Drug Use Research & Management Program
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Class Update: Treatment for Opioid Use Disorder

Month/Year of Review: January 2015
PDL Class: Opioid Dependence
Literature Search End Date: October 2014

Date of Last Review: July 2013
Source Document: OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: buprenorphine sublingual tablets, buprenorphine/naloxone sublingual tablets, and buprenorphine/naloxone sublingual film (Suboxone®)
- Non-Preferred Agents: naltrexone extended-release injection (Vivitrol®), buprenorphine/naloxone buccal film (Bunavail®)

Research Questions:

- Is there any new comparative evidence of meaningful difference in efficacy/effectiveness for different drugs and formulations approved to treat opioid dependence?
- Is there any new comparative evidence of meaningful difference in safety for different drugs and formulations approved to treat opioid dependence?
- Are there any subpopulations in which a particular drug or formulation approved for opioid dependence may be more effectives or more safe?

Previous Conclusions and Recommendations:

- There is moderate level evidence that buprenorphine is an effective intervention for maintenance treatment of opioid dependence/addiction with or without adjunctive counseling.
- All buprenorphine and buprenorphine/naloxone products should be preferred agents; continue requiring prior authorization criteria to ensure appropriate diagnosis and prescribing privileges.
- There is moderate level evidence that when compared to placebo for the treatment of opioid dependence, naltrexone extended-release injectable suspension is associated with reduced opioid use after detoxification and improves abstinence in patients when studied for 24 weeks in combination with drug counseling.
- Retain naltrexone extended-release injections as non-preferred on PDL for the treatment of opioid dependence and require prior authorization criteria to ensure appropriate diagnosis and prescribing privileges, to verify the patient is unable to tolerate oral treatment for opioid dependence, is enrolled in a comprehensive treatment program that includes a psychosocial support system, and is opioid-free for at least 7 days prior to initiating therapy.

PA Criteria: Prior authorization (PA) criteria are currently in place for buprenorphine, buprenorphine/naloxone, and extended-release naltrexone (**Appendix 1**).

Conclusions and Recommendations:

- New evidence is still insufficient to determine if there is any difference in efficacy/effectiveness or safety between different opioid dependence treatments, including different buprenorphine formulations.
- New evidence is insufficient to determine if a specific subpopulation may benefit more with a specific drug or formulation approved for opioid dependence.
- Evaluate comparative costs in the executive session.

Methods:

A PubMed search was conducted using the following search terms: opioid dependence, methadone, buprenorphine, naloxone, and naltrexone. The search was limited to comparative randomized controlled trials (RCTs), systematic review, English language, and studies conducted in humans since the last literature search was conducted in preparation for P&T Committee review until the second week of October 2014. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

New Systematic Reviews:

Since the last evidence review, there were several meta-analyses and systematic reviews conducted. Please see **Appendix 2** for abstracts.

A Cochrane Review by Perry, et al.[2] examined the effectiveness of pharmacological interventions for drug-using offenders in reducing criminal activity and/or drug use. Eleven trials evaluating a total of 2,678 participants were evaluated. Nine of the 11 studies primarily studied male subjects. Pharmacological interventions (buprenorphine, methadone and naltrexone) were compared to non-pharmacological therapy (e.g., counseling) and then methadone was compared to buprenorphine, diamorphine and naltrexone. The methodological trial quality was poorly described and most study methodologies were unclear to the reviewers. The largest threats to risk of bias were generated through inappropriate blinding (performance and assessment bias) and incomplete outcome data (attrition bias). When combined, the results suggest that pharmacological interventions significantly reduce subsequent drug use using biological measures such as urine drug tests or hair sample drug concentrations (relative risk (RR) 0.71, 95% confidence interval (CI) 0.52 to 0.97, three studies, 300 participants), self-reported dichotomous drug use data (i.e., yes/no) (RR 0.42, 95% CI 0.22 to 0.81, three studies, 317 participants) and continuous measures (i.e. mean days of drug use) (MD -59.66, 95% CI -120.60 to 1.28, one study, 51 participants). Criminal activity was significantly reduced favoring the dichotomous measures of re-arrest, (RR 0.60, 95% CI 0.32 to 1.14, one study, 62 participants), re-incarceration (RR 0.33, 95% CI 0.19 to 0.56, three studies, 142 participants) and continuous measures (MD -74.21, 95% CI -133.53 to -14.89, one study, 51 participants). Findings on the effects of individual pharmacological interventions on drug use and criminal activity yielded mixed results. Buprenorphine compared to non-pharmacological treatment tended to favor buprenorphine, but not significantly, with self-reported drug use (RR 0.58, 95% CI 0.25 to 1.35, one study, 36 participants). There was a significant reduction for self-reported dichotomous drug use with methadone and cognitive behavioral skills compared to standard psychiatric services (RR 0.43, 95% CI 0.33 to 0.56, one study, 253 participants) but not for self-reported continuous data (MD -0.52, 95% CI -1.09 to 0.05, one study, 51 participants) or re-incarceration (RR 1.23, 95% CI 0.53 to 2.87). Naltrexone was favored significantly over routine parole and probation for re-incarceration (RR 0.36, 95% CI 0.19 to 0.69, two studies 114 participants) but no data were available on drug use. No significant differences were found when methadone was compared to buprenorphine in regard to self-reported dichotomous drug use (RR 1.23, 95% CI 0.86 to 1.76, one study, 193 participants), continuous measures of drug use (MD 0.70, 95% CI -5.33 to 6.73) or criminal activity (RR 1.25, 95% CI 0.83 to

1.88). Similar results were found for comparisons of methadone with diamorphine, with no significant differences in self-reported dichotomous drug use that led to arrest (RR 1.25, 95% CI 1.03-1.51, one study, 825 participants), and when compared to naltrexone, with no significant differences in dichotomous measures of re-incarceration (RR 1.10, 95% CI 0.37 to 3.26, one study, 44 participants) and continuous outcome measures of crime (MD -0.50, 95% CI -8.04 to 7.04) or self-reported drug use (MD 4.60, 95% CI -3.54 to 12.74).

A Cochrane Review by Mattick, et al.[3] evaluated buprenorphine maintenance treatment compared to placebo or methadone maintenance treatment for opioid dependence, including its ability to retain people in treatment, suppress illicit drug use, reduce criminal activity and mortality. Thirty-one trials with 5,430 participants were included in the meta-analysis. There was high quality evidence that buprenorphine was superior to placebo in retention of participants in treatment at all doses examined. Specifically, buprenorphine retained participants better than placebo at low doses (2-6 mg daily, RR 1.50, 95% CI 1.19 to 1.88, 5 studies, 1131 participants), at medium doses (7-15 mg daily, RR 1.74, 95% CI 1.06 to 2.87, 4 studies, 887 participants) and at high doses (≥16 mg daily, RR 1.82, 95% CI 1.15 to 2.90, 5 studies, 1001 participants). There was high quality of evidence that buprenorphine at flexible doses adjusted to participant needs was less effective than methadone in retaining participants (RR 0.83; 95% CI 0.72 to 0.95, 5 studies, 788 participants). Low daily doses of methadone (≤40 mg daily) were more likely to retain participants than low doses of buprenorphine (2-6 mg daily) (RR 0.67, 95% CI 0.52 to 0.87, 3 studies, 253 participants). However, the authors found contrary results when higher doses of methadone were compared to buprenorphine. There was no difference between medium doses of buprenorphine (7-15 mg daily) and medium doses of methadone (40-85 mg daily) in terms of therapy retention (RR 0.87, 95% CI 0.69 to 1.10, 7 studies, 780 participants) or in suppression of illicit opioid use as measured by urinalysis (standardized mean difference (SMD) 0.25, 95% CI -0.08 to 0.58, 4 studies, 476 participants) or self-reported illicit opioid use (SMD -0.82, 95% CI -1.83 to 0.19, 2 studies, 174 participants). Similarly, there was no difference between high doses of buprenorphine (≥ 16 mg daily) and high doses of methadone (≥ 85 mg daily) in retention (RR 0.79, 95% CI 0.20 to 3.16) or suppression of self-reported heroin use (SMD -0.73, 95% CI -1.08 to -0.37, 1 study, 134 participants). Few studies reported adverse events; two studies compared adverse events statistically, finding no difference between methadone and buprenorphine except for one study finding more sedation among those using methadone. Based on placebo-controlled trials, the authors concluded buprenorphine is an effective medication in the maintenance treatment of heroin dependence, retaining people in treatment at any dose higher than 2 mg daily, and suppressing illicit opioid use at doses 16 mg daily or higher. However, buprenorphine retains fewer people when doses are flexibly adjusted to meet patient needs or at low fixed doses compared to methadone, though both drugs under these conditions equally suppress illicit opioid use. If fixed medium or high doses are used, buprenorphine and methadone are not different in effectiveness outcomes such as retention in treatment and suppression of illicit opioid use.

