Buprenorphine
Buprenorphine/naloxone
Drug Monograph

Drug Requested:
Buprenorphine Sublingual Tablet, 2mg, 8mg
Buprenorphine/Naloxone Sublingual Tablet, 2/0.5mg, 8/2mg

SUMMARY:
Since FDA approval in October 2002, buprenorphine and buprenorphine/naloxone combination remain the only opioid agonist available for the treatment of opioid dependence that can be prescribed in an outpatient setting. The efficacy and safety of buprenorphine is well demonstrated[1-8]. Although Schedule II opioid agonists such as methadone remain a viable option of treatment in opioid dependence, restriction to access or the lack of convenience remains a barrier to patients seeking treatment. Under the Drug Addiction Treatment Act (DATA) of 2000, specially trained providers who are registered with the Drug Enforcement Administration (DEA) can prescribe buprenorphine for initially up to 30 patients per month[9]. Buprenorphine can thus provide patients with improved access to treatment and may also facilitate their general medical care.

Among several pharmacological treatments, opioid agonists including methadone and buprenorphine have been reported to effectively reduce substance abuse and overdose rates[67]. However, methadone maintenance programs have not been able to keep up with the rapidly growing rate of the opioid epidemic, leading to the development of buprenorphine treatment programs as an alternative option. With the majority of published studies of buprenorphine induction and maintenance taking place in an outpatient, office-based setting, only very few interventions focused on opioid dependent patients in the hospital settings[1,68]. Intravenous drug use with opioids puts patients at risk for hospitalization, therefore initiating opioid agonist treatment in the hospital and establishing a referral system to Office-Based Opioid Treatment (OBOT) can be a key step in preventing opioid overdose deaths[69-70]. Randomized clinical trials have demonstrated positive results in the entry and retention in buprenorphine treatment program in opioid dependent patients by providing induction therapy in the hospital and linking patients to OBOT program with buprenorphine[12]. The purpose of this monograph is to provide clinical and economic evidence of buprenorphine-naloxone and buprenorphine as part of the initiative to expand treatment options for opioid use disorder by establishing a system where patients can be initiated on buprenorphine inpatient, and subsequently transitioned to outpatient therapy with a buprenorphine prescriber.

THERAPEUTIC CLASS:
Buprenorphine: partial mu-opioid receptor agonist
Naloxone: mu-opioid antagonist

INDICATION:
Buprenorphine Sublingual Tablet
FDA Approval Indication: Treatment of opioid dependence (induction therapy)
Off-label Use: Acute and chronic pain management

Buprenorphine/Naloxone Sublingual Tablet:
FDA Approval Indication: Treatment of opioid dependence (maintenance therapy)
Off-label Use: Induction therapy for opioid dependence, acute and chronic pain management

HAZARDOUS DRUG:
Not on NIOSH (National Institute for Occupational Safety and Health) list

This monograph was developed and released in conjuction with

SHOUT
SUPPORT FOR HOSPITAL OPIOID USE TREATMENT

TABLE 1: PRODUCTS INDICATED FOR THE TREATMENT OF OPIOID DEPEDENCE[13-22]

Generic (Scheduled Class)	**Brand** (Available Strength)	**Manufacturer** (FDA Approval Date)	**[LOCAL FORMULARY STATUS]**	**MediCal FFS Formulary**
Buprenorphine/ Naloxone Sublingual Tablet or Film (CIII)	Suboxone® SL tablet • 2 mg/0.5 mg • 8 mg/2 mg SL film • 2 mg/0.5 mg • 4 mg/1 mg • 8 mg/2 mg • 12 mg/3 mg	Reckitt Benckiser (October 2002)		SL film: 2mg/0.5mg, 4mg/1mg, 8mg/2mg, 12mg/3mg SL tablet: 2mg/0.5mg, 8mg/2mg • Limited to use for treatment of opioid addiction by providers with a DATA 2000 waiver • Restricted to 120 tablets/films and a 30 day supply per dispensing
Buprenorphine (CIII)	Subutex® SL tablet • 2 mg • 8 mg	Reckitt Benckiser (October 2002)		SL tablet: 2mg, 8mg • Limited to use for treatment of opioid addiction by providers with a DATA 2000 waiver • Restricted to 120 tablets and a 30 day supply per dispensing
Buprenorphine/ Naloxone Tablet (CIII)	Zubsolv® SL tablet • 1.4mg/0.36 mg • 5.7 mg/1.4 mg	Orexo (July 2013)		SL tablet: 1.4mg/0.36mg, 5.7mg/1.4mg, 11.4mg/2.9mg • Limited to use for treatment of opioid addiction by providers with a DATA 2000 waiver • Restricted to 120 tablets and a 30 day supply per dispensing
Buprenorphine/ Naloxone Buccal Film (CIII)	Bunavail® Buccal film • 2.1 mg/0.3 mg • 4.1 mg/0.7 mg • 6.3 mg/1 mg	BioDelivery Sciences (June 2014)		Buccal film: 2.1mg/0.3mg, 4.2mg/0.7mg, 63/1.0mg • Limited to use for treatment of opioid addiction by providers with a DATA 2000 waiver • Restricted to 120 tablets and a 30 day supply per dispensing
Methadone (CII)	Methadose®/ Methadose® Sugar-Free Oral concentrate • 10mg/mL	Mallinckrodt (January 1982)		Not a pharmacy benefit
Methadone (CII)	Methadone HCl Intensol® Oral concentrate • 10mg/mL	Roxane (September 1988)		Not a pharmacy benefit
Methadone (CII)	Dolophine® Tablet • 5mg • 10mg	Boehringer Ingelheim (November 2009)		Not a pharmacy benefit

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(CONTINUED) TABLE 1: PRODUCTS INDICATED FOR THE TREATMENT OF OPIOID DEPEDENCE[13-22]

