

Therapeutic Class Overview Opioid Dependence Agents

Overview/Summary:

Partial opioid agonists and opioid antagonists are used alone or in combination in the treatment of opioid use disorder.¹⁻⁷ Buprenorphine (Subutex[®]) buprenorphine/naloxone (Bunavail[®], Suboxone[®], Zubsolv[®]) and naltrexone (ReVia[®], Vivitrol[®]) are Food and Drug Administration (FDA)-approved for the treatment of opioid dependence.¹⁻⁷ Naltrexone is also FDA-approved for use in alcohol dependence.^{2,3} Buprenorphine is available as a sublingual tablet, buprenorphine/naloxone is available as sublingual tablet sublingual film and buccal film, and naltrexone is available as a tablet and extended-release suspension for injection.¹⁻⁷ Products which contain buprenorphine are classified as Schedule III controlled substances. The transdermal and injectable formulations of buprenorphine, Butrans[®] and Buprenex[®], respectively, are FDA-approved for use in the management of pain and will not be discussed within this review.^{8,9} Buprenorphine and buprenorphine/naloxone sublingual tablets and naltrexone tablets are currently available generically.

Buprenorphine is a partial opioid agonist at the μ -opioid receptor (associated with analgesia and dependence) and an antagonist at the κ -opioid receptor (related to dysphoria). Partial opioid agonists reach a ceiling effect at higher doses and will displace full opioid agonists from the μ -opioid receptor. Buprenorphine is associated with a lower abuse potential, a lower level of physical dependence and is safer in overdose when compared to full opioid agonists.^{1,4-7} Naloxone and naltrexone are antagonists at the μ -opioid receptor.²⁻⁷ Naloxone has measurable blood levels following sublingual buprenorphine/naloxone administration. However, due to naloxone's low oral bioavailability, there are no significant physiological or subjective differences when compared to the administration of buprenorphine alone. Following intramuscular or intravenous administration, buprenorphine/naloxone is associated with symptoms of opioid withdrawal and dysphoria which is caused by a stronger affinity of naloxone for the opioid receptor compared to buprenorphine.⁴⁻⁷ Therefore, the addition of naloxone to buprenorphine results in a decreased risk of diversion compared to buprenorphine monotherapy.¹⁰

The United States Substance Abuse and Mental Service Clinical Guideline for the Use of Buprenorphine in the Treatment of Opioid Addiction recommends the use of buprenorphine/naloxone for the induction, stabilization and maintenance phases of opioid addiction treatment for most patients. This guideline also notes that buprenorphine alone should be used for pregnant patients and for the induction therapy of patients who are transitioning from methadone treatment.¹¹

Table 1. Current Medications Available in Therapeutic Class¹⁻⁷

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Buprenorphine	Opioid dependence, treatment induction*†; opioid dependence, treatment maintenance*†	Sublingual tablet: 2 mg 8 mg	a
Naltrexone (ReVia [®] , Vivitrol [®])	Alcohol dependence; opioid dependence [‡] (ReVia [®]); opioid dependence, prevention of relapse following opioid detoxification (Vivitrol [®])	Suspension for injection, extended-release (Vivitrol [®]): 380 mg Tablet (ReVia [®]): 50 mg	-
Combination Product			
Buprenorphine/naloxone	Opioid dependence, treatment induction [†] (Suboxone [®]); opioid	Buccal film (Bunavail [®]): 2.1/0.3 mg 4.2/0.7 mg	-

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	dependence, treatment maintenance [†]	6.3/1 mg Sublingual film (Suboxone [®]): 2/0.5 mg 4/1 mg 8/2 mg 12/3 mg Sublingual tablet: 2/0.5 mg 8/2 mg Sublingual tablet (Zubsolv [®]): 1.4/0.36 mg 5.7/1.4 mg	

* According to the manufacturer, buprenorphine sublingual tablets are preferred for use only during induction of treatment for opioid dependence, but can be used for maintenance treatment in patients who cannot tolerate the presence of naloxone.

[†] As part of a complete treatment plan to include counseling and psychosocial support.

[‡] As part of a comprehensive plan of management that includes some measure to ensure the patient takes the medication.

Evidence-based Medicine

- Buprenorphine and buprenorphine/naloxone significantly improve many different outcomes for patients with opioid dependence compared to placebo and no treatment, but are generally found to not be significantly different from one another.^{16-26, 37-44}
- FDA-approval of buprenorphine buccal film (Bunavail[®]) and buprenorphine/naloxone tablet (Zubsolv[®]) was via the 505(b)(2) pathway. Clinical and safety data for these medications is based on previously approved buprenorphine or buprenorphine/naloxone formulations.^{5,7}
- Buprenorphine has been compared to methadone in several clinical studies and reviewed in multiple meta-analyses. Overall, studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence.^{18, 27-34}
- A meta-analysis of 1,158 participants in 13 randomized trials compared oral naltrexone maintenance treatment to either placebo or non-medication. No difference was seen between the active and control groups in sustained abstinence or most other primary outcomes.
 - Considering only studies in which patient's adherence were strictly enforced, there was a statistically significant difference in retention and abstinence with naltrexone over non therapy (relative risk [RR], 2.93; 95% CI, 1.66 to 5.18).⁵⁴
- The efficacy and safety of Vivitrol[®] (naltrexone extended-release) for opioid dependence was evaluated in a 24-week, placebo-controlled randomized control trial. The percentage of subjects achieving each observed percentage of opioid-free weeks was greater in the naltrexone extended release group compared to the placebo group. Complete abstinence (opioid-free at all weekly visits) was sustained by 23% of subjects in the placebo group compared with 36% of subjects in the naltrexone extended release group from Week 5 to Week 24.⁵⁵

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - The United States Substance Abuse and Mental Service Clinical Guideline for the Use of Buprenorphine in the Treatment of Opioid Addiction recommends the use of buprenorphine/naloxone for the induction, stabilization and maintenance phases of opioid addiction treatment for most patients.¹¹
 - This guideline also notes that buprenorphine alone should be used for pregnant patients and for the induction therapy of patients who are transitioning from methadone treatment.¹¹
 - Naltrexone is generally reserved as an alternative regimen after buprenorphine-containing products and methadone.¹³