A meta-analysis by Larney, et al.[5] assessed the safety and efficacy of naltrexone implants for the treatment of opioid dependence. Outcomes assessed included induction to treatment, retention in treatment, opioid and non-opioid use, adverse events, non-fatal overdose and mortality. Five randomized trials (n = 576) and four non-randomized studies (n = 8,358) were eligible for review. The quality of the evidence ranged from moderate to very low. Naltrexone implants at doses between 1 gram to 2.2 grams were superior to placebo implants (RR 0.57, 95% CI 0.48 to 0.68; k = 2) and oral naltrexone (RR 0.57, 95% CI 0.47 to 0.70; k = 2) in suppressing opioid use. No difference in opioid use measured by either urine drug tests or self-reporting was observed between naltrexone implants and methadone maintenance (SMD -0.33, 95% CI -0.93 to 0.26; k = 1); however, this finding was based on low-quality evidence from one study. The authors concluded better designed research is needed to establish the safety and efficacy of naltrexone implants.

A Cochrane Review by Minozzi, et al.[1] assessed the effectiveness of any maintenance opioid treatment alone or in combination with psychosocial intervention during pregnancy or child birth, compared to either no intervention, another pharmacological intervention or psychosocial intervention alone. Focused endpoints included child health status, neonatal mortality, retaining pregnant women in treatment and reducing the use of substances for opioid-dependent pregnant women. Four trials with 271 pregnant women were included in the analysis. Three trials compared methadone with buprenorphine and one trial

compared methadone with oral slow-release morphine. Three out of four studies had adequate allocation concealment and were double-blinded. The major flaw in the included studies was attrition bias: three out of four had a high attrition rate (30% to 40%) which was unbalanced between groups. When methadone was compared to buprenorphine, the attrition rate from treatment was lower in the methadone group (RR 0.64, 95% CI 0.41 to 1.01, three studies, 223 participants). However, there was no statistically significant difference in the use of primary substances between the methadone and buprenorphine participants (RR 1.81, 95% CI 0.70 to 4.69, two studies, 151 participants). For both endpoints, the authors judged the quality of evidence to be low. Birth weight was higher in the buprenorphine group in the two of the three trials where data could be pooled (mean difference [MD] -365.45 grams; 95% CI -673.84 to -57.07, two studies, 150 participants); the third study reported no statistically significant difference. Neither of the studies which compared methadone with buprenorphine found a significant difference in Apgar scores when assessing newborns but the authors rated the quality of evidence as low. Many measures were used in the studies to assess neonatal abstinence syndrome. The number of newborns treated for neonatal abstinence syndrome did not significantly differ between groups but the quality of evidence was rated as very low. Attrition rates were minimal in trials that compared methadone with slow-release morphine. Oral slow-release morphine seemed superior to methadone for abstinence from heroin use during pregnancy (RR 2.40, 95% CI 1.00 to 5.77, one study, 48 participants) and the quality of evidence was rated as moderate. There was only one study which compared reported adverse events to methadone and buprenorphine and there was no statistically significant difference for the mothers; however, there were significantly fewer serious adverse events in the newborns of mothers on buprenorphine compared to methadone. In the comparison between methadone and slow-release morphine, no adverse events were reported for the mothers, whereas one child in the methadone group experienced central apnea and one child in the morphine group experienced obstructive apnea. The authors concluded there was insufficient evidence to suggest significant differences between methadone and buprenorphine or slow-release morphine to make a conclusion that one treatment is superior to another for all relevant outcomes.

In the systematic review by Soyka[4], the author reviewed RCTs and one national cohort sample between 2011 and 2013 in the management of opioid dependence in pregnancy. Most of the studies compared buprenorphine with methadone. When maternal outcomes were examined, most studies found buprenorphine to have similar effects as methadone. There were very few data from small studies evaluating the effect of buprenorphine on neurodevelopment of the fetus. Neonatal abstinence syndrome is common in infants of both buprenorphine- and methadone-maintained mothers. Overall, buprenorphine had similar neonatal clinical outcomes as methadone, although some newer studies suggest that buprenorphine may cause fewer withdrawal symptoms. There were few studies investigating the combination of buprenorphine with naloxone in pregnant women because of the possible teratogenic effects from naloxone. The authors acknowledged the role of buprenorphine in pregnant opioid users, but also recognized the need of long-term studies to explore the impact of maintenance therapy on child development, including neurological, psychiatric and neuropsychological updates.

In 2013, CADTH[6] reviewed the clinical- and cost-effectiveness of buprenorphine/naloxone versus methadone for the treatment of opioid dependence. Four RCTs (a secondary analysis on data from one RCT was performed), two non-randomized trials, and two economic evaluations were identified. Based on the results from RTC data, no difference was found in terms of opioid use measured by urine drug tests between buprenorphine/naloxone and methadone. Three out four RTCs reported similar retention time between the two groups. The Greek economic evaluation estimated patient total costs for one year were lower for treatment with buprenorphine/naloxone compared to methadone, whereas the Australian economic analysis found the mean treatment costs over a 6-month period were relatively equal between the two treatments. Most of the included clinical trials had small sample sizes, power calculations were not described and the economic data are not specific to the U.S.; therefore, results should be interpreted with caution. In addition, all studies reported results from the evaluable population or from patients who had completed the studies even though participant retention rates were low.

New drugs:

In June 2014, the FDA approved a new buprenorphine/naloxone buccal film (Bunavail®). Like buprenorphine/naloxone sublingual tablet and film, the buccal film formulation was approved as maintenance treatment for opioid dependence.[7] The buccal formulation is absorbed faster than the sublingual tablet or film, allowing it to be administered in doses of 2.1/0.3 mg, 4.2/0.7 mg, or 6.3/1 mg instead of corresponding doses of 2/0.5 mg, 4/1 mg, 8/2 mg or 12/3 mg for the sublingual film. However, there is no evidence to suggest there are any differences in efficacy and safety between these formulations.[8]

New FDA Indications:
None

New FDA safety alerts:
None

New Trials (Appendix 2):
A total of 107 citations were identified from the initial literature search. Articles were excluded due to wrong study design (observational), comparator (placebo), or outcome (non-clinical). After inclusion for further review, 41 citations were further evaluated but only 7 potentially relevant comparative randomized trials were identified through abstract review for appropriate medication, indication, study design, and outcomes. The trials are briefly described in Table 1.

Table 1: Potentially Relevant New Trials.