Generic (Scheduled Class)	**Brand** (Available Strength)	**Manufacturer** (FDA Approval Date)	**[LOCAL FORMULARY STATUS]**	**MediCal FFS Formulary**
Naltrexone (Not scheduled)	ReVia® Tablet • 50mg	Teva Womens (November 1984)		Tablet: 50mg **Not formulary:** Treatment Authorization Request (TAR) required • Restricted to use in the treatment of alcohol dependence and for the prevention of relapse in opioid dependent patients, following opioid detoxification. • Restricted to prescription only by prescribers trained in substance use disorder treatment. • Restricted to a maximum dispensing quantity of 100 tablets and a maximum of three (3) dispensings in any 75-day period.
Naltrexone (Not scheduled)	Vivitrol® Injectable • 380mg/4mL	Alkermes (October 2010)		Extended-release injectable suspension: 380mg/4mL Not formulary: Treatment Authorization Request (TAR) required • The treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment. Patients should not be actively drinking at the time of initial administration • The prevention of relapse to opioid dependence, following opioid detoxification • Part of a comprehensive management program that includes psychosocial support

CLINICAL PHARMACOLOGY

Buprenorphine is a partial mu-opioid receptor agonist with low intrinsic activity, high binding affinity, and a slow dissociation rate, leading to prolonged effects in suppressing opioid withdrawal and displacing full agonists such as morphine and methadone. As a partial agonist, buprenorphine produces a ceiling effect in which higher doses do not result in increased pharmacological effects. Buprenorphine thus effectively functions as a dual agonist and antagonist in modulating opioid withdrawal symptoms by blocking the effects of exogenous opioids[23,24]. Buprenorphine is also a kappa-opioid receptor antagonist. This mechanism of action has been suggested as a strategy in modulating relapse, since the kappa-opioid receptor may be involved in anxiety and depression at certain stages of the addiction cycle[25].

Methadone is a long-acting full mu-opioid receptor agonist with a long half-life[24]. Its pharmacological action prevents withdrawal symptoms, reduces cravings, and blocks mu-opioid-receptor-mediated euphoric effects from illicit opiates. However, full agonists have the highest abuse potential[26].

Naltrexone is a mu-opioid antagonist with a higher affinity for receptors than heroin, morphine, or methadone; it displaces opioid full and partial agonists to block their effects[24]. Because of its antagonistic action, it can precipitate withdrawal symptoms in patients not abstinent from short-acting opioids for 7 days or long-acting opioids for 10 days, limiting to its use to highly motivated individuals. [26]. As an antagonist, naltrexone does not have abuse potential or withdrawal upon discontinuation of the medication.

Safety concerns with opioid agonists are mostly due to mu-opioid-receptor activation, which may be responsible for adverse effects of buprenorphine and methadone such as respiratory depression and constipation[23]. As a partial agonist, buprenorphine exhibits a ceiling effect when used alone and severe mu-opioid-medicated adverse effects such as respiratory depression are less likely to occur[23,27]. However, caution is advised when combining with additional CNS depressants such as benzodiazepines, as its ceiling effect is lost in this combination. Methadone exhibits the narrowest margin of safety in pharmacology studies and has been associated with potentially fatal cardiac arrhythmia from QT interval prolongation[29,30]. For buprenorphine, no effect of QT prolongation was reported in the sublingual tablet formulation[71].

Safety concerns with an opioid antagonist involve the loss of opioid tolerance, which increases the risk of death from opioid overdose if opioid use is resumed following naltrexone therapy[27].

TABLE 2: PHARMACOKINETICS[31-35]

Parameters	Buprenorphine/ Naloxone SL*	Buprenorphine SL	Naltrexone PO	Methadone PO
Dose (mg/day)	2-32 mg buprenorphine		50 mg	80-120 mg
Bioavailability	29%		5-40%	36-100%
Absorption	Widely variable among patients, but consistent for individual patients		Almost complete	Rapid absorption in stomach
Time to peak concentration	30 min-1 h		60 min	1-7.5 h
Plasma Protein binding	96%		21%	85-90%
Volume of distribution	97-187 L/kg		19.2 L/kg**	1-8 L/kg
Active metabolite (s)	Norbuprenorphine***		Inactive metabolites	Inactive metabolites
Protein binding	96%		21%	85-90%
Half-life	24-42 h	37 h	4 h	8-59 h
Excretion	Feces: 70% Urine: 27-30%		Primarily urine	Urine
CYP Substrate	CYP3A4		Non-CYP dehydrogenase conversion, glucuronidation	CYP3A4, CYP2B6, CYP2C19

*PK information is only for buprenorphine: naloxone does not change the PK parameters of Buprenorphine
**Vd/kg calculated from 1350L/70kg
***Norbuprenorphine is a more efficacious (higher Emax) but less potent (higher EC50) mu-opioid receptor partial agonist compared to buprenorphine[36], it also has potent respiratory depressor activity. These properties indicate that norbuprenorphine likely contribute to the pharmacological effects of buprenorphine; however, its exact role is unclear[37].

CLINICAL STUDIES[12,38-41]