- Other Key Facts:
 - According to the Drug Addiction Treatment Act of 2000, the ability to prescribe buprenorphine or buprenorphine/naloxone for the maintenance or detoxification of opioid dependence is limited to physicians who have obtained a waiver and a unique Drug Enforcement Agency number beginning with an X.¹⁴
 - Naltrexone extended-release suspension for injection is injected intramuscularly in the gluteal muscle every 4 weeks by a healthcare provider.³

References

1. Buprenorphine tablet [package insert]. Columbus (OH): Roxane Laboratories, Inc.; 2012 Sep.
2. ReVia[®] [package insert]. Horsham (PA): Teva Select Brands; 2013 Oct.
3. Vivitrol[®] [package insert]. Waltham (MA): Alkermes, Inc.; 2013 Jul.
4. Buprenorphine and naloxone sublingual tablet [package insert]. Columbus (OH): Roxane Laboratories, Inc.; 2013 Nov.
5. Bunavail[®] [package insert]. Raleigh (NC): BioDelivery Sciences International, Inc.; 2014 Jun.
6. Suboxone[®] [package insert]. Richmond (VA). Reckitt Benckiser Pharmaceuticals Inc.; 2014 Apr.
7. Zubsolv[®] [package insert]. New York (NY). Orexo US, Inc.; 2013 Jul.
8. Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2013 [cited 2014 Dec 10]. Available from: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.
9. Butrans[®] [package insert]. Stamford (CT). Purdue Pharma L.P.; 2014 Jun.
10. Buprenex[®] [package insert]. New York (NY). Richmond (VA). Reckitt Benckiser Pharmaceuticals Inc.; 2015 Apr.
11. Center for Substance Abuse Treatment. Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction: a treatment improvement protocol TIP 40. Rockville (MD): Substance Abuse and Mental Health Services Administration (SAMHSA); DHHS Publication No. (SMA) 04-3939. 2004.
12. Veterans Health Administration, Department of Defense. VA/DoD clinical practice guideline for the management of substance use disorders (SUD). Washington (DC): Veterans Health Administration, Department of Defense; 2009 Aug [cited 2014 Dec 10]. Available at: http://www.guideline.gov/summary/summary.aspx?doc_id=4812&nbr=3474.
13. American Psychiatric Association Workgroup on Substance Use Disorders, Kleber HD, Weiss RD, Anton RF, Rounsaville BJ, George TP, et al. Treatment of patients with substance use disorders, second edition. American Psychiatric Association. *Am J Psychiatry*. 2006;163(8 Suppl):5-82.
14. U.S. Department of Health and Human Services: Substance Abuse and Mental Health Services. Drug addiction treatment act of 2000 [guideline on the internet] Washington (DC): U.S. Department of Health and Human Services [cited 2014 Dec 10] Available from: <http://buprenorphine.samhsa.gov/data.html>.
15. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance vs placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2008 Apr;(2):CD002207.
16. Fudala PJ, Bridge TP, Herbert S, Williford WO, Chiang CN, Jones K, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med*. 2003 Sep;349(10):949-58.
17. Daulouède JP, Caer Y, Galland P, Villegier P, Brunelle E, Bachellier J, et al. Preference for buprenorphine/naloxone and buprenorphine among patients receiving buprenorphine maintenance therapy in France: a prospective, multicenter study. *J Subst Abuse Treat*. 2010 Jan;38(1):83-9.
18. Strain EC, Harrison JA, Bigelow GE. Induction of opioid-dependent individuals onto buprenorphine and buprenorphine/naloxone soluble-films. *Clin Pharmacol Ther*. 2011 Mar;89(3):443-9.
19. Kakko J, Svanborg KD, Kreek MJ, Heilig M. One-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomized, placebo-controlled trial. *Lancet*. 2003 Feb;361(9358):662-8.
20. Woody GE, Poole SA, Subramaniam G, Dugosh K, Bogenschutz M, Abbott P, et al. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. *JAMA*. 2008 Nov;300(17):2003-11.
21. Weiss RD, Potter JS, Fiellin DA, Byrne M, Connery HS, Dickinson W, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a two-phase randomized controlled trial. *Arch Gen Psychiatry*. 2011 Dec;68(12):1238-46.
22. Polsky D, Glick HA, Yang J, Subramaniam GA, Poole SA, Woody GE. Cost-effectiveness of extended buprenorphine-naloxone treatment for opioid-dependent youth: data from a randomized trial. *Addiction*. 2010 Sep;105(9):1616-24.
23. Fareed A, Vayalapalli S, Casarella J, Drexler K. Effect of buprenorphine dose on treatment outcome. *J Addict Dis*. 2012;31(1):8-18.
24. Bickel WK, Amass L, Crean JP, Badger GJ. Buprenorphine dosing every one, two or three days in opioid-dependant patients. *Psychopharmacology (Berl)*. 1999 Sep;146(2):111-8.
25. Petry NM, Bickel WK, Badger GJ. A comparison of four buprenorphine dosing regimens in the treatment of opioid dependence. *Clin Pharmacol Ther*. 1999 Sep;66(3):306-14.
26. Schottenfeld RS, Pakes J, O'Connor P, Chawarski M, Oliveto A, Kosten TR. Thrice-weekly vs daily buprenorphine maintenance. *Biol Psychiatry*. 2000 Jun;47(12):1072-9.
27. Gibson A, Degemhardt L, Mattick RP, Ali R, White J O'Brien S. Exposure to opioid maintenance treatment reduces long term mortality. *Addiction*. 2008; 103(3):462-468.
28. Farré M, Mas A, Torrens M, Moreno V, Cami J. Retention rate and illicit opioid use during methadone maintenance interventions: a meta-analysis. *Drug Alcohol Depend*. 2002;65:283-90.
29. Gowing L, Ali R, White JM. Buprenorphine for the management of opioid withdrawal. *Cochrane Database Syst Rev*. 2009 Jul 8;(3):CD002025.
30. Johnson RE, Jaffe JH, Fudala PJ: A controlled trial of buprenorphine treatment for opioid dependence. *JAMA*. 1992;267:2750-5.