Study	Comparison	Population	Primary Outcome	Results
Fiellin, et al. 2014[9]	Buprenorphine taper (n=57) vs. ongoing maintenance therapy (n=56)	Adults with opioid dependence treated at primary care setting	Illicit opioid use via results of urinalysis and patient report and treatment retention.	The mean percentage of urine samples negative for opioids was lower for patients in the taper group (35.2% [95% CI, 26.2%-44.2%]) compared with those in the maintenance group (53.2% [95% CI, 44.3%-62.0%]). Patients in the taper group reported more days per week of illicit opioid use than those in the maintenance group once they were no longer receiving buprenorphine (mean use, 1.27 [95% CI, 0.60-1.94] vs. 0.47 [95% CI, 0.19-0.74] days). Patients in the taper group had fewer maximum consecutive weeks of opioid abstinence compared with those in the maintenance group (mean abstinence, 2.70 [95% CI, 1.72-3.75] vs. 5.20 [95% CI, 4.16-6.20] weeks).
Liebschutz, et al. 2014[10]	Buprenorphine detoxification only (n=67) vs. detoxification linked to office-based buprenorphine treatment (n=72)	Post-discharge adults with opioid dependence identified during medical hospitalization.	Entry and sustained engagement with buprenorphine at 1, 3, and 6 months (medical record verified) and prior 30-day use of illicit opioids (self-report).	Participants referred to office-based buprenorphine treatment (linkage participant) were more likely to enter office-based therapy than those in the detoxification group (52 [72.2%] vs. 8 [11.9%], P < .001). At 6 months, 12 linkage participants (16.7%) and 2 detoxification participants (3%) were receiving buprenorphine (P = .007). Compared with those in the detoxification group, participants in the linkage group reported less illicit opioid use in the 30 days before the 6-month interview (incidence rate ratio, 0.60; 95% CI, 0.46-0.73; P < .01) in an intent-to-treat analysis.
Sigmon, et al. 2013[11]	Buprenorphine 1- (n=24), 2- (n=24), and 4-	Adults with prescription opioid following a brief	The percentage of participants negative for	Opioid abstinence at the end of phase 1 was greater in the 4-week compared to the 2- and 1-week taper (P=0.02), with 63% (n=14), 29% (n=7),

	(b=22) week taper regimens with subsequent naltrexone therapy.	period of buprenorphine stabilization.	illicit opioid use, retention, naltrexone ingestion, and favorable treatment response (i.e., retained in treatment, opioid abstinence, and receiving naltrexone at the end of the study).	and 29% (n=7) of participants abstinent with the 4-, 2-, and 1-week tapers, respectively. Abstinence at the end of phase 2 was also greater in the 4-week compared with the 2- and 1-week tapers (P=0.03), with 50% (n = 11), 16% (n = 4), and 20% (n = 5) of participants abstinent with the 4-, 2-, and 1-week tapers, respectively. There were more treatment responders with the 4-week taper (P=0.03), with 50% (n = 11), 17% (n = 4), and 21% (n = 5) of participants with the 4-, 2-, and 1-week tapers considered responders at the end of treatment, respectively. Treatment retention and naltrexone use were also higher in the 4-week taper vs. briefer tapers (both P=0.04).
Neumann, et al. 2013[12]	Methadone (n=26) vs. buprenorphine/ naloxone (n=28)	Adults with opioid addiction receiving opioids for the treatment of nonmalignant chronic pain.	Compare the influence of 6 months of methadone and buprenorphine/ naloxone treatment on analgesia, illicit drug use, treatment retention, and functioning.	The 26 participants (48.1%) who remained in the study noted a 12.75% reduction in pain (P=0.043). No participants in the methadone group, compared to 5 in the buprenorphine group, reported illicit opioid use (P=0.039). Other differences, such as treatment retention and functioning, were not found between methadone and buprenorphine/naloxone groups.
Otiashvili, et al. 2013[13]	Buprenorphine/naloxone (n=40) vs. methadone (n=40)	Adults with opioid dependence.	The impact of continuing treatment with buprenorphine/naloxone or methadone in buprenorphine injectors on substance use and HIV risk behaviors.	In both study arms, treatment resulted in a marked reduction in unprescribed buprenorphine and other opioid use, but the methadone arm had more reported positive urine tests compared with buprenorphine/naloxone (P=0.03). However, there was no significant differences in self-reported HIV risk behaviors, such as needle sharing, between the two treatment groups (P=1.0).
Lintzeris, et al. 2013[14]	Buprenorphine/naloxone tablets (n=46) vs. film (n=46)	Opioid-dependent adults on buprenorphine/naloxone treatment	Subjective dose effects and equivalence, trough plasma levels, adverse events, patient satisfaction, supervised dosing time, and impact upon treatment outcomes (substance use, psychosocial function)	No significant group differences were observed for subjective dose effects, trough plasma buprenorphine or norbuprenorphine levels, adverse events or treatment outcomes. The only difference between the two formulations was the buprenorphine/naloxone film took significantly less time to dissolve than tablets (173 ±71 seconds vs. 242 ±141 seconds, p=0.007).
Rosenthal, et al. 2013[15]	Buprenorphine implant (BI) (n=114) vs. placebo implant (PI) (n=54)	Adults (age 18 - 65) with DSM-IV-TR opioid dependence	Percentage of urine samples negative for opioids collected from weeks 1 to 24, examined as a cumulative distribution function (CDF).	The BI CDF was significantly different from placebo ($P < 0.0001$) with mean proportions (95% CI) of urine samples negative for opioids (BI = 31.2% [25.3, 37.1] vs. PI = 13.4% [8.3, 18.6]).

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Appendix 1: Current Prior Authorization Criteria.

Buprenorphine and Buprenorphine/Naloxone Fixed Combinations

Goal(s):

- Expand access to opioid dependence/addiction treatment
- Treatment of pain remains a priority, including opioid-dependent patients with injury or illness. Buprenorphine must be held during opioid treatment, especially with long-acting opioids.
- Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction, TIP 40, available at *http://buprenorphine.samhsa.gov/Bup_Guidelines.pdf*.

Initiative: Opioid Use Disorder

Length of Authorization: up to 6 months; 2 months if the prescription is for immediate need pending certification.

Requires PA:

Brand Names	Generic
Buavail, Suboxone, Zubsolv	buprenorphine/naloxone
Buprenex, Butrans, Subutex	buprenorphine

Covered Alternatives: Preferred alternatives available at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is diagnosis one of the following? • 304.00 Opioid type dependence unspecified use • 304.01 Opioid type dependence continuous use • 304.70 Opioid type dependence continuous use • 304.70 Combinations of opioid type drug with other drug dependence unspecified use • 304.71 Combinations of opioid type drug with any other drug dependence continuous.	**Yes**: GO TO #3	**No**: PASS TO RPH; deny for medical appropriateness
3. Is prescriber a physician assistant or nurse practitioner? (NPs and PAs may not prescribe)	**Yes:** PASS TO RPH; deny for medical appropriateness	**No:** GO TO #4