Study	Design/Methods	Results/Conclusion
Randomized Controlled Trial (3 studies)		
1. Liebschutz JM et. al. 2014 (NCT00987961) *Category: Providing Linkage to Hospital Initiated Buprenorphine*	**Design:** Randomized, interventional, parallel assignment, open label **Length of Study:** 6 months **Setting:** Medical Center, inpatient **Study Size:** N=139 **Purpose:** To evaluate whether the initiation of buprenorphine during hospitalization and the provision of linkage to an outpatient buprenorphine opioid agonist treatment (OAT) program increase access and retention, while decrease opioid use 6 months after hospitalization **Intervention(s):** ▪ Detoxification (n=67): bup induction for 5 days with no linkage ▪ Linkage (n=72): bup induction, with facilitated linkage to hospital-affiliated outpatient OAT program **Inclusion Criteria:** 18-75 yo, currently hospitalized, opioid-dependent, English speaking, non-treatment seeking **Exclusion Criteria:** Received methadone or buprenorphine maintenance prior to admission, harmful to self or others, history of alcohol/benzodiazepine dependence, pregnancy, in need of opioids for pain post-hospitalization **Primary Outcome(s):** ▪ Entry into OAT program by 6 mo of study ▪ Maintenance in OAT program at 6 mo interview ▪ Self-reported illicit opioid use **Secondary Outcome(s):** ▪ OAT days ▪ Time to entry into OAT program ▪ Self-reported illicit opioid use **Sponsor**: NIDA	**PRIMARY OUTCOMES:** **Outcomes measured at 6 mo follow-up appointment N=139** Outcome(s) / Detoxification (n=67) / Linkage (n=72) / P-Value Entry to OAT program: 8 (11.9%) / 52 (72.2%) / <0.001 Maintenance in OAT program: 2 (3%) / 12 (16.7%) / 0.007 Self-reported no illicit opioid use 30 days prior to interview: 5 (9%) / 24 (37.5%) / <0.01 Linkage participants were more likely to enter an Opioid Agonist Treatment (OAT) program, stay in the OAT program, and reported less illicit opioid use compared to detox group. **SECONDARY OUTCOMES:** **Secondary and other outcomes at 6 mo follow-up N=139** Outcome(s) / Detoxification (n=67) / Linkage (n=72) / P-Value # of days received buprenorphine treatment: 6.8 (SD=26.2) / 64.4 (SD=61.7) / <0.001 # of days of self-reported illicit opioid use at 6 mo follow-up: Mean=13.9 Median=15 / Mean=8.4 Median=4 / <0.01 **Other Outcomes**: Time to entry to OAT program was significantly shorter for linkage group (p<0.001), median was 16 days. No results can be analyzed from detox group due to low rate of entry. **Adverse Events:** 6 participants died during course of study, but no deaths were attributed to buprenorphine: CHF (n=2), postoperative pulmonary embolism (n=1), liver failure (n=1), renal failure (n=1), drug overdose (n=1) **Limitations:** ▪ Self-reported outcome of illicit opioid use ▪ Limited generalizability: roughly 30% of participants were White, 20% were African American, and 15% Hispanic ▪ Limited applicability: participants were English-speaking **Conclusion:** Initiation and linkage to buprenorphine OAT program was effective in engaging hospitalized, non-treatment seeking opioid-dependent patients compared to detoxification with buprenorphine.

Study	Design/Methods	Results/Conclusion
2. Fudala PJ. et al. 2003 (NCT00007527) *Category: Fixed High Doses Buprenorphine-naloxone vs placebo*	**Design**: 2 part study: multicenter, randomized, double-blind, placebo-controlled 1) study of efficacy and 2) open-label on safety **Length of Study:** Double-blind: 4 wk, Open-label: 48–52 wk **Setting:** 12 office-based clinics **Study Size:** Double-blind: N=323, Open-label: N=472 **Purpose:** To evaluate the safety and efficacy of buprenorphine/naloxone **Intervention(s):** ▪ Placebo (n=109) ▪ Bup 16 mg alone (n=105) ▪ Bup-naloxone 16/4 mg (n=109) In the double-blind study, participants were to pick up medication at clinic every day. In the open-label study, all participants were given bup-naloxone; up to 10 day take home supplies were given after 2 wk. **Inclusion Criteria:** 18–59 yo, DSM-IV opioid dependence, treatment seeking **Exclusion Criteria:** Pregnancy or lactation, hazardous medical illness, abnormal AST/ALT, current Axis I psychiatric diagnosis other than opiate or nicotine dependence, use of methadone, LAAM, or naltrexone within 14 days **Primary Outcome(s):** ▪ % of opiates-negative urine samples ▪ Self-reported craving for opiates **Secondary Outcome(s):** ▪ Participants' and clinicians' perspectives on overall status ▪ % urine samples free of other drugs (amphetamines, barbiturates, benzodiazepines, cocaine, methadone) ▪ Subject retention ▪ Rate of adverse events ▪ Findings on electrocardiography ▪ Results of chemical and hematologic analyses **Sponsor(s)**: Dept of Veterans Affairs, NIDA	**Primary Outcomes:** **% of urine samples free of opiates N=323** Placebo (n=109) | Bup 16mg alone (n=105) | Bup-naloxone 16/4mg (n=109) | P-value 5.8% | 20.7% | 17.8% | <0.001 Compared to the placebo group, buprenorphine alone and buprenorphine-naloxone resulted in significantly greater % of opiate-negative urine samples. **Self-reported craving for opiates** Measured using 100-mm Visual Analog Scale (0="no craving", 100="the most intense craving I ever had"). Mean score of opioid craving was statistically significantly lower in the bup-alone and bup-naloxone arms compared to placebo (p<0.001). **Adverse Events:** **Double-blind** Overall adverse events did not differ among arms (80% placebo, 85% bup-alone, 78% bup-naloxone). **Statistically Significant Adverse Events** | | Placebo (n=107) | Bup-alone (n=103) | Bup-naloxone (n=107) | p-value Headache | 24(22.4%) | 30(29.1%) | 39(36.4%) | 0.08 Withdrawal symptoms | 40(37.4%) | 19(18.4%) | 27(25.2%) | 0.008 Rhinitis | 14(13.1%) | 10(9.7%) | 5(4.7%) | 0.09 Diarrhea | 16(15.0%) | 5(4.9%) | 4(3.7%) | 0.005 Constipation | 3(2.8%) | 8(7.8%) | 13(12.1%) | 0.03 14 participants reported serious adverse events (7 placebo, 3 bup-alone, 4 bup-naloxone). Most common were inpatient detoxification (n=5) and suicidal ideation/attempt (n=2, bup-only arms). **Open-label** 14 participants dropped out due to adverse events, detoxification and withdrawal symptoms being the most common. Other common adverse events included abnormal ALT/AST (n=10), with 7 cases probably or possibility related. 8 of these 10 patients presented serologic evidence of hepatitis at baseline. **Limitations:** ▪ Self-reported outcome ▪ Raw data (%) was not available for self-reported opiate craving; only a graph was provided **Conclusion:** Both bup/naloxone and bup alone were effective and safe in reducing the use and craving of opiates in opiate-addicted individuals in an office based setting.

Study	Design/Methods	Results/Conclusion
3. Ling W et al. 1998 *Category: Fixed Dose Bup-alone vs placebo*	**Design**: double-blind, randomized, multicenter **Length of Study:** 16 wk (36 wk extension) **Setting:** 12 outpatient opiate maintenance treatment centers (U.S.) **Study Size:** N=736 **Purpose:** To compare the safety and efficacy of 8mg and 1mg bup **Intervention(s):** ▪ Bup 1mg ▪ Bup 4mg ▪ Bup 8mg ▪ Bup 16mg All participants received a weekly 1 hr counseling session. Participants missing 4-6 consecutive days of dosing were re-inducted. Participants required ≥3 re-inductions or missing ≥7 consecutive days were removed from the study. Participants who were hospitalized were switched to methadone or other medications and remained in the study if bup was started <7 days ago. (During the 36 wk extension, prescribers are allowed to double or halve doses, with a 32 mg/day maximum) **Inclusion Criteria:** DSM-III opioid dependence, daily use of opioids during the past 6 mo, met federal criteria for methadone treatment **Exclusion Criteria:** Participation in methadone treatment program within the past 30 days, diagnosis of alcohol dependence or certain medically hazardous illnesses (active TB, DM, AIDS, unstable CV or liver diseases), patients using neuroleptics, anticonvulsants, or disulfiram, pregnancy **Primary Outcome(s):** ▪ Retention in treatment ▪ Urine toxicology ▪ Craving (Heroin Craving Scale) and rating of global severity of all aspects of current drug problems **Secondary Outcome(s):** ▪ Outcomes for 4 mg and 16 mg **Sponsor(s)**: US NIDA, Reckitt, FDA, Dept of Veterans Affairs	**Primary Outcomes:** **Treatment Retention Rate N=736** Reason for termination: Bup 1mg (n=185) / Bup 4mg (n=182) / Bup 8mg (n=188) / Bup 16mg (n=181) / Total Completed treatment at 16 weeks: 74 **(40.0%)*** / 93 **(51.1%)** / 98 **(52.1%)*** / 110 **(60.8%)** / 375 **(51.0%)** Missed 7 consecutive days: 85 (45.9%) / 62 (34.1%) / 66 (35.1%) / 48 (26.5%) / 261 (35.5%) Subject's request: 18 (9.7%) / 8 (4.4%) / 9 (4.8%) / 7 (3.9%) / 42 (5.7%) Bup toxicity: 1 (0.5%) / 1 (0.5%) / 1 (0.5%) / 3 (1.7%) / 6 (0.8%) Unrelated medical event: 1 (0.5%) / 2 (1.1%) / 2 (1.1%) / 2 (1.1%) / 7 (1.0%) Required 4th re-induction: 2 (1.1%) / 3 (1.6%) / 5 (2.7%) / 4 (2.2%) / 14 (1.9%) Other: 4 (2.2%) / 13 (7.1%) / 7 (3.7%) / 7 (3.9%) / 31 (4.2%) *The overall retention rate was 51%. The retention rate of the 1mg group was significantly lower than that of the 8 mg (p=0.019) and 16mg (p<0.001) group. **Urine Toxicology on Opioids** Outcome measured: **1 mg** / **4 mg** / **8 mg** / **16 mg** Mean % negative of opioids: 18.5 / 29.2 / 32.9 / 38.3 % of patients with 13 consecutive negative urine test results: **8.6**** / **14.3**** / 17.6 / **26.8**** Mean # of negative urine test results: 5.6 / 9.6 / 10.3 / 13.9 Total: 185 / 182 / 188 / 181 The 8mg group did significantly better than the 1mg group on all urine toxicology measures. The 1 mg group did significantly worse than the 4mg, 8mg, and 16mg on the mean % negative of opioids. **The 16mg group had a significantly higher % of patients with 13 consecutive negative urine test results than the 1 mg group (p<0.001) and the 4mg group (p<0.006). **Craving** The heroin craving score is significantly higher in the 1 mg group compared to 8 mg at week 4 (p<0.01), week 8 (p<0.01), and week 12 (p=0.04). **Global Rating** In patient reported rating, significantly higher scores were reported in the 8mg group than the 1mg group at week 4, 8, and 12. For staff reported rating, higher scores were reported at week 4,8,12, and 16. **Limitation:** ▪ High dropout rate: only 51% total retention rate ▪ Limited generalizability: roughly 50% of participants were White, 20% were African American, and 30% Hispanic ▪ It is not explicitly clear whether participants were heroin-dependent. Although study stated that it aimed to address efficacy and safety of buprenorphine in the maintenance of heroin addicts, inclusion criteria did not explicitly stated that participants have to be heroin-dependent **Conclusion:** The 8 mg/day treatment arm provides superior efficacy compared to the 1 mg in all 4 outcome measurements.

Study	Design/Methods	Results/Conclusion
Comparative Efficacy (2 studies)		
4. Mattick RP et al. 2014 Category: Systematic Review	**Included Studies**: 31 published/unpublished RCTs **Total Study Size:** N=5430 **Setting:** Inpatient and outpatient **Purpose**: To evaluate the effectiveness of bup maintenance in the management of opioid dependence when compared to placebo and methadone. **Comparison**: Methadone ▪ Low-dose methadone: up to 40mg ▪ Medium-dose methadone: 40-85mg ▪ High-dose methadone: >85mg Buprenorphine ▪ Low-dose buprenorphine: 2-6mg ▪ Medium-dose buprenorphine: 7-15mg ▪ High-dose buprenorphine: 16mg **Primary Outcome(s):** ▪ Treatment retention = defined as the number of participants still in treatment at the end of study measured by intention-to-treat ▪ Urine analysis for heroin and its metabolites ▪ Self-reported heroin use ▪ Urine analysis for cocaine or benzodiazepines ▪ Self-reported criminal activity ▪ Mortality **Secondary Outcome(s):** ▪ Physical Health ▪ Psychological health ▪ Adverse events **Sponsor(s)**: The Cochrane Collaboration	**Primary Outcomes:** **I. Bup vs placebo** **Treatment Retention** Bup (no. of RCT included) / Bup / Placebo / Risk Ratio Low-dose bup (5) / 564 / 567 / 1.50 [1.19,1.88] Medium-dose bup (4) / 430 / 457 / 1.74 [1.06,2.87] High-dose bup (5) / 580 / 421 / 1.82 [1.15,2.90] Treatment retention rates are greater in all doses of buprenorphine compared to placebo. There were no differences in other comparisons such as morphine-positive or cocaine-positive urine among the three categories of buprenorphine. **II. Fixed-dose Bup vs Fixed-dose Methadone** **Treatment Retention** Comparison (no. of RCT included) / Bup / Methadone / Risk Ratio Low-dose bup vs low-dose methadone (3) / 142 / 111 / 0.67 [0.52,0.87] Medium-dose bup vs medium methadone (7) / 408 / 372 / 0.87 [0.69,1.10] High-dose bup vs high-dose methadone (1) / 58 / 76 / 0.79 [0.20,3.16] Low-dose methadone is more likely to retain participants than low-dose bup; while there is no difference between medium-dose methadone and medium-dose buprenorphine, as well as high-dose methadone and high-dose buprenorphine in treatment retention. **III. Flexible-dose Bup vs Flexible-dose Methadone** **Treatment Retention** Comparison (no. of RCT included) / Bup / Placebo / Risk Ratio Bup vs methadone (5) / 390 / 398 / 0.83[0.72,0.95] Treatment retention is greater in methadone compared to buprenorphine. **Limitation:** The use of 1mg buprenorphine as "active placebo" is included; therefore this review could have underestimated the effects of buprenorphine.

Study	Design/Methods	Results/Conclusion
5. Kamien JB. et al. 2008 *Category: Fixed Medium & High Dose Bup-naloxone vs methadone*	**Design**: Randomized, double-blind, double dummy **Length of Study:** 17 wk **Setting:** Adult opioid outpatient clinic **Study Size:** N=268 **Purpose:** To compare the efficacy of bup-naloxone sublingual tablet to methadone as maintenance therapy of opioid dependence **Intervention(s):** ▪ Bup-naloxone 8/2 mg (n=82) ▪ Bup-naloxone 16/4 mg (n=58) ▪ Methadone 45 mg (n=52) ▪ Methadone 90 mg (n=76) All participants received behavioral counseling. **Inclusion Criteria:** ≥18 yo, DSM-IV heroin dependence **Exclusion Criteria:** active psychosis, manic-depressive illness, organic psychiatric disorders, serious medical illness **Primary Outcome(s):** ▪ Retention in treatment ▪ Urine analysis **Secondary Outcome(s):** ▪ Proportion of participants achieving 12 consecutive opioid-negative samples ▪ Proportion of participants with successful inductions ▪ Medication compliance ▪ Non-opioid illicit drug use ▪ Treatment retention ▪ Change in overall functioning **Sponsor(s)**: US NIDA	**Primary Outcomes:** **Urine Analysis**: Percentages of opioid-free urine samples did not differ significantly between bup and methadone or their doses. **≥12 Negative Urine Analysis N=268** Bup-naloxone 8/2 mg (n=82): 10 Bup-naloxone 16/4 mg (n=58): 17* (p<0.001) Methadone 45 mg (n=52): 12 Methadone 90 mg (n=76): 16* (p=0.02) Percentages of participants who received a higher dose of either bup-naloxone or methadone were more likely to have at least 12 consecutive opioid-negative urine samples (bup-naloxone 8/2 mg vs 16/4 mg, p<0.001; methadone 45mg vs 90 mg, p=0.02). When comparing the lower and higher doses of the two drugs, both bup-naloxone and methadone resulted in similar percentages of participants who had at least 12 consecutive urine samples (bup-naloxone 8/2mg vs 45mg methadone, p=0.18; bup-naloxone 16/4mg vs 90 methadone, p=0.22). Compared to lower doses, higher doses of bup-naloxone or methadone were associated with larger reduction in self-reported heroin use in the past 30 days. **Secondary Outcomes:** **Mean Treatment Retention Time (weeks) N=268** Bup-naloxone 8/2mg (n=82): 12.1 Bup-naloxone 16/4mg (n=58): 12.5 Methadone 45mg (n=52): 13.2 Methadone 90mg (n=76): 12.3 **Adverse Effects:** 5 serious adverse events reported, 4 in the methadone arm and 1 in bup-naloxone arm. Types of adverse events not specified. **Limitations:** ▪ Self-reported patient outcomes, high drop-out rates while intention-to-treat analysis not carried out, limited generalizability ▪ Raw data of % of opioid negative urine samples were not provided **Conclusion:** No difference was found in induction success, compliance, abstinence of opioid use and retention among treatment arms. Bup-naloxone is a viable alternative to methadone.

ABBREVIATION: Bup = buprenorphine, yo = years old, mo = months, wk = weeks, hr = hours, NIDA = National Institute on Drug Abuse

QUALITY OF LIFE DATA

Although quality of life is more commonly assessed for the use of opioids for pain management[42], the WHOQOL-BREF (a brief version of the World Organization Quality of Life assessment) is accepted as a useful and valid measure for quality of life to evaluate the physical, psychological, social, and environmental effects of opioid substitution treatment over time[43,44]. However, the questionnaire's test-retest reliability and sensitivity have not been confirmed[45]. Various studies have demonstrated quality of life improvements following opioid maintenance treatment, with preliminary data suggesting improvement across more domains for buprenorphine and buprenorphine/naloxone compared to methadone:

- Buprenorphine and buprenorphine/naloxone improve the quality of life in WHOQOL-BREF physical, psychological, and environmental domains, though studies differ with respect to their conclusion on social relationship effects[46,47]
- Methadone improves quality of life in WHOQOL-BREF psychological and social domains[48]
- A review of the literature failed to identify quality of life studies for naltrexone

NATIONAL GUIDELINES

The American Psychiatric Association recommends the use of buprenorphine or methadone in patients with a history of one year or more of opioid dependence[49]. The Department of Veterans Affairs and the Department of Defense strongly recommends methadone or buprenorphine/naloxone as the first line treatment for patients who are diagnosed with chronic opioid dependence[50].

The American Society of Addiction Medicine (ASAM) and the Substance Abuse and Mental Health Services Administration (SAMHSA) also conclude that buprenorphine provides comparable therapeutic outcomes to that of methadone[66,51].

PREGNANCY CONSIDERATIONS

Due to the incomplete data and the lack of FDA approval regarding the use of buprenorphine in pregnant women, it should be used only if the prescribers deem that the potential benefit outweighs the harm.

- Buprenorphine monotherapy should be used because of the lack of data on the effects of naloxone in fetal exposure.
- Buprenorphine may result in neonatal abstinence syndrome, though the relation is not well established and there is no dose-response relationship. Buprenorphine taken prior to delivery may result in respiratory depression in the newborn, as is cautioned with all opioids.
- Limited data show that buprenorphine does not increase the risk of malformations.

LACTATION [31,52]

In clinical decision-making, the mother's need for buprenorphine/naloxone and potential effects from the maternal condition should be balanced with the risks to the breastfed child.

- A study of 13 lactating women demonstrated buprenorphine and its metabolite norbuprenorphine to be at low levels in human milk and infant urine, but the breastfed infants did not appear to show adverse reactions.
- There is no data in lactating populations for buprenorphine/naloxone; however, oral naloxone absorption is minimal.

TABLE 3: ADVERSE EFFECTS[31-35]

Adverse Event	Placebo*	Buprenorphine/naloxone (Subxone)*	Buprenorphine (Subutex)*	Naltrexone PO**	Methadone***
Whole Body					
Asthenia	6.5%	6.5%	4.9%	>10%	X
Chills	7.5%	7.5%	7.8%	1-10%	
Dizziness				1-10%	X (common)
Edema					X
Headache	22.4%	36.4%	29.1%	>10%	X
Hypokalemia					X
Hypomagnesemia					X
Infection	6.5%	5.6%	11.7%		
Increased energy				>10%	
Irritability				1-10%	
Malaise				1-10%	
Pain	18.7%	22.4%	18.4%		
Pain in abdomen	6.5%	11.2%	11.7%	>10%	X
Pain in back	11.2%	3.7%	7.8%		
Sedation					X (common)
Withdrawal syndrome	37.4%	25.2%	18.4%		X
Cardiovascular system					
Arrhythmias					X
Bradycardia					X
ECG abnormalities					X
Heart failure					X
Hypogonadism					X
Hypotension					X
Palpitations					X
Tachycardias					X
Vasodilation	6.5%	3.9%	9.3%		
Digestive system					
Constipation	2.8%	12.1%	7.8%	1-10%	X
Diarrhea	15.0%	3.7%	4.9%	1-10%	
Increased thirst				1-10%	
Loss of appetite				1-10%	
Nausea	11.2%	15.0%	13.6%		X (common)
Vomiting	4.7%	7.5%	7.8%	>10%	X (common)
Nervous system				>10%	
Anxiety				>10%	
Confusion					X
Hallucination					X
Insomnia	15.9%	14.0%	21.4%	>10%	X
Nervousness				>10%	X
Renal system					
Antidiuretic eff ect					X
Urinary retention					X
Reproductive system					
Amenorrhea					X
Erectile dysfunction				1-10%	X
Sperm abnormalities					X
Respiratory system					
Pulmonary edema					X
Respiratory depression					X
Rhinitis	13.1%	4.7%	9.7%		
Skin/ musculoskeletal					
Joint/muscle pain				>10%	
Skin rash				1-10%	
Sweating	10.3%	14.0%	12.6%		X (common)

As reported in the prescribing information:
*Adverse events occurring in at least 5% of patients in a 4-week study of 16mg/4mg buprenorphine and naloxone (Buprenorphine/naloxone) and buprenorphine (Subutex) sublingual tablets, compared to placebo
**Adverse events in over 1%, occurring at baseline and during clinical trials of oral naltrexone (Revia) for opioid addiction
***Adverse event frequency not defined. Prescribing information for methadone formulations emphasize lightheadedness, dizziness, sedation, nausea, vomiting, and sweating to be the most frequently observed adverse reactions; the major hazards are respiratory depression and systemic hypotension.

TABLE 4: DRUG INTERACTIONS[31]

Drug Name	Reaction
CYP3A4 inhibitors (azole antifunguals, macrolide antibiotics, HIV protease inhibitors)	May decrease metabolism of CYP3A4 substrates, leading to increased serum concentration of buprenorphine Risk C (moderate CYP3A4 inhibitors): Monitor therapy Risk D (strong CYP3A4 inhibitors): Consider therapy modification
CYP3A4 inducers (efavirenz, phenobarbital, carbamazepine, phenytoin, rifampicin)	May increase metabolism of CYP3A4 substrates, leading to decreased serum concentration of buprenorphine. Recommended monitoring for signs and symptoms of opioid withdrawal. Risk D (strong CYP3A4 inducers): Consider therapy modification
Non-nucleoside reverse transcriptase inhibitors (CYP3A4 inducers: efavirenz, etravirine)	May decrease serum concentration of buprenorphine Risk C: Monitor therapy
Protease inhibitors (CYP3A4 inhibitor: atazanavir)	May decrease serum concentration of atazanavir and increase serum concentration of buprenorphine, leading to increased sedation Risk X: Avoid combination in patients taking un-boosted atazanavir (not contraindicated in patients also taking ritonavir: monitor for buprenorphine toxicity)
Benzodiazepines	Post-marketing reports of coma and death, due to an altered ceiling effect on buprenorphine-induced respiratory depression Prescribe with caution

CONTRAINDICATIONS[31]

Hypersensitivity to buprenorphine, naloxone, or any other component of the formulation.

GENERAL WARNINGS/PRECAUTIONS[14,15,31]

- **General:** Buprenorphine/naloxone should be given with caution to patients in a debilitated state, or with myxedema or hypothyroidism, adrenal cortical insufficiency, CNS depression or coma, toxic psychoses, prostatic hypertrophy or urethral stricture, acute alcoholism, delirium, or kyphoscoliosis.
- **Respiratory and CNS depression:** Buprenorphine taken with CNS depressants such as opioid analgesics, benzodiazepines, and sedatives may increase CNS depression. Concomitant use of benzodiazepines and buprenorphine has been associated with respiratory depression, coma, and death. Buprenorphine/naloxone may produce orthostatic hypotension. Dose reduction may be necessary.
- **Dependence and withdrawal:** Chronic buprenorphine use produces opioid dependence and abrupt discontinuation can precipitate withdrawal, though milder than that of full opioid agonists. If misused parenterally, buprenorphine/naloxone likely produces withdrawal due to naloxone. Withdrawal may also occur from the partial agonist activity of buprenorphine if buprenorphine/naloxone is taken before full opioid agonist effects have subsided. In infants of mothers taking buprenorphine, neonatal withdrawal syndrome may occur. Adverse events include hypertonia, neonatal tremor, neonatal agitation, and myoclonus, as well as case reports of convulsions, apnea, respiratory depression, and bradycardia.
- **Impaired hepatic function and hepatitis:** In patients with hepatic impairment, there is a much greater decrease in naloxone than buprenorphine clearance. The resultant increase in naloxone exposure could compromise the efficacy of buprenorphine and induce withdrawal. Buprenorphine/naloxone is not recommended in patients with severe hepatic impairment. It is possible that buprenorphine plays a role in the development of hepatic abnormality, with case reports ranging from transient transaminase elevation to hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. However, in some cases the etiology was unclear and may have been attributed to pre-existing transaminase abnormalities, hepatitis B or C virus infection, or use of other hepatotoxic drugs. Baseline and periodic liver function tests are recommended.
- **Opioid naïve patients:** There have been reports of death in opioid naïve patients taking 2 mg buprenorphine for analgesia.
- **Elevated cerebrospinal fluid and intracholedochal pressure:** Because buprenorphine may increase cerebrospinal fluid pressure and intracholedochal pressure like other opioids, it should be used with caution in patients with head injury and biliary tract dysfunction, respectively.
- **Clinical exams:** Buprenorphine can cause miosis and changes in consciousness levels, which may interfere with patient evaluation. It may also obscure the diagnosis and clinical course of acute abdominal conditions.

SPECIAL POPULATIONS[31]

Geriatrics: Clinical trials of buprenorphine/naloxone have not included sufficient numbers of subjects 65 years old or older, but clinical experience has not reported clinically significant differences between more elderly and younger subjects. Caution with dose selection is recommended, starting at lower doses and taking into consideration compromised hepatic, renal, or cardiac function and other concomitant diseases or medications.

Pediatrics: The safe and effective use of buprenorphine/naloxone has not been established in patients below the age of 16. It should not be used to treat neonatal abstinence syndrome, since it contains the opioid antagonist naloxone. Protocols do exist to treat neonatal abstinence syndrome with sublingual buprenorphine, and preliminary data shows shorter duration of treatment than when morphine is used[72]. Several studies had reported the adverse effects of unintended exposure in pediatrics and neonatal populations. Children between 13 months to 2 years old had been reported to suffer from mild drowsiness and CNS depression[53], cortical blindness[54], to death[55]. The American Association of Poison Control Centered reported about 900 cases of unintended buprenorphine exposure in children < 6 years old in 2008. Other studies evaluated the efficacy and toxicity of buprenorphine for the indication of pain relief. Only one retrospect study reviewed the retention rates of adolescents receiving buprenorphine/naloxone in an outpatient clinic[56].

Hepatic Impairment: Buprenorphine and naloxone can be used safely with mild hepatic impairment. The half-lives of both buprenorphine and naloxone are prolonged with moderate and severe hepatic impairment. If the combination product is used, the half-life of naloxone is prolonged to a greater extent than that of buprenorphine potentially leading to accumulation and precipitated withdrawal[31]. The combination product is contraindicated in severe hepatic impairment and should be used cautiously in moderate hepatic impairment. Buprenorphine alone may be used cautiously in both scenarios.

Renal Impairment: The effects of renal failure had no difference in the pharmacokinetic of buprenorphine in 9 patients depending on dialysis. The effects of renal failure remain unknown in the pharmacokinetic of naloxone.

POTENTIAL FOR ERRORS AND ABUSE

Sound-alike/look-alike issues: N/A
Abuse risk: As a Schedule III partial opioid agonist, the risk for abuse in buprenorphine/naloxone is less than that of Schedule II full opioid agonists such as methadone. The addition of the opioid antagonist naloxone further prevents abuse.

SENTINEL EVENT ADVISORIES[57]

While there are no sentinel event advisories to date for buprenorphine/naloxone, the Joint Commission has published a sentinel event alert concerning the safe use of opioids in hospitals. Although opioid use is considered safe, opioid analgesics such as methadone carry adverse events, the most serious of which is respiratory depression. Additionally, opioids are associated with usage problems such as underprescribing, overprescribing, tolerance, dependence, and drug abuse. To prevent accidental opioid overdose, the Joint Commission suggests screening for respiratory depression risk factors, assessing potential opioid tolerance or intolerance from previous use, using an individualized and multimodal pain management treatment plan, taking extra precautions when starting or restarting opioids, consulting an expert when converting opioids, avoiding rapid dose escalation, taking extra precautions when transporting patients, and avoiding the use of opioids for an arbitrary pain rating or discharge date. The Joint Commission has outlined actions for effective policies and procedures, safe technology, appropriate education and training, and effective tools.

MONITORING PARAMETERS[13,14,58,59]

Important clinical monitoring:

- Liver function tests
- CNS depression: respiratory depression, mental status
- Withdrawal symptoms
- Signs of addiction, abuse, misuse

COST-EFFECTIVENESS DATA

A search of the literature for international economic evaluations of buprenorphine/naloxone for opioid dependence suggests that in other countries, it is a cost-effective and potentially cost-saving treatment for opioid dependence compared to methadone:

- Limited evidence from a review suggests buprenorphine/naloxone may be more cost-effective than methadone, though subgroups such as children and pregnant women have not been studied[60]
    - In a retrospective analysis performed in Greece, buprenorphine/naloxone combination therapy dominated methadone because it had favorable clinical outcomes (increased treatment completion and decreased death) and was also less costly (for direct and indirect costs).
    - The evaluation from Australia compared buprenorphine/naloxone with methadone from a treatment provider perspective[61] and found buprenorphine/naloxone to be more costly than methadone but resulted in a greater change

in the number of heroin-free days from baseline.

- A budgetary impact analysis concluded buprenorphine/naloxone to be a cost-effective addition to the National Healthcare System in Spain[62]. Despite the increased cost of treatment, the study predicted a gradual decrease in costs due to logistics, production, and monitoring. The study also argues for advantages in clinical considerations, such as the association with less QT prolongation in buprenorphine/naloxone.

Studies show that buprenorphine/naloxone is more cost-effective when used for extended treatment and at higher doses, and that observation of administration is unnecessary:

- In a randomized trial in opioid-dependent youth, cost-effectiveness was compared between extended buprenorphine/naloxone treatment (nine weeks of treatment, tapered to zero at the end of twelve weeks) and brief detoxification treatment (tapered to zero in four days)[63]. Costs included direct and indirect costs, clinical effectiveness was measured as opioid-free years, and economic effectiveness was based the QALY reflected by the EQ-5D. Extended buprenorphine/naloxone treatment was found to have an ICER of $25,049 per QALY for an outpatient treatment program and $1,376 per QALY for a one-year direct medical cost. At a threshold of $100,000 per QALY, the study concludes that extended buprenorphine/naloxone treatment is likely to be accepted as cost-effective compared to brief detoxification in the outpatient treatment of opioid-dependent youth in the US health care setting.
- In an analysis on the impact of buprenorphine/naloxone dosing on treatment duration and costs, a retrospective analysis of US public and private health care claims favored higher doses[64]. Over twelve months, patients in the higher dose group (15 and 15.7 mg daily for publicly and privately insured patients, respectively) were found to have a lower risk of discontinuation and a lower probability of a psychiatric hospitalization. Both groups had comparable total costs, resulting in the conclusion that treatment with higher doses of buprenorphine/naloxone is associated with a longer time to treatment discontinuation, less resource use, and lower total medical costs.
- In a comparison of observed versus unobserved buprenorphine/naloxone for heroin dependence, there was a lack of a statistically significant difference in treatment retention and heroin use[65]. The lack of difference was consistent in secondary outcome measures of non-opioid drug use, psychological symptoms, and quality of life. Because traditional observed administration showed no difference in outcomes compared to the significantly less costly treatment without direct observation of administration, unobserved administration (retaining close clinical monitoring) was concluded to be significantly more cost-effective.

TABLE 5: PRODUCT AVAILABILITY[13,14,51]

Drug name	Strength/Form	Induction Dose	Maintenance Dose	Special Instructions
Buprenorphine SL tablet	2 mg, 8 mg	Day1: 2-8mg buprenorphine Day2: switch to buprenorphine/naloxone if not pregnant	Recommended dose range: 16-24mg/day, up to a maximum of 32mg/day	Short-acting opioid dependence: Begin treatment after withdrawal symptoms present 12-24 hours after last opioid dose Long-acting opioid dependence: Taper down opioid, then begin treatment after withdrawal symptoms present 24+ hours after last opioid dose Adjust in increments/ decrements of 2 or 4 mg
Buprenorphine /naloxone SL tablet	2/0.5mg, 8/2mg	Day1: 4-8mg buprenorphine Day2: repeat dose plus an additional of 4mg buprenorphine, up to a maximum of 16mg Day3 and after: up to 32mg buprenorphine		
Naltrexone tablet	50 mg	25 mg	50 mg	Alternative maintenance dose: 50mg weekdays with 100 mg Saturday, 100 mg every other day, 150 mg every 3 days
Methadone tablet and PO solution	5, 10 mg. Solution: 1 mg/ml, 5mg/5ml, 10mg/ml	20-30 mg, can add 5-10 mg if withdrawal symptoms are not suppressed or reappear after 2-4 hours. Do not exceed 40 mg on first day	Target Range: 80-120 mg/day	Titrate to a dose that prevents withdrawal symptoms for 24 hours (5mg every 5-7 days)

TABLE 6: DRUG COST DEMONSTRATION

Drug	Dosage Form	Strength	Inpatient Cost/Unit	Outpatient Cost/Unit	Outpatient Cost for 1 Month Supply	Outpatient Cost for 1 Year Supply
Buprenorphine	SL Tablet	2 mg				
Buprenorphine	SL Tablet	8 mg				
Buprenorphine/ Naloxone	SL Tablet	2 mg/0.5 mg				
Buprenorphine/ Naloxone	SL Tablet	8 mg/2 mg				
Naltrexone	Tablet	50 mg				
Methadone	Concentrated liquid	10 mg/ml				
Methadone	Tablet	10 mg				

***Cost based on maintenance dose of** 16 mg/day of buprenorphine
** **Cost based on maintenance dose of** 50 mg/day of naltrexone
*** **Cost based on maintenance dose of** 80 mg/day of methadone

CONCLUSION

The superiority of sublingual buprenorphine compared to placebo has been well established. Although some studies demonstrate buprenorphine is as clinically efficacious as low to moderate dose methadone (up to 60mg/day), there are mixed results in the comparisons between fixed and flexible dose buprenorphine and methadone. However, buprenorphine, especially buprenorphine/naloxone, offers several significant safety and clinical advantages over traditional treatments such as methadone or naltrexone. These advantages include:

- Better safety profile due to its ceiling/partial agonist effects (however, the ceiling effect is lost when combined with CNS depressants such as benzodiazepines)
- Increased flexibility in dispensing method (office-based settings treatment setting)
- No treatment requirements other than a DATA 2000 waiver (ex: number of counseling sessions, length of opioid use)
- Reduced potential for abuse or diversion with the addition of naloxone

These advantages should not be overlooked as they could be crucial factors to increases access to opioid maintenance treatment. Given the support from literature and guidelines for the use of buprenorphine, increased access during hospitalization and facilitated linkage to ensure patients receive follow-up care can improve rates of treatment for opioid-dependence and potentially reduce future re-hospitalization rates in this patient population.

RECOMMENDATION

[WRITE FORMULARY RECOMMENDATION HERE]

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