31. Kamien J, Branstetter S, Amass L. Buprenorphine-naloxone vs methadone maintenance therapy: a randomized double-blind trial with opioid-dependent patients. *Heroin Addict Relat Clin. Probl* 2008;10:5-18.
32. Meader N. A comparison of methadone, buprenorphine and alpha(2) adrenergic agonists for opioid detoxification: a mixed treatment comparison meta-analysis. *Drug Alcohol Depend*. 2010 Apr;108(1-2):110-4.
33. Petitjean S, Stohler R, Deglon J, Livoti S, Waldovogel D, Uehlinger C. Double-blind randomized trial of buprenorphine and methadone in opiate dependence. *Drug Alcohol Depend*. 2001;62:97-104.
34. Soyka M, Zingg C, Koller G, Kuefner H. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: results from a randomized study. *Int J Neuropsychopharmacol*. 2008;11:641-53.
35. Ling W, Wesson D, Charuvastra C, Klett C. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. *Arch Gen Psychiatry*. 1996;53:401-7.
36. Schottenfeld R, Pakes J, Oliveto A, et al. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Arch Gen Psychiatry*. 1997;54:713-20.
37. Ling W, Charuvastra C, Collins JF, Batki S, Brown LS Jr, Kintaudi P, et al. Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. *Addiction*. 1998;93(4):475-86.
38. Lintzeris N. Buprenorphine dosing regime in the management of out-patient heroin withdrawal. *Drug Alcohol Rev*. 2002 Mar;21(1):39-45.
39. Kornor H, Waal H, Sandvik L. Time-limited buprenorphine replacement therapy for opioid dependence: two-year follow-up outcomes in relation to program completion and current agonist therapy status. *Drug Alcohol Rev*. 2007 Mar;26(2):135-41.
40. Fareed A, Vayalapalli S, Casarella J, Drexler K. Treatment outcome for flexible dosing buprenorphine maintenance treatment. *Am J Drug Alcohol Abuse*. 2012 Mar;38(2):155-60.
41. Assadi SM, Hafezi M, Mokri A, Razzaghi EM, Ghaelo P. Opioid detoxification using high doses of buprenorphine in 24 hours: A randomized, double blind, controlled clinical trial. *J Subst Abuse Treat*. 2004 Jul;27(1):75-82.
42. Minozzi S, Amato L, Davoli M. Detoxification treatments for opiate dependent adolescents. *Cochrane Database Syst Rev*. 2009 Apr 15;(2):CD006749.
43. Amass L, Ling W, Freese TE, Reiber C, Annon JJ, Cohen AH, et al. Bringing buprenorphine-naloxone to community treatment providers: the NIDA clinical trials network field experience. *Am J Addict*. 2004;13 Suppl 1:S42-66.
44. Correia CJ, Walsh SL, Bigelow GE, Strain EC. Effects associated with double-blind omission of buprenorphine/naloxone over a 98-h period. *Psychopharmacology (Berl)*. 2006 Dec;189(3):297-306.
45. Maremmani I, Pani P, Pacini M, et al. Substance use and quality of life over 12 months among buprenorphine maintenance-treated and methadone maintenance-treated heroin-addicted patients. *J Subst Abuse Treat*. 2007 Jul;33(1):91-8.
46. Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *NEJM*. 2010;363:2320-31.
47. Pinto H, Maskrey V, Swift L, et al. The SUMMIT trial: a field comparison of buprenorphine vs methadone maintenance treatment. *J Subst Abuse Treat*. 2010;394:340-52.
48. Fiellin D, Moore B, Sullivan L, et al. Long-term treatment with buprenorphine/naloxone in primary care: results at 2-5 years. *Am J Addict*. 2008;17:116-20.
49. Kakko J, Grönbladh L, Svanborg K, et al. A stepped care strategy using buprenorphine and methadone vs conventional methadone maintenance in heroin dependence: a randomized controlled trial. *Am J Psychiatry*. 2007;164:797-803.
50. Strain E, Stitzer M, Liebson I, Bigelow G. Comparison of buprenorphine and methadone in the treatment of opioid dependence. *Am J Psychiatry*. 1994;151:1025-30.
51. Cornish R, Macleod J, Strang J, et al. Risk of death during and after opiate substitution in primary care: prospective observational study in UK General Practice Research Database. *BMJ*. 2010;341:c5475.
52. Strain E, Stoller K, Walsh S, et al. Effects of buprenorphine vs buprenorphine/naloxone tablets in non-dependent opioid abusers. *Psychopharmacology*. 2000;148:374-83.
53. Bell J, Shanahan M, Mutch C, et al. A randomized trial of effectiveness and cost-effectiveness of observed vs unobserved administration of buprenorphine-naloxone for heroin dependence. *Addiction*. 2007;102:1899-907.
54. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev*. 2011 Apr 13;(4):CD001333.
55. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomized trial. *Lancet* 2011; 377:1506-1513.

Therapeutic Class Review Opioid Dependence Agents

Overview/Summary

Partial opioid agonists and opioid antagonists are used alone or in combination in the treatment of opioid use disorder.¹⁻⁷ Buprenorphine (Subutex[®]) buprenorphine/naloxone (Bunavail[®], Suboxone[®], Zubsolv[®]) and naltrexone (ReVia[®], Vivitrol[®]) are Food and Drug Administration (FDA)-approved for the treatment of opioid dependence.¹⁻⁷ Naltrexone is also FDA-approved for use in alcohol dependence.^{2,3} Buprenorphine is available as a sublingual tablet, buprenorphine/naloxone is available as sublingual tablet sublingual film and buccal film, and naltrexone is available as a tablet and extended-release suspension for injection.¹⁻⁷ Products which contain buprenorphine are classified as Schedule III controlled substances. The transdermal and injectable formulations of buprenorphine, Butrans[®] and Buprenex[®], respectively, are FDA-approved for use in the management of pain and will not be discussed within this review.^{8,9} Buprenorphine and buprenorphine/naloxone sublingual tablets and naltrexone tablets are currently available generically.