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Approval Criteria		
4. Does prescribing physician have a Drug Addiction Treatment Act (DATA)-2000 waiver ID number (also termed a special X-DEA license or certification)? OR Prescriber provides copy of SAMSHA certification request pending with "Immediate Need" checked? (once prescriber meets criteria SAMHSA may take 45 days to process.) *Note: Physicians do not have to list their license on the SAMHSA Buprenorphine Physician Locator website, which is publicly available. Pharmacists may call the Buprenorphine Information Center at 1-866-BUP-CSAT to verify unlisted or application under review prescribers.*	**Yes**: Document number or attach copy of SAMSHA request to PA record. GO TO #6	**No**: GO TO #5
5. Does the prescriber qualify for waiver from separate registration? a) Must have a valid DEA license AND b) Board certified in addiction medicine OR c) Employed by an opioid treatment program OR d) Federally employed physicians (e.g. IHS or VA)	**Yes**: GO TO #6	**No:** PASS TO RPH; deny for medical appropriateness. Encourage physician to get training & register at SAMSHA http://buprenorphine.samhsa.gov/howto.html or FAX "intent" form to 240-276-1630 at DEA.
6. Is patient concurrently on long-acting opioids (check claim record and inform prescriber of any current claims)? Examples of long-acting opioids include: • methadone (e.g. Dolophine, Methadose) • levorphanol (e.g. Levo-Dromoran) • morphine, extended-release (e.g. MS Contin, Oramorph SR, Kadian, Avinza) • oxycodone, extended-release (e.g. OxyContin) • fentanyl transdermal (e.g. Duragesic) • oxymorphone, extended-release (e.g. Opana ER)	**Yes:** PASS TO RPH; deny for medical appropriateness. DO NOT GIVE methadone, or any long-acting opiate CONCURRENTLY with buprenorphine. If currently on methadone, reduce to stable state of 30 mg methadone equivalent (methadone 40 mg = buprenorphine 6 mg), then wait 24 hours to initiate buprenorphine.	**NO:** GO TO #7

Approval Criteria		
7. Is patient concurrently on other opioids (check claim record and prescriber of any current claims in STC 40)?	**Yes:** PASS TO RPH; deny for medical appropriateness. If physician can provide rationale for concurrent therapy, document in PA and record and GO TO #8.	**No:** GO TO #8
8. Is dose ≤ 24 mg/day? (may average every other day therapy, e.g., 48 mg QOD)	**Yes:** GO TO #9	**No:** PASS TO RPH; deny for medical appropriateness.
9. What is patient's pharmacy-of-choice? - Document pharmacy name and NPI or address in PA record. - Lock patient into their pharmacy of choice for 6 months. - **Use reason code: Suboxone**	Inform prescriber patient will be locked to a single pharmacy for all prescriptions. GO TO #10	
10. What is the expected length of treatment? Document treatment length in PA record.	a) If prescriber is waiting for SAMSHA certification subsequent approvals dependent on certification: Approve for 2 months. b) If prescriber is certified: Approve for anticipation length of treatment or 6 months, whichever is shorter.	

P&T / DUR Action: *1/15 (AG), 9/09, 5/09*
Revision(s): *9/13*
Initiated: *1/10*

Author: B. Liang, Pharm.D. and A. Gibler, Pharm.D.

Naltrexone Extended Release Inj. (Vivitrol®)

Goal:

Promote safe and cost effective therapy for the treatment of alcohol and opioid dependence.

Length of Authorization:

- Initial – 3 months; Renewal – 1 year

Covered Alternatives:

- Acamprosate, naltrexone tablets, disulfiram. Preferred alternatives available at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Does the member have a diagnosis of alcohol dependence (DSM-IV-TR) or alcohol use disorder (AUD: DSM5)?	**Yes:** GO TO #3	**No:** GO TO #4
3. Has the requesting prescriber provided documentation and/or confirmation of abstinence from alcohol as assessed by the provider and/or objective testing?	**Yes:** GO TO #6	**No:** PASS TO RPH; Deny for medical appropriateness. Patients must have demonstrated alcohol abstinence prior to administration.
4. Does the member have a diagnosis of opioid dependence (DSM-IV-TR) or opioid use disorder (OUD: DSM5)?	**Yes:** GO TO #5	**No:** PASS TO RPH; deny for medical appropriateness. Naltrexone extended release injection is only approved for alcohol and opioid dependence.
5. Has the patient tried and failed other oral agents for the treatment of opioid dependency (buprenorphine, methadone) **OR** Is the patient unable to take oral therapy or does the patient require injectable therapy due to adherence issues?	**Yes:** GO TO #6	**No:** PASS TO RPH; Deny for medical appropriateness.

Author: B. Liang, Pharm.D. and A. Gibler, Pharm.D.

Approval Criteria		
6. Is the member part of a comprehensive treatment program for substance abuse that includes a psychosocial support system?	**Yes:** GO TO #7	**No:** PASS TO RPH; deny for medical appropriateness. Naltrexone extended release injection therapy must be part of a comprehensive treatment program including psychosocial support.
7. Has the patient received any opioid prescription within the last 30 days from a prescriber other than the requesting provider based on prescription claims history?	**Yes:** Notify requesting provider of the opioid prescriber, drug, dose, prescription date and the day supply; GO TO #8	**No:** GO TO #8
8. Has the patient abstained from the use of any opioids for at least 7 to 10 days, including street opioids such as heroin or prescription opioids as assessed by the provider and/ or objective testing?	**Yes:** Approve for 3 months for initial therapy, 12 months for continuation therapy.	**No:** PASS TO RPH; **d**eny for medical appropriateness. Patient must be opioid-free for 7 to 10 days prior to administration to minimize risk of acute opioid withdrawal syndrome.

P&T / DUR Action: *1/15 (AG), 5/14, 11/13*
Revision(s): *1/15*
Initiated: *11/13*

Appendix 2: Abstracts of Systematic Reviews and Randomized Clinical Trials.

1. **Minozzi S, Amato L, Bellisario C, Ferri M, Davoli M. Maintenance agonist treatments for opiate-dependent pregnant women. Cochrane Database of Systematic Reviews 2013, Issue 12.**

Abstract

Background: The prevalence of opiate use among pregnant women can range from 1% to 2% to as high as 21%. Heroin crosses the placenta and pregnant, opiate-dependent women experience a six-fold increase in maternal obstetric complications such as low birth weight, toxaemia, third trimester bleeding, malpresentation, puerperal morbidity, fetal distress and meconium aspiration. Neonatal complications include narcotic withdrawal, postnatal growth deficiency, microcephaly, neuro-behavioural problems, increased neonatal mortality and a 74-fold increase in sudden infant death syndrome.

Objectives: To assess the effectiveness of any maintenance treatment alone or in combination with psychosocial intervention compared to no intervention, other pharmacological intervention or psychosocial interventions for child health status, neonatal mortality, retaining pregnant women in treatment and reducing the use of substances.

Search methods: We searched the Cochrane Drugs and Alcohol Group Trials Register (September 2013), PubMed (1966 to September 2013), CINAHL (1982 to September 2013), reference lists of relevant papers, sources of ongoing trials, conference proceedings and national focal points for drug research. We contacted authors of included studies and experts in the field.

Selection criteria: Randomised controlled trials assessing the efficacy of any maintenance pharmacological treatment for opiate-dependent pregnant women.

Data collection and analysis: We used the standard methodological procedures expected by The Cochrane Collaboration.

Main results: We found four trials with 271 pregnant women. Three compared methadone with buprenorphine and one methadone with oral slow-release morphine. Three out of four studies had adequate allocation concealment and were double-blind. The major flaw in the included studies was attrition bias: three out of four had a high drop-out rate (30% to 40%) and this was unbalanced between groups.

Methadone versus buprenorphine: the drop-out rate from treatment was lower in the methadone group (risk ratio (RR) 0.64, 95% confidence interval (CI) 0.41 to 1.01, three studies, 223 participants). There was no statistically significant difference in the use of primary substance between methadone and buprenorphine (RR 1.81, 95% CI 0.70 to 4.69, two studies, 151 participants). For both, we judged the quality of evidence as low. Birth weight was higher in the buprenorphine group in the two trials that could be pooled (mean difference (MD) -365.45 g (95% CI -673.84 to -57.07), two studies, 150 participants). The third study reported that there was no statistically significant difference. For APGAR score neither of the studies which compared methadone with buprenorphine found a significant difference. For both, we judged the quality of evidence as low. Many measures were used in the studies to assess neonatal abstinence syndrome. The number of newborns treated for neonatal abstinence syndrome, which is the most critical outcome, did not differ significantly between groups. We judged the quality of evidence as very low.

Methadone versus slow-release morphine: there was no drop-out in either treatment group. Oral slow-release morphine seemed superior to methadone for abstinence from heroin use during pregnancy (RR 2.40, 95% CI 1.00 to 5.77, one study, 48 participants). We judged the quality of evidence as moderate.

Only one study which compared methadone with buprenorphine reported side effects. For the mother there was no statistically significant difference; for the newborns in the buprenorphine group there were significantly fewer serious side effects.

In the comparison between methadone and slow-release morphine no side effects were reported for the mother, whereas one child in the methadone group had central apnoea and one child in the morphine group had obstructive apnoea.

Authors' conclusions: We did not find sufficient significant differences between methadone and buprenorphine or slow-release morphine to allow us to conclude that one treatment is superior to another for all relevant outcomes. While methadone seems superior in terms of retaining patients in treatment, buprenorphine seems to lead to less severe neonatal abstinence syndrome. Additionally, even though a multi-centre, international trial with 175 pregnant women has recently been completed and its results published and included in this review, the body of evidence is still too small to draw firm conclusions about the equivalence of the treatments compared. There is still a need for randomised controlled trials of adequate sample size comparing different maintenance treatments.

2. Perry AE, Neilson M, Martyn-St James M, Glanville JM, McCool R, Duffy S, Godfrey C, Hewitt C. Pharmacological interventions for drug-using offenders. Cochrane Database of Systematic Reviews 2013, Issue 12.

Abstract

Background: The review represents one in a family of four reviews focusing on a range of different interventions for drug-using offenders. This specific review considers pharmacological interventions aimed at reducing drug use and/or criminal activity for illicit drug-using offenders.

Objectives: To assess the effectiveness of pharmacological interventions for drug-using offenders in reducing criminal activity and/or drug use.

Search Methods: Fourteen electronic bibliographic databases (searched between 2004 and 21 March 2013) and five additional Web resources (searched between 2004 and 11 November 2011) were searched. Experts in the field were contacted for further information.

Selection Criteria: Randomised controlled trials assessing the efficacy of any pharmacological interventions for reducing, eliminating or preventing relapse in drug-using offenders were included. Data on the cost and cost-effectiveness of interventions were reported.

Data Collection and Analysis: We used standard methodological procedures as expected by The Cochrane Collaboration.

Main Results: A total of 76 trials across the four reviews were identified. After a process of prescreening had been completed, 17 trials were judged to meet the inclusion criteria for this specific review (six of the 17 trials are awaiting classification for the review). The remaining 11 trials contained a total of 2,678 participants. Nine of the eleven studies used samples with a majority of men. The interventions (buprenorphine, methadone and naltrexone) were compared to non pharmacological treatments (e.g., counselling) and other pharmacological drugs. The methodological trial quality was poorly described, and most studies were rated as 'unclear' by the reviewers. The biggest threats to risk of bias were generated through blinding (performance and detection bias) and incomplete outcome data (attrition bias). When combined, the results suggest that pharmacological interventions do significantly reduce subsequent drug use using biological measures, (three studies, 300 participants, RR 0.71 (95% CI 0.52 to 0.97)), self report dichotomous data (three studies, 317 participants, RR 0.42, (95% CI 0.22 to 0.81)) and continuous measures (one study, MD -59.66 (95% CI -120.60 to 1.28)) . In the subgroups analysis for community setting, (two studies, 99 participants: RR 0.62 (95% CI 0.35 to 1.09)) and for secure establishment setting, (one study, 201 participants: RR 0.76 (95% CI 0.52 to 1.10)), the results are no longer statistically significant. Criminal activity was significantly reduced favouring the dichotomous measures of re arrest, (one study, 62 participants, RR 0.60 (95% CI 0.32 to 1.14)), re-incarceration, (three studies, 142 participants, RR 0.33 (95% CI 0.19 to 0.56)) and continuous measures (one study, 51 participants, MD -74.21 (95% CI -133.53 to -14.89)). Findings on the effects of individual pharmacological interventions on drug use and criminal activity show mixed results. Buprenorphine in comparison to a non pharmacological treatment seemed to favour buprenorphine but not significantly with self report drug use, (one study, 36 participants, RR 0.58 (95% CI 0.25 to 1.35)). Methadone and cognitive behavioural skills in comparison to standard psychiatric services, did show a significant reduction for self report dichotomous drug use (one study, 253 participants, RR 0.43 (95% CI 0.33 to 0.56)) but not for self report continuous data (one study 51 participants) MD -0.52 (95% CI -1.09 to 0.05)), or re incarceration RR 1.23 (95% CI 0.53 to 2.87)). Naltrexone was favoured significantly over routine parole and probation for re incarceration (two studies 114 participants, RR 0.36 (95% CI 0.19 to 0.69)) but no data was available on drug use. Finally, we compared each pharmacological treatment to another. In each case we compared methadone to: buprenorphine, diamorphine and naltrexone. No significant differences were displayed for either treatment for self report dichotomous drug use (one study, 193 participants RR 1.23 (95% CI 0.86 to 1.76)), continuous measures of drug use MD 0.70 (95% CI -5.33 to 6.73) or criminal activity RR 1.25 (95% CI 0.83 to 1.88)) between methadone and

buprenorphine. Similiar results were found for comparisons with Diamorphine with no significant differences between the drugs for self report dichotomous drug use for arrest (one study, 825 participants RR 1.25 (95% CI 1.03-1.51)) or Naltrexone for dichotomous measures of re incarceration (one study, 44 participants, RR 1.10 (95% CI 0.37 to 3.26)), and continuous outcome measure of crime MD -0.50 (95% CI -8.04 to 7.04)) or self report drug use MD 4.60 (95% CI -3.54 to 12.74)).

Author's Conclusions: Pharmacological interventions for drug-using offenders do appear to reduce overall subsequent drug use and criminal activity (but to a lesser extent). No statistically significant differences were displayed by treatment setting. Individual differences are displayed between the three pharmacological interventions (buprenorphine, methadone and naltrexone) when compared to a non pharmacological intervention, but not when compared to each other. Caution should be taken when interpreting these findings, as the conclusions are based on a small number of trials, and generalisation of these study findings should be limited mainly to male adult offenders. Additionally, many studies were rated at high risk of bias because trial information was inadequately described.

3. **Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database of Systematic Reviews 2014, Issue 2. Art. No.: CD002207.**

Abstract

Background: Buprenorphine maintenance treatment has been evaluated in randomised controlled trials against placebo medication, and separately as an alternative to methadone for management of opioid dependence.

Objectives: To evaluate buprenorphine maintenance compared to placebo and to methadone maintenance in the management of opioid dependence, including its ability to retain people in treatment, suppress illicit drug use, reduce criminal activity, and mortality.

Search methods: We searched the following databases to January 2013: Cochrane Drugs and Alcohol Review Group Specialised Register, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, Current Contents, PsycLIT, CORK, Alcohol and Drug Council of Australia, Australian Drug Foundation, Centre for Education and Information on Drugs and Alcohol, Library of Congress, reference lists of identified studies and reviews. We sought published/unpublished randomised controlled trials (RCTs) from authors.

Selection criteria: Randomised controlled trials of buprenorphine maintenance treatment versus placebo or methadone in management of opioid-dependent persons.

Data collection and analysis: We used Cochrane Collaboration methodology.

Main results: We include 31 trials (5430 participants), the quality of evidence varied from high to moderate quality.

There is high quality of evidence that buprenorphine was superior to placebo medication in retention of participants in treatment at all doses examined. Specifically, buprenorphine retained participants better than placebo: at low doses (2 - 6 mg), 5 studies, 1131 participants, risk ratio (RR) 1.50; 95% confidence interval (CI) 1.19 to 1.88; at medium doses (7 - 15 mg), 4 studies, 887 participants, RR 1.74; 95% CI 1.06 to 2.87; and at high doses (≥ 16 mg), 5 studies, 1001 participants, RR 1.82; 95% CI 1.15 to 2.90. However, there is moderate quality of evidence that only high-dose buprenorphine (≥ 16 mg) was more effective than placebo in suppressing illicit opioid use measured by urinanalysis in the trials, 3 studies, 729 participants, standardised mean difference (SMD) -1.17; 95% CI -1.85 to -0.49, Notably, low-dose, (2 studies, 487 participants, SMD 0.10; 95% CI -0.80 to 1.01), and medium-dose, (2 studies, 463 participants, SMD -0.08; 95% CI -0.78 to 0.62) buprenorphine did not suppress illicit opioid use measured by urinanalysis better than placebo.

There is high quality of evidence that buprenorphine in flexible doses adjusted to participant need, was less effective than methadone in retaining participants, 5 studies, 788 participants, RR 0.83; 95% CI 0.72 to 0.95. For those retained in treatment, no difference was observed in suppression of opioid use as measured by urinalysis, 8 studies, 1027 participants, SMD -0.11; 95% CI -0.23 to 0.02 or self report, 4 studies, 501 participants, SMD -0.11; 95% CI -0.28 to 0.07, with moderate quality of evidence.

Consistent with the results in the flexible-dose studies, in low fixed-dose studies, methadone (≤ 40 mg) was more likely to retain participants than low-dose buprenorphine (2 - 6 mg), (3 studies, 253 participants, RR 0.67; 95% CI: 0.52 to 0.87). However, we found contrary results at medium dose and high dose: there was no difference between medium-dose buprenorphine (7 - 15 mg) and medium-dose methadone (40 - 85 mg) in retention, (7 studies, 780 participants, RR 0.87; 95% CI 0.69 to 1.10) or in suppression of illicit opioid use as measured by urines, (4 studies, 476 participants, SMD 0.25; 95%

CI -0.08 to 0.58) or self report of illicit opioid use, (2 studies, 174 participants, SMD -0.82; 95% CI -1.83 to 0.19). Similarly, there was no difference between high-dose buprenorphine (≥ 16 mg) and high-dose methadone (≥ 85 mg) in retention (RR 0.79; 95% CI 0.20 to 3.16) or suppression of self-reported heroin use (SMD -0.73; 95% CI -1.08 to -0.37) (1 study, 134 participants).

Few studies reported adverse events ; two studies compared adverse events statistically, finding no difference between methadone and buprenorphine, except for a single result indicating more sedation among those using methadone.

Authors' conclusions: Buprenorphine is an effective medication in the maintenance treatment of heroin dependence, retaining people in treatment at any dose above 2 mg, and suppressing illicit opioid use (at doses 16 mg or greater) based on placebo-controlled trials. However, compared to methadone, buprenorphine retains fewer people when doses are flexibly delivered and at low fixed doses. If fixed medium or high doses are used, buprenorphine and methadone appear no different in effectiveness (retention in treatment and suppression of illicit opioid use); however, fixed doses are rarely used in clinical practice so the flexible dose results are more relevant to patient care. Methadone is superior to buprenorphine in retaining people in treatment, and methadone equally suppresses illicit opioid use.

4. **Larney S, Gowing L, Mattick RP, Farrell M, Hall W, Degenhardt L. A systematic review and meta-analysis of naltrexone implants for the treatment of opioid dependence. *Drug Alcohol Rev* 2014;33(2):115-128.**

Abstract

Introduction and Aims: Naltrexone implants are used to treat opioid dependence, but their safety and efficacy remain poorly understood. We systematically reviewed the literature to assess the safety and efficacy of naltrexone implants for treating opioid dependence.

Design and Methods: Studies were eligible if they compared naltrexone implants with another intervention or placebo. Examined outcomes were induction to treatment, retention in treatment, opioid and non-opioid use, adverse events, non-fatal overdose and mortality. Quality of the evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation approach. Data from randomised studies were combined using meta-analysis. Data from non-randomised studies were presented narratively.

Results: Five randomised trials (n = 576) and four non-randomised studies (n = 8358) were eligible for review. The quality of the evidence ranged from moderate to very low. Naltrexone implants were superior to placebo implants [risk ratio (RR): 0.57; 95% confidence interval (CI) 0.48, 0.68; k = 2] and oral naltrexone (RR: 0.57; 95% CI 0.47, 0.70; k = 2) in suppressing opioid use. No difference in opioid use was observed between naltrexone implants and methadone maintenance (standardised mean difference: -0.33; 95% CI -0.93, 0.26; k = 1); however, this finding was based on low-quality evidence from one study.

Discussion: The evidence on safety and efficacy of naltrexone implants is limited in quantity and quality, and the evidence has little clinical utility in settings where effective treatments for opioid dependence are used.

Conclusions: Better designed research is needed to establish the safety and efficacy of naltrexone implants. Until such time, their use should be limited to clinical trials. [Larney S, Gowing L, Mattick RP, Farrell M, Hall W, Degenhardt L. A systematic review and meta-analysis of naltrexone implants for the treatment of opioid dependence.

5. **Soyka M. Buprenorphine Use in Pregnant Opioid Users: A Critical Review. *CNS Drugs* 2013;27(8):653-662.**

Abstract

Pregnancy in opioid users poses a number of problems to treating physicians. Most guidelines recommend maintenance treatment to manage opioid addiction in pregnancy, with methadone being the gold standard. More recently, buprenorphine has been discussed as an alternate medication. The use and efficacy of buprenorphine in pregnancy is still controversial. This article reviews the current database on the basis of a detailed and critical literature search performed in MEDLINE (206 counts). Most of the relevant studies (randomised clinical trials and one national cohort sample) were published in the last 2 years and mainly compared buprenorphine with methadone. Some studies are related to maternal outcomes, others to foetal, neonatal or older child outcomes. With respect to maternal outcomes, most studies suggest that buprenorphine has similar effects to methadone. Very few data from small studies discuss an effect of buprenorphine on neurodevelopment of the foetus. Neonatal abstinence syndrome is common in infants of both buprenorphine- and methadone-maintained mothers. As regards neonatal outcomes, buprenorphine has the same clinical outcome as methadone, although some newer studies suggest that it causes fewer withdrawal symptoms. Since hardly any studies have investigated the combination of buprenorphine with naloxone (which has been suggested to possibly have teratogenic effects) in pregnant women, a switch to buprenorphine monotherapy is recommended in women who become pregnant while receiving the combination product. These novel findings indicate that buprenorphine is emerging as a first-line treatment for pregnant opioid users.

6. **CADTH Rapid Response.** ***Suboxone versus Methadone for the Treatment of Opioid Dependence: A Review of the Clinical and Cost-Effectiveness*****. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2013.**

Excerpt

Addiction to opioids causes major medical, social, and economic problems to both the individual and society. Opioid dependence is defined as a strong desire to use the substance, difficulty in controlling its use, the presence of a physiological withdrawal state, tolerance of the use of the drug, neglect of alternative pleasures and interests and persistent use of the drug, despite harm to oneself and others. It is a complex disease involving physiological, psychological, genetic, behavioral and environmental factors. In Canada, it is estimated that there were more than 80,000 regular illegal opioid users in 2003. The number of illegal drug-related overdose deaths in Canada was 958 in 2002. Opioid dependence is related to the abuse of not only illegal opioid drugs (e.g. heroin), but also some of the most commonly prescription drugs, such as codeine-containing Tylenol, hydromorphone, oxycodone, morphine and others. Treatment of opioid dependence includes three approaches: stabilization, detoxification and maintenance. Stabilization is usually achieved by opioid substitution treatments to ensure that the drug use becomes independent of mental state (such as craving and mood) and independent of circumstances (such as finance and physical location). The next stage is detoxification that is to withdraw from opioids. The final step is maintenance to prevent relapse. Detoxification refers to the process by which the effects of opioid drugs are eliminated in a safe and effective manner, such that withdrawal symptoms are minimized. Appropriate use of the detoxification agents plays a crucial role in increasing the successful detoxification rate, while minimizing the side effects and withdrawal symptoms. Methadone (μ-opioid receptor agonist) or buprenorphine (μ-opioid receptor agonist and κ-opioid receptor antagonist) are recommended first-line treatments in opioid detoxification. Naloxone is an opioid antagonist without agonist properties. In opioid-dependent patients, naloxone precipitates withdrawal. Suboxone (buprenorphine/naloxone) was approved by Health Canada in 2007 for substitution treatment in opioid drug dependence in adults. It is a fixed combination of buprenorphine (a partial μ-opioid receptor agonist) with naloxone (an opioid antagonist) in a 4:1 ratio. The addition of naloxone to buprenorphine is expected to decrease the intravenous abuse of buprenorphine, because when taken sublingually, absorption of naloxone is minimal, however it can rapidly precipitate opioid withdrawal when injected. Suboxone is recommended for the treatment of opioid dependence for patients in whom methadone is contraindicated (such as patients at high risk of, or with QT prolongation, or hypersensitivity to methadone). The purpose of this review is to provide evidence on the comparative clinical effectiveness and cost-effectiveness of use of Suboxone compared with methadone, for the treatment of patients with opioid dependence. Subgroups such as children and pregnant women may also have access to opioids thus, the clinical benefits and risks of Suboxone for these patients will be examined as well, when evidence is available.

7. **Fiellin DA, Schottenfeld RS, Cutter CJ, Moore BA, Barry DT, O'Connor PG. Primary Care-Based Buprenorphine Taper vs Maintenance Therapy for Prescription Opioid Dependence: A Randomized Clinical Trial. *JAMA Intern Med* 2014.**

Abstract

Importance: Prescription opioid dependence is increasing and creates a significant public health burden, but primary care physicians lack evidence-based guidelines to decide between tapering doses followed by discontinuation of buprenorphine hydrochloride and naloxone hydrochloride therapy (hereinafter referred to as buprenorphine therapy) or ongoing maintenance therapy.

Objective: To determine the efficacy of buprenorphine taper vs ongoing maintenance therapy in primary care-based treatment for prescription opioid dependence.

Design, Setting, and Participants: We conducted a 14-week randomized clinical trial that enrolled 113 patients with prescription opioid dependence from February 17, 2009, through February 1, 2013, in a single primary care site.

Interventions: Patients were randomized to buprenorphine taper (taper condition) or ongoing buprenorphine maintenance therapy (maintenance condition). The buprenorphine taper was initiated after 6 weeks of stabilization, lasted for 3 weeks, and included medications for opioid withdrawal, after which patients were offered naltrexone treatment. The maintenance group received ongoing buprenorphine therapy. All patients received physician and nurse support and drug counseling.

Main Outcomes and Measures: Illicit opioid use via results of urinanalysis and patient report, treatment retention, and reinitiation of buprenorphine therapy (taper group only).

Results: During the trial, the mean percentage of urine samples negative for opioids was lower for patients in the taper group (35.2% [95% CI, 26.2%-44.2%]) compared with those in the maintenance group (53.2% [95% CI, 44.3%-62.0%]). Patients in the taper group reported more days per week of illicit opioid use than those in the maintenance group once they were no longer receiving buprenorphine (mean use, 1.27 [95% CI, 0.60-1.94] vs 0.47 [95% CI, 0.19-0.74] days). Patients in the taper group had fewer maximum consecutive weeks of opioid abstinence compared with those in the maintenance group (mean abstinence, 2.70 [95% CI, 1.72-3.75] vs 5.20 [95% CI, 4.16-6.20] weeks). Patients in the taper group were less likely to complete the trial (6 of 57 [11%] vs 37 of 56 [66%]; $P < .001$). Sixteen patients in the taper group reinitiated buprenorphine treatment after the taper owing to relapse.

Conclusions and Relevance: Tapering is less efficacious than ongoing maintenance treatment in patients with prescription opioid dependence who receive buprenorphine therapy in primary care.

8. **Liebschutz JM, Crooks D, Herman D, et al. Buprenorphine treatment for hospitalized, opioid-dependent patients: A randomized clinical trial. *JAMA Intern Med* 2014;174(8):1369-1376.**

Abstract

Importance: Buprenorphine opioid agonist treatment (OAT) has established efficacy for treating opioid dependency among persons seeking addiction treatment. However, effectiveness for out-of-treatment, hospitalized patients is not known.

Objective: To determine whether buprenorphine administration during medical hospitalization and linkage to office-based buprenorphine OAT after discharge increase entry into office-based OAT, increase sustained engagement in OAT, and decrease illicit opioid use at 6 months after hospitalization.

Design, Setting, and Participants: From August 1, 2009, through October 31, 2012, a total of 663 hospitalized, opioid-dependent patients in a general medical hospital were identified. Of these, 369 did not meet eligibility criteria. A total of 145 eligible patients consented to participation in the randomized clinical trial. Of these, 139 completed the baseline interview and were assigned to the detoxification (n = 67) or linkage (n = 72) group.

Interventions: Five-day buprenorphine detoxification protocol or buprenorphine induction, intrahospital dose stabilization, and postdischarge transition to maintenance buprenorphine OAT affiliated with the hospital's primary care clinic (linkage).

Main Outcomes and Measures: Entry and sustained engagement with buprenorphine OAT at 1, 3, and 6 months (medical record verified) and prior 30-day use of illicit opioids (self-report).

Results: During follow-up, linkage participants were more likely to enter buprenorphine OAT than those in the detoxification group (52 [72.2%] vs 8 [11.9%], P < .001). At 6 months, 12 linkage participants (16.7%) and 2 detoxification participants (3.0%) were receiving buprenorphine OAT (P = .007). Compared with those in the detoxification group, participants randomized to the linkage group reported less illicit opioid use in the 30 days before the 6-month interview (incidence rate ratio, 0.60; 95% CI, 0.46-0.73; P < .01) in an intent-to-treat analysis.

Conclusions and Relevance: Compared with an inpatient detoxification protocol, initiation of and linkage to buprenorphine treatment is an effective means for engaging medically hospitalized patients who are not seeking addiction treatment and reduces illicit opioid use 6 months after hospitalization. However, maintaining engagement in treatment remains a challenge.

9. **Sigmon SC, Dunn KE, Saulsgiver K, et al. A randomized, double-blind evaluation of buprenorphine taper duration in primary prescription opioid abusers. *JAMA Psychiatry* 2013;70(12):1347-1354.**

Abstract

Importance: Although abuse of prescription opioids (POs) is a significant public health problem, few experimental studies have investigated the treatment needs of this growing population.

Objective: To evaluate, following brief stabilization with a combination of buprenorphine hydrochloride and naloxone hydrochloride dihydrate, the relative efficacy of 1-, 2-, and 4-week buprenorphine tapering regimens and subsequent naltrexone hydrochloride therapy in PO-dependent outpatients.

Design, Setting, and Participants: A double-blind, 12-week randomized clinical trial was conducted in an outpatient research clinic. Following a brief period of buprenorphine stabilization, 70 PO-dependent adults were randomized to receive 1-, 2-, or 4-week tapers followed by naltrexone therapy.

Intervention: During phase 1 (weeks 1-5 after randomization), participants visited the clinic daily; during phase 2 (weeks 6-12), visits were reduced to thrice weekly. Participants received behavioral therapy and urine toxicology testing throughout the trial.

Main Outcomes and Measures: The percentage of participants negative for illicit opioid use, retention, naltrexone ingestion, and favorable treatment response (ie, retained in treatment, opioid abstinent, and receiving naltrexone at the end of the study).

Results: Opioid abstinence at the end of phase 1 was greater in the 4-week compared with the 2- and 1-week taper conditions (P = .02), with 63% (n = 14), 29% (n = 7), and 29% (n = 7) of participants abstinent in the 4-, 2-, and 1-week conditions, respectively. Abstinence at the end of phase 2 was also greater in the 4-week compared with the 2- and 1-week conditions (P = .03), with 50% (n = 11), 16% (n = 4), and 20% (n = 5) of participants abstinent in the 4-, 2-, and 1-week conditions, respectively. There were more treatment responders in the 4-week condition (P = .03), with 50% (n = 11), 17% (n = 4), and 21% (n = 5) of participants in the 4-, 2-, and 1-week groups considered responders at the end of treatment, respectively. Retention and naltrexone ingestion also were superior in the 4-week vs briefer tapers (both P = .04). Experimental condition (ie, taper duration) was the strongest predictor of treatment response, followed by buprenorphine stabilization dose.

Conclusions and Relevance: This study represents a rigorous experimental evaluation of outpatient buprenorphine stabilization, brief taper, and naltrexone maintenance for treatment of PO dependence. Results suggest that a meaningful subset of PO-dependent outpatients may respond positively to a 4-week taper plus naltrexone maintenance intervention.

10. **Neumann AM, Blondell RD, Jaanimägi U, et al. A preliminary study comparing methadone and buprenorphine in patients with chronic pain and coexistent opioid addiction. *J Addict Dis* 2013;32(1):68-78.**

Abstract

Patients with opioid addiction who receive prescription opioids for treatment of nonmalignant chronic pain present a therapeutic challenge. Fifty-four participants with chronic pain and opioid addiction were randomized to receive methadone or buprenorphine/naloxone. At the 6-month follow-up examination, 26 (48.1%) participants who remained in the study noted a 12.75% reduction in pain (P = 0.043), and no participants in the methadone group compared to 5 in the buprenorphine group reported illicit opioid use (P = 0.039). Other differences between the two conditions were not found. Long-term, low-dose methadone or buprenorphine/naloxone treatment produced analgesia in participants with chronic pain and opioid addiction.

11. **Otiashvili D, Piralishvili G, Sikharulidze Z, Kamkamidze G, Poole S, Woody GE. Methadone and buprenorphine-naloxone are effective in reducing illicit buprenorphine and other opioid use, and reducing HIV risk behavior--outcomes of a randomized trial. *Drug Alcohol Depend* 2013;133(2):376-382.**

Abstract

Aims: Determine the extent to which buprenorphine injectors continue treatment with buprenorphine-naloxone or methadone, and the impact of these treatments on substance use and HIV risk in the Republic of Georgia.

Methods: Randomized controlled 12-week trial of daily-observed methadone or buprenorphine-naloxone followed by a dose taper, referral to ongoing treatment, and follow-up at week 20 at the Uranti Clinic in Tbilisi, Republic of Georgia. Eighty consenting treatment-seeking individuals (40/group) aged 25 and above who met ICD-10 criteria for opioid dependence with physiologic features and reported injecting buprenorphine 10 or more times in the past 30 days. Opioid use according to urine tests and self-reports, treatment retention, and HIV risk behavior as determined by the Risk Assessment Battery.

Results: Mean age of participants was 33.7 (SD5.7), 4 were female, mean history of opioid injection use was 5.8 years (SD4.6), none were HIV+ at intake or at the 12-week assessment and 73.4% were HCV+. Sixty-eight participants (85%) completed the 12-week medication phase (33 from methadone and 35 from buprenorphine/naloxone group); 37 (46%) were in treatment at the 20-week follow-up (21 from methadone and 16 from the buprenorphine/naloxone group). In both study arms, treatment resulted in a marked reduction in unprescribed buprenorphine, other opioid use, and HIV injecting risk behavior with no clinically significant differences between the two treatment arms.

Conclusions: Daily observed methadone or buprenorphine-naloxone are effective treatments for non-medical buprenorphine and other opioid use in the Republic of Georgia and likely to be useful for preventing HIV infection.

12. **Lintzeris N, Leung SY, Dunlop AJ, et al. A randomised controlled trial of sublingual buprenorphine-naloxone film versus tablets in the management of opioid dependence. *Drug Alcohol Depend* 2013;131(1-2):119-126.**

Abstract

Background: Buprenorphine-naloxone sublingual film was introduced in 2011 in Australia as an alternative to tablets. This study compared the two formulations on subjective dose effects and equivalence, trough plasma levels, adverse events, patient satisfaction, supervised dosing time, and impact upon treatment outcomes (substance use, psychosocial function).

Methods: 92 buprenorphine-naloxone tablet patients were recruited to this outpatient multi-site double-blind double-dummy parallel group trial. Patients were randomised to either tablets or film, without dose changes, over a 31 day period.

Results: No significant group differences were observed for subjective dose effects, trough plasma buprenorphine or norbuprenorphine levels, adverse events and treatment outcomes. Buprenorphine-naloxone film took significantly less time to dissolve than tablets (173±71 versus 242±141s, p=0.007, F=7.67).

Conclusions: The study demonstrated dose equivalence and comparable clinical outcomes between the buprenorphine-naloxone film and tablet preparations, whilst showing improved dispensing times and patient ratings of satisfaction with the film.

13. **Rosenthal, R. N., Ling, W., Casadonte, P., Vocci, F., Bailey, G. L., Kampman, K., Patkar, A., Chavoustie, S., Blasey, C., Sigmon, S. and Beebe, K. L. (2013), Buprenorphine implants for treatment of opioid dependence: randomized comparison to placebo and sublingual buprenorphine/naloxone. Addiction, 108: 2141–2149.**

Abstract

Aims: To evaluate the safety and efficacy of buprenorphine implants (BI) versus placebo implants (PI) for the treatment of opioid dependence. A secondary aim compared BI to open-label sublingual buprenorphine/naloxone tablets (BNX).

Design: Randomized, double-blind, placebo-controlled trial. Subjects received either four buprenorphine implants (80 mg/implant) (*n* = 114), four placebo implants (*n* = 54) or open-label BNX (12–16 mg/day) (*n* = 119).

Setting: Twenty addiction treatment centers.

Participants: Adult out-patients (ages 18–65) with DSM-IV-TR opioid dependence.

Measurements: The primary efficacy end-point was the percentage of urine samples negative for opioids collected from weeks 1 to 24, examined as a cumulative distribution function (CDF).

Findings: The BI CDF was significantly different from placebo ($P < 0.0001$). Mean [95% confidence interval (CI)] proportions of urines negative for opioids were: BI = 31.2% (25.3, 37.1) and PI = 13.4% (8.3, 18.6). BI subjects had a higher study completion rate relative to placebo (64 versus 26%, $P < 0.0001$), lower clinician-rated ($P < 0.0001$) and patient-rated ($P < 0.0001$) withdrawal, lower patient-ratings of craving ($P < 0.0001$) and better subjects' ($P = 0.031$) and clinicians' ($P = 0.022$) global ratings of improvement. BI also resulted in significantly lower cocaine use ($P = 0.0016$). Minor implant-site reactions were comparable in the buprenorphine [27.2% (31 of 114)] and placebo groups [25.9% (14 of 54)]. BI were non-inferior to BNX on percentage of urines negative for opioids [mean (95% CI) = 33.5 (27.3, 39.6); 95% CI for the difference of proportions = (−10.7, 6.2)].

Conclusions: Compared with placebo, buprenorphine implants result in significantly less frequent opioid use and are non-inferior to sublingual buprenorphine/naloxone tablets.