid withdrawal scales, and physiological and pharmacokinetic outcomes.

CONCLUSIONS AND RELEVANCE:

CAM2038 weekly, 24 and 32 mg, was safely tolerated and produced immediate and sustained opioid blockade and withdrawal suppression.

The results support the use of this depot formulation for treatment initiation and stabilization of patients with OUD, with the further benefit of obviating the risk for misuse and diversion of daily buprenorphine while retaining its therapeutic benefits.

RRies 2014

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More weekly and monthly Buprenorhine Injections coming --within months

A new buprenorphine preparation (RBP-6000; Indivior, Richmond, VA, USA) that has been developed for monthly administration contains 200 mg/mL of buprenorphine base in a precipitation delivery system of biodegradable polylactide-co-glycolide polymer and biocompatible solvent (N-methyl-pyrrolidone), which in contact with water, solidifies at the surface in the subcutaneous space72 and provides sustained release of buprenorphine over a minimum of 28 days through diffusion and polymer degradation.73

A depot buprenorphine preparation that uses a different delivery strategy from poly lactide-coglycolide microcapsules is based on the characteristics of certain low-viscosity lipids in contact with aqueous media to self-assemble into reversed-phase "water-in-oil" nonlamellar liquid crystal nanoparticle gels.77,78 The preparation CAM2038 uses this technology (FluidCrystal®; Camurus AB, Lund, Sweden) to deliver buprenorphine in a low-viscosity two-lipid medium that can be delivered through a small 23-gauge needle as a premixed weekly or monthly subcutaneous injection

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Arch Gen Psychiatry.
2012 Sep;69(9):973-81. **/archgenpsychiatry.2012.1a**.

Randomized trial of long-acting sustained-release naltrexone implant vs oral naltrexone or placebo for preventing relapse to opioid dependence.

Krupitsky E[1],

CONCLUSIONS The implant is more effective than oral naltrexone or placebo. More patients in the NI+OP than in the other groups develop wound infections or local irritation, but none are serious and all resolve with treatment. TRIAL REGISTRATION clinicaltrials.gov Identifier:

** Implant is NOT available in the USA but is reported to block between 60-90 days

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LONG ACTING BUP

- To date no studies have shown superior but studies not yet done
- Will probably be more expensive
- But we all know patients with hugely variable adherence
- Who should get it?
  - Only stable (as in the studies)?
  - Unstable frequent relapsers ?
  - Pain?
  - Others?

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ON BUP BUT…. CONTINUED OTHER DRUG USE?

- How about two “Tracks” with flexibility between
  - **Recovery Track** members are motivated to
    - Give up ALL illegal drugs/alcohol
    - Use recovery groups and 12 step to work on
      - Honesty, Responsibility, Dependability
      - Move away from using “friends”
      - Work on housing, jobs, education etc
  - **Harm Reduction Track**
    - Want to reduce or maybe give up Opioids
    - Unable to stay away from opioids, meth, benzos etc
    - May also have major mental illness
    - Need Bup and other meds to increase chances of staying alive

RRies 2017

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YOUR CASE EXAMPLES:

- 1.
- 2.
- 3.

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