Buprenorphine is a partial opioid agonist at the μ -opioid receptor (associated with analgesia and dependence) and an antagonist at the κ -opioid receptor (related to dysphoria).^{1,4-7} Compared to full opioid agonists, partial agonists bind to the μ -opioid receptor at a higher degree while activating the receptor to a lesser degree. Partial opioid agonists reach a ceiling effect at higher doses and will displace full opioid agonists from the μ -opioid receptor. Although buprenorphine is associated with significant respiratory depression when used intravenously, or by patients with concomitant benzodiazepine or alcohol abuse, it is associated with a lower abuse potential, a lower level of physical dependence and is safer in overdose when compared to full opioid agonists.¹¹ During buprenorphine administration, opioid-dependent patients experience positive subjective opioid effects which are limited by ceiling effect.⁴⁻⁷

Naloxone and naltrexone are antagonists at the μ -opioid receptor.²⁻⁷ Naloxone has measurable blood levels following sublingual buprenorphine/naloxone administration. However, due to naloxone's low oral bioavailability, there are no significant physiological or subjective differences when compared to the administration of buprenorphine alone. Following intramuscular or intravenous administration, buprenorphine/naloxone is associated with symptoms of opioid withdrawal and dysphoria which is caused by a stronger affinity of naloxone for the opioid receptor compared to buprenorphine.⁴⁻⁷ Therefore, the addition of naloxone to buprenorphine results in a decreased risk of diversion compared to buprenorphine monotherapy.¹⁰

The United States Substance Abuse and Mental Service Clinical Guideline for the Use of Buprenorphine in the Treatment of Opioid Addiction recommends the use of buprenorphine/naloxone for the induction, stabilization and maintenance phases of opioid addiction treatment for most patients. This guideline also notes that buprenorphine alone should be used for pregnant patients and for the induction therapy of patients who are transitioning from methadone treatment.¹¹ Transitioning patients to buprenorphine/naloxone as early as possible to minimize potential diversion associated with buprenorphine monotherapy is also recommended.¹¹ Veterans Health Administration and American Psychiatric Association guidelines outline a similar strategy with methadone and buprenorphine first line.¹²⁻¹³ Only the American Psychiatric Association guidelines recommend naltrexone use as an alternative regimen.¹³

According to the Drug Addiction Treatment Act of 2000, the ability to prescribe buprenorphine or buprenorphine/naloxone for the maintenance or detoxification of opioid dependence is limited to physicians who have obtained a waiver and a unique Drug Enforcement Agency number beginning with an X.¹⁴

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Agents		
Buprenorphine	Partial opioid agonist	a
Naltrexone (ReVia [®] , Vivitrol [®])	Opioid antagonist	-
Combination Product		
Buprenorphine/naloxone (Bunavail [®] , Suboxone [®] , Zubsolv [®])	Partial opioid agonist/ opioid antagonist	a [†]

*Generic available in one dosage form or strengths.

† Buprenorphine/naloxone 2/0.5 mg and 8/2 mg sublingual tablets only.

Indications

Table 2. Food and Drug Administration (FDA)-Approved Indications¹⁻⁷

Indication	Single Entity		Combination
	Buprenorphine	Naltrexone	Buprenorphine/ Naloxone
Alcohol dependence		a	
Opioid dependence, treatment induction [†]	a [*]		a [¶]
Opioid dependence, treatment maintenance [†]	a [*]		a
Opioid dependence [‡]		a [§]	
Opioid dependence, prevention of relapse following opioid detoxification		a	

* According to the manufacturer, buprenorphine sublingual tablets are preferred for use only during induction of treatment for opioid dependence, but can be used for maintenance treatment in patients who cannot tolerate the presence of naloxone.

† As part of a complete treatment plan to include counseling and psychosocial support.

‡ As part of a comprehensive plan of management that includes some measure to ensure the patient takes the medication.

§ Indication is for ReVia[®] only.

|| Indication is for Vivitrol[®] only.

¶ Indication is for Suboxone[®] only.

Pharmacokinetics

The inter-patient variability in the sublingual absorption of buprenorphine and naloxone is wide; however, the variability within subjects is low.⁴⁻⁷ Pharmacokinetic parameters for the combination products are similar to that observed for the individual components.

Table 3. Pharmacokinetics¹⁻⁷

Generic Name	Bioavailability (%)	Metabolism	Protein Binding (%)	Excretion (%)	Half-Life (hours)
Buprenorphine	15 to 31	Cytochrome P450 3A4	96	Urine:30 Feces:69	24 to 42
Naloxone	3	Glucuronidation, N-dealkylation, and reduction	45	Primarily in the urine	2 to 12
Naltrexone	5 to 40	Not specified (>98% metabolized)	21	Primarily in the urine	4(13)*

*The half-life of parent molecule, naltrexone, is four hours; the half-life of the active metabolite 6-β-naltrexol is 13 hours.

Clinical Trials

The safety and efficacy of buprenorphine, buprenorphine/naloxone and naltrexone in the treatment of opioid dependence were demonstrated in several clinical trials outlined in Table 4.

Studies have shown that in adult patients with opioid dependence, the percentage of opioid negative urine tests was significantly higher for both buprenorphine 16 mg daily and buprenorphine/naloxone 16/4 mg daily compared to placebo, while no significant difference was seen between the two active treatment groups.^{16,17} A smaller, randomized controlled trial (N=32) also showed no significant difference in withdrawal symptoms between buprenorphine and buprenorphine/naloxone.¹⁸

FDA-approval of buprenorphine buccal film (Bunavail[®]) and buprenorphine/naloxone tablet (Zubsolv[®]) was via the 505(b)(2) pathway, which allows a manufacturer to compare a new product to a previously-approved drug (or drugs) and utilize data from studies that were performed on the reference drug. These medications have not been specifically studied in clinical trials evaluating their efficacy. Clinical and safety data for these medications is based on previously approved buprenorphine or buprenorphine/naloxone formulations.^{5,7}

Several studies have compared the effectiveness of short-term detoxification to medium- or long-term maintenance treatment with buprenorphine monotherapy or buprenorphine/naloxone. Three studies have shown higher treatment retention rate or lower self-reported drug use with longer treatment duration compared to detoxification; however, one of the studies (Woody et al) showed no significant difference in the percentage of positive urine tests between the two treatment groups at 12 weeks.¹⁹⁻²¹ A cost-effectiveness analysis showed that compared to two-week detoxification, a 12-week outpatient treatment program with buprenorphine/naloxone was associated with an incremental first-year direct medical cost of \$1,376 per quality-adjusted life year and had an 86% chance of being accepted as cost-effective for a threshold of \$100,000 per quality-adjusted life year.²²

In a meta-analysis of 21 randomized controlled trials, buprenorphine at doses ≥ 16 mg/day was demonstrated to be more likely to retain in treatment compared to doses < 16 mg/day; however, no significant difference was seen in the percentage of opioid positive urine tests between the high and low dose groups.²³ Studies that compared different dosing regimens of buprenorphine showed no differences in rate of treatment retention, percentage of urine tests positive for opioids or withdrawal symptoms.²⁴⁻²⁷

Buprenorphine has been compared to methadone in several clinical studies and reviewed in multiple meta-analyses. Overall, studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence.^{18, 27-34} However, when low doses of buprenorphine were studied (≤ 8 mg/day), high doses of methadone (≥ 50 mg/day) proved to be more efficacious.^{28, 35-37}

A meta-analysis of 1,158 participants in 13 randomized trials compared oral naltrexone maintenance treatment to either placebo or non-medication. No difference was seen between the active and control groups in sustained abstinence or most other primary outcomes. Considering only studies in which patient's adherence were strictly enforced, there was a statistically significant difference in retention and abstinence with naltrexone over non therapy (relative risk [RR], 2.93; 95% CI, 1.66 to 5.18).⁵⁴

The efficacy and safety of Vivitrol[®] (naltrexone extended-release) for opioid dependence was evaluated in a 24-week, placebo-controlled randomized control trial. The percentage of subjects achieving each observed percentage of opioid-free weeks was greater in the naltrexone extended release group compared to the placebo group. Complete abstinence (opioid-free at all weekly visits) was sustained by 23% of subjects in the placebo group compared with 36% of subjects in the naltrexone extended release group from Week 5 to Week 24.⁵⁵

Table 4. Clinical Trials

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Mattick et al¹⁵</p> <p>Buprenorphine maintenance therapy</p> <p>vs</p> <p>methadone maintenance therapy (17 studies) or placebo (seven studies)</p>	<p>MA (24 RCTs)</p> <p>Patients with opioid dependence</p>	<p>N=4,497</p> <p>2 to 52 weeks</p>	<p>Primary: Treatment retention, use of opioids, use of other substances, criminal activity and mortality; physical health, psychological health and adverse events</p> <p>Secondary: Not reported</p>	<p>Primary: Buprenorphine at low, medium and high doses was significantly more effective than placebo in retaining patients in treatment but was not as effective as methadone when delivered at adequate doses.</p> <p><i>Flexible dose buprenorphine vs flexible dose methadone</i> Results from eight studies (N=1,068) showed lower retention rate with buprenorphine compared to methadone (RR, 0.85; 95% CI, 0.73 to 0.98). No significant differences were seen in the percentage of opioid positive urine tests (SMD, -0.12; 95% CI, -0.26 to 0.02), self-reported opioid use (SMD, -0.12; 95% CI, -0.31 to 0.07), cocaine use (SMD, 0.11; 95% CI, -0.03 to 0.25), benzodiazepine use (SMD, 0.11; 95% CI, -0.04 to 0.26) or criminal activity (SMD, -0.14; 95% CI, -0.41 to 0.14).</p> <p><i>Low dose buprenorphine vs low dose methadone</i> Results from three studies (N=253) showed lower retention rate with buprenorphine compared to methadone (RR, 0.67; 95% CI, 0.52 to 0.87). No significant differences were seen in percentage of opioid positive urine tests (SMD, -0.35; 95% CI, -0.87 to 0.16), self-reported opioid use (SMD, -0.29; 95% CI, -0.38 to 0.96) or cocaine use (SMD, 0.08; 95% CI, -0.43 to 0.59).</p> <p><i>Low dose buprenorphine vs medium dose methadone</i> Results from three studies (N=305) showed lower retention rate with buprenorphine compared to methadone (RR, 0.67; 95% CI, 0.55 to 0.81). More patients had opioid positive urine tests with buprenorphine compared to methadone (SMD, 0.88; 95% CI, 0.33 to 1.42). One study showed no significant difference in self-reported opioid use (SMD, -0.10; 95% CI, -0.48 to 0.68) while a second study showed significantly fewer reports with methadone. No significant difference was seen in cocaine use (SMD, -0.08; 95% CI, -0.60 to 0.44).</p> <p><i>Medium dose buprenorphine vs low dose methadone</i> One study showed lower retention rate with buprenorphine compared to methadone while three studies showed no statistically significant</p>

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				<p>difference between the two groups. Pooled analysis on treatment retention was not performed due to significant study heterogeneity. Fewer patients had opioid positive urine tests with buprenorphine compared to methadone (SMD, -0.23; 95% CI, -0.45 to -0.01). No significant difference was seen in cocaine use (SMD, 0.38; 95% CI, -0.14 to 0.89).</p> <p><i>Medium dose buprenorphine vs medium dose methadone</i> Two studies (N=312) showed lower retention rate with buprenorphine compared to methadone while four studies (N=335) showed no statistically significant difference between the two groups. Pooled analysis on treatment retention was not performed due to significant study heterogeneity. More patients had opioid positive urine tests with buprenorphine compared to methadone (SMD, 0.27; 95% CI, 0.05 to 0.50). No significant difference was seen in self-reported opioid use (SMD, -0.27; 95% CI, -0.90 to 0.35) or cocaine use (SMD, 0.22; 95% CI, -0.30 to 0.74).</p> <p><i>Low dose buprenorphine vs placebo</i> Results from five studies (N=1,131) showed higher retention rate with buprenorphine compared to placebo (RR, 1.50; 95% CI, 1.19 to 1.88). No significant differences were seen in percentage of opioid positive urine tests (SMD, 0.10; 95% CI, -0.80 to 1.01), cocaine use (SMD, 0.26; 95% CI, -0.10 to 0.62) or benzodiazepine use (SMD, 0.03; 95% CI, -0.33 to 0.38).</p> <p><i>Medium dose buprenorphine vs placebo</i> Results from four studies (N=887) showed higher retention rate with buprenorphine compared to placebo (RR, 1.74; 95% CI, 1.06 to 2.87). Fewer patients had opioid positive urine tests (SMD, -0.28; 95% CI, -0.47 to -0.10) and benzodiazepine use (SMD, -0.81; 95% CI, -1.27 to -0.36) with buprenorphine compared to placebo. One study showed more cocaine use with buprenorphine compared to placebo (SMD, 0.50; 95% CI, 0.05 to 0.94).</p> <p><i>High dose buprenorphine vs placebo</i> Results from four studies (N=728) showed higher retention rate with</p>

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				<p>buprenorphine compared to placebo (RR, 1.74; 95% CI, 1.02 to 2.96). Fewer patients had opioid positive urine tests with buprenorphine compared to placebo (SMD, -1.23; 95% CI, -0.95 to -0.51). No significant difference was seen in cocaine use (SMD, 0.08; 95% CI, -0.20 to 0.36) or benzodiazepine use (SMD, -0.25; 95% CI, -0.52 to 0.02).</p> <p>Secondary: Not reported</p>
<p>Fudala et al¹⁶</p> <p>Phase 1 Buprenorphine 16 mg daily</p> <p>vs</p> <p>buprenorphine/naloxone 16/4 mg daily</p> <p>vs</p> <p>placebo</p> <p>Phase 2 Buprenorphine 8 to12 mg for two days, then buprenorphine/naloxone 24/6 mg daily</p>	<p>MC, PC, RCT with OL phase</p> <p>Patients 18 to 59 years of age who met the DMS-IV criteria for opioid dependence and who were seeking opioid-substitution pharmacotherapy</p>	<p>Phase 1 N=326</p> <p>Phase 2 N=472</p> <p>52 weeks</p>	<p>Primary: Efficacy measured by percentage of urine samples negative for opioids and the patients' self-reported craving for opioids</p> <p>Secondary: Patients' and clinicians' impressions of overall status and adverse events</p>	<p>Primary: The percentages of urine tests that were opioid-negative were 17.8% in the combined-treatment group and 20.7% in the buprenorphine group, as compared to 5.8% in the placebo group (P<0.001 for both comparisons).</p> <p>For each of the four study weeks, the mean scores for opioid craving in the combined-treatment and buprenorphine groups were significantly lower than those in the placebo group (P<0.001 for both comparisons each week).</p> <p>Secondary: Each week scores for patients' and clinicians' global impression were significantly higher in both the combined treatment group and buprenorphine alone group than those in the placebo group (P<0.001 for both comparisons each week).</p> <p>The overall rate of adverse events did not differ significantly among the groups (78% in the combined treatment group, 85% in the buprenorphine only group and 80% in the placebo group).</p> <p>The only adverse events that showed a significant difference in occurrences between treatment groups and placebo were withdrawal syndrome, constipation and diarrhea. (P=0.008, P=0.03 and P=0.005 respectively), with the withdrawal syndrome and diarrhea occurring more frequently in the placebo group and constipation occurring more frequently in the treatment groups.</p>

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<p>Daulouede et al¹⁷</p> <p>Buprenorphine at patient's current dosage SL</p> <p>vs</p> <p>buprenorphine/naloxone at the same buprenorphine dose SL</p>	<p>MC, OL, PRO, XO</p> <p>Patients ≥18 years of age who were receiving stable, maintenance treatment with buprenorphine 2 to 16 mg/day for at least six months</p>	<p>N=53</p> <p>5 days</p>	<p>Primary: Patient-rated global satisfaction with study medication</p> <p>Secondary: Well-being in the past 24 hours, tablet taste, tablet size, SL dissolution time, patient preference and adverse events</p>	<p>Primary: Daily mean VAS score for global satisfaction was similar between buprenorphine (6.83 to 7.04) and buprenorphine/naloxone (6.89 to 7.38; P=0.781).</p> <p>Secondary: Daily mean VAS score for well-being in the past 24 hours were similar between buprenorphine (7.17) and buprenorphine/naloxone (6.33 to 7.04; P=0.824).</p> <p>Patients preferred buprenorphine/naloxone over buprenorphine with regard to tablet size (6.83 to 7.02 vs 5.29 to 5.76; P=0.151), tablet taste (6.83 to 6.98 vs 2.45 to 2.74; P=0.57) and SL dissolution time (6.62 to 6.84 vs 3.73 to 3.92; P=0.751), though no statistical significance was reached.</p> <p>On day five, 54 and 31% of patients indicated preference to buprenorphine/naloxone and buprenorphine, respectively. Fifteen percent of patients indicated that they had no preference (P value not reported). Seventy-one percent of patients also indicated that they would like to continue treatment with buprenorphine/naloxone. Patients were more likely to want to continue treatment with buprenorphine/naloxone if they had a history of injecting buprenorphine.</p> <p>Twenty-three adverse events were reported during study period. The most commonly reported adverse events were fatigue, hyperhidrosis, diarrhea and headache.</p>
<p>Strain et al¹⁸</p> <p>Buprenorphine soluble film 16 mg SL daily</p> <p>vs</p> <p>buprenorphine/naloxone soluble film 16 mg SL daily</p>	<p>RCT</p> <p>Patients 25 to 56 years of age with opioid dependence</p>	<p>N=34</p> <p>5 days</p>	<p>Primary: Change in COWS scores</p> <p>Secondary: Pupillometry, VAS and subjective adjective rating scales and adverse</p>	<p>Primary: No significant differences were observed between buprenorphine and buprenorphine/naloxone with respect to baseline COWS scores (9.1 and 10.1, respectively) and peak post-administration COWS scores (4.2 and 5.7, respectively). COWS scores improved significantly at one hour after dose administration in both treatment groups compared to baseline (P values not reported).</p> <p>Secondary:</p>

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			events	<p>In both treatment groups, pupil diameter decreased, rating on good effects were elevated, and ratings on bad effects and high feeling remained relatively low after dose administration (data not reported).</p> <p>The most common adverse events were those consistent with opioid withdrawal. Four patients reported mild non-ulcerous irritation of oral mucosa, and one patient with a history of hepatitis C had clinically significant elevation of liver function tests.</p>
<p>Kakko et al¹⁹</p> <p>Buprenorphine 16 mg SL daily</p> <p>vs</p> <p>buprenorphine SL six-day taper (8 mg for two days, 4 mg for two days, 2 mg for two days) followed by placebo</p>	<p>PC, RCT</p> <p>Patients >20 years of age with opioid dependence who were seeking admission for medically-assisted heroin withdrawal and who had a history of heroin dependence (as defined by the DSM-IV criteria) for at least one year</p>	<p>N=40</p> <p>1 year</p>	<p>Primary: One-year retention in treatment</p> <p>Secondary: ASI</p>	<p>Primary: One-year retention was significantly higher in the buprenorphine daily group compared to the taper/placebo group (RR, 58.7; 95% CI, 7.4 to 467.4; P=0.001).</p> <p>Secondary: The buprenorphine daily group had a significant reduction in ASI scores over time from baseline (P<0.0001).</p>
<p>Woody et al²⁰</p> <p>Buprenorphine/naloxone up to 14 mg/day of buprenorphine SL for two weeks; dose taper ended by day 14 (detoxification)</p> <p>vs</p> <p>buprenorphine/naloxone up to 24 mg/day of buprenorphine SL for 12</p>	<p>MC, RCT</p> <p>Patients 14 to 21 years of age who met DSM-IV criteria for opioid dependence with physiologic features and who sought outpatient treatment</p>	<p>N=152</p> <p>12 weeks</p>	<p>Primary: Opioid-positive urine test results at weeks four, eight and 12</p> <p>Secondary: Treatment retention rate, self-reported use, injecting, enrollment in addiction treatment outside of the study, other drug use and</p>	<p>Primary: General estimating equation models were used for longitudinal data analysis. When missing data were inputted as positive urine test results, patients in the two-week group were more likely to provide opioid positive urine tests than those in the 12-week group at weeks four (61 vs 26%; OR, 7.05; 95% CI, 2.87 to 17.29; P<0.001) and eight (54 vs 23%; OR, 5.07; 95% CI, 2.02 to 12.79; P=0.001) but not at week 12 (51 vs 43%; OR, 1.84; 95% CI, 0.75 to 4.49; P=0.18).</p> <p>Secondary: At week 12, fewer patients in the two-week group were remained in the study compared to the 12-week group (20.5 vs 70.0%; OR, 0.13; 95% CI, 0.07 to 0.26; P<0.001). The most common reason for study drop-out was</p>

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<p>weeks; dose taper began at week 9 and ended by week 12</p> <p>All patients received 12 weeks of individual and group counseling.</p>			<p>adverse events</p>	<p>missing counseling sessions for at least two weeks.</p> <p>More patients in the two-week group reported use of opioid (OR, 4.30; 95% CI, 2.25 to 8.22; P<0.001), marijuana (OR, 6.15; 95% CI, 2.10 to 18.01; P=0.001), cocaine (OR, 16.39; 95% CI, 3.07 to 87.47; P<0.001) and injection (OR, 3.54; 95% CI, 1.27 to 9.87; P=0.01). Alcohol use was similar between the two groups (OR, 1.35; 95% CI, 0.66 to 2.77; P=0.42).</p> <p>Patients in the two-week group were also more likely to be receiving other addiction treatments (OR, 13.09; 95% CI, 3.73 to 45.89; P<0.001).</p> <p>The most commonly reported adverse events were headaches, nausea, insomnia, stomachache, vomiting and anxiety in both groups.</p>
<p>Weiss et al²¹</p> <p>Phase 1 Buprenorphine/naloxone induction and two-week stabilization at 8 to 32 mg/day of buprenorphine, followed by two-week taper and eight-week post medication follow-up</p> <p>Phase 2 buprenorphine/naloxone at 8 to 32 mg/day of buprenorphine for 12 weeks followed by four-week taper and eight-week follow-up (Phase 2)</p> <p>Patients who did not have successful outcome at week 12 proceeded to Phase 2.</p>	<p>MC, RCT</p> <p>Patients ≥18 years of age who met DSM-IV criteria for opioid dependence and who were seeking treatment</p>	<p>Phase 1 N=653</p> <p>12 weeks</p> <p>Phase 2 N=360</p> <p>24 weeks</p>	<p>Primary: Percentage of patients achieving successful outcome</p> <p>Secondary: Adverse events</p>	<p>Primary: In Phase 1, successful outcome was defined by self-reported opioid use on no more than four days in a month, absence of two consecutive opioid-positive urine test results, no additional substance use disorder treatment and no more than one missing urine sample during the past 12 weeks. Overall, 43 of 653 patients (6.6%) had successful outcome with brief buprenorphine/naloxone treatment.</p> <p>In Phase 2, successful outcome was defined by abstinence from opioids during week 12 and at least two of the previous three weeks (during weeks nine to 11). One hundred and seventy-seven of 360 patients (49.2%) achieved successful outcome in the extended buprenorphine/naloxone treatment. However, the success rate at week 24 dropped to 8.6% (P<0.001 compared to week 12).</p> <p>No differences were seen between patients who received standard medical management and those who received additional opioid dependence counseling.</p> <p>Secondary: The most common adverse events were headache, constipation, insomnia, nasopharyngitis and nausea. Twelve and 24 serious adverse events were reported in Phase 1 and 2, respectively. Psychiatric</p>

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<p>All patients were randomized to receive standard medical management or standard medical management plus opioid dependence counseling prior to entering each study phase.</p>				<p>symptoms, particularly depression leading to hospitalization (N=5), were the most common serious adverse events, all of which occurred soon after completion of treatment taper.</p>
<p>Polsky et al²²</p> <p>Buprenorphine/naloxone up to 14 mg/day of buprenorphine SL for two weeks; dose taper ended by week 2 (detoxification)</p> <p>vs</p> <p>buprenorphine/naloxone up to 24 mg/day of buprenorphine SL for 12 weeks; dose taper began at week 9 and ended by week 12</p> <p>All patients received 12 weeks of individual and group counseling.</p>	<p>MC, RCT</p> <p>Patients 15 to 21 years of age who met DSM-IV criteria for opioid dependence with physiologic features and who sought outpatient treatment</p>	<p>N=152</p> <p>12 weeks</p>	<p>Primary: Treatment cost, opioid-free years, QALY, one-year direct medical cost per QALY and one-year direct medical cost per opioid-free years</p> <p>Secondary: Net social cost</p>	<p>Primary: The cost of the 12-week outpatient treatment program was \$1,514 higher in the 12-week group compared to the two-week group (P<0.001). The point estimate for the incremental direct medical costs during the first year was \$83 higher with the 12-week treatment (P=0.97).</p> <p>During the first year since the start of treatment, patients who received 12-weeks of treatment had an increase in opioid-free years by 0.27 year (P<0.001) and an increase in QALY by 0.06 year (P=0.08) compared to those who received two-week detoxification.</p> <p>The incremental one-year direct medical cost per QALY was \$1,376 for the 12-week treatment program. The outpatient treatment program cost per QALY was \$25,049.</p> <p>The incremental one-year direct medical cost per opioid-free year was \$308, and the outpatient treatment program cost per opioid-free year was \$5,610.</p> <p>The acceptability curve suggested that the cost-effectiveness ratio of 12-week treatment relative to two-week treatment has an 86% chance of being accepted as cost-effective for a threshold of \$100,000 per QALY.</p> <p>Secondary: During the first year, total net social cost, which included total direct medical costs, were lower by \$31,264 for the 12-week group compared to the two-week group (P=0.2).</p>

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Fareed et al ²³ Buprenorphine ≥16 mg/day vs buprenorphine <16 mg/day	MA (21 RCTs) Patients with opioid dependence who were receiving buprenorphine maintenance treatment	N=2,703 3 to 48 weeks	Primary: Treatment retention rate and percentage of urine drug screens positive for opioids or cocaine Secondary: Not reported	Primary: Patients receiving the higher doses of buprenorphine had a higher treatment retention rate compared to those receiving the lower doses (69±12 vs 51±14%; P=0.006). The incidence of positive urine drug screen for opioids and cocaine was similar between the higher and lower dose groups (41±16 vs 47±13%; P=0.35, 44±13 vs 49±20%; P=0.64, respectively). Secondary: Not reported
Bickel et al ²⁴ Buprenorphine maintenance dose (range from 4 to 8 mg/70 kg) SL every 24 hours vs double maintenance dose SL every 48 hours vs triple maintenance dose SL every 72 hours Maintenance dose was administered to patients for 13 consecutive days prior to the initiation of the above dosing schedules.	DB, PC Patients ≥18 years of age who were in good health and met DSM-III criteria for opioid dependence and FDA qualification criteria for methadone treatment	N=16 Approximately 80 days	Primary: Self-report measures (i.e., VAS and adjective rating scales) and observer measures Secondary: Not reported	Primary: Overall, there were no statistically significant differences among the different dosing schedules in any of the outcome measures, including opioid agonist and withdrawal effects observed during the study (P values not reported). Significant differences were observed in some of the measures (i.e., percent identifications as placebo, percent identification as greater than maintenance dose, ARCI subscales) when comparing the daily maintenance dosing to those measures obtained 24, 48 and 72 hours following dosing schedules. Secondary: Not reported
Petry et al ²⁵ Buprenorphine maintenance dose (ranged from 4 to 8	DB, PC, XO Patients ≥18 years of age who were in	N=14 Approximately 43 days	Primary: Subjective opioid agonist and withdrawal effects	Primary: There were no statistically significant differences among the different dosing schedules in any of the outcome measures, including subjective opioid agonist and withdrawal effects (P values not reported).

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<p>mg/70 kg) SL every 24 hours vs double maintenance dose SL every 48 hours vs triple maintenance dose SL every 72 hours vs quadruple maintenance dose SL every 96 hours</p> <p>Patients were administered 10 days of their daily SL maintenance dose to ensure stabilization.</p>	<p>good health and met DSM-III criteria for opioid dependence and FDA qualification criteria for methadone treatment</p>		<p>Secondary: Not reported</p>	<p>When patients received quadrupled doses, there were no significant increases observed in opioid agonist effects compared to their usual maintenance dose (P values not reported).</p> <p>Subjects did report some differences in withdrawal effects (i.e., VAS, ARCI subscales) as the time between buprenorphine doses increased, but the clinical significance of these differences may be limited.</p> <p>Secondary: Not reported</p>
<p>Schottenfeld et al²⁶</p> <p>Buprenorphine 16 mg/70 kg SL daily vs buprenorphine 34 mg/70 kg SL on Fridays and Sundays and 44 mg/70 kg SL on Tuesdays</p> <p>There was a three-day buprenorphine induction phase prior to randomization.</p>	<p>DB, RCT</p> <p>Patients who met FDA criteria for methadone maintenance, had a urine toxicology test positive for opioids and met the DMS-IV criteria for opioid dependence</p>	<p>N=92 12 weeks</p>	<p>Primary: Retention, three times per week urine toxicology tests and weekly self-reported illicit drug use</p> <p>Secondary: Not reported</p>	<p>Primary: There was no difference in percentage of patients who completed the 12 weeks of treatment between the daily and thrice-weekly groups (76.6 vs 71.1%; P value not reported). There was also no statistical difference observed between the two treatment groups in the average number of weeks in treatment (11.0±4.0 and 11.2±3.7 weeks, respectively; P=0.64).</p> <p>A significant decline in the proportion of opioid-positive urine tests was observed during the study (P<0.001), but there was no statistical difference between the two treatment groups (57% in the daily group vs 58% in the thrice-weekly group; P=0.84).</p> <p>A significant decline in the number of self-reported days per week of heroin use was observed during the study (P<0.001), but there was no statistical difference between the two treatment groups (1.30±0.23 in the</p>

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				<p>daily group vs 1.70±0.22 in the thrice-weekly group; P=0.27).</p> <p>Secondary: Not reported</p>
<p>Gibson et al²⁷</p> <p>Buprenorphine (dosing not specified)</p> <p>vs</p> <p>methadone (dosing not specified)</p>	<p>DB, MC, RCT</p> <p>Patients ≥18 years of age who were heroin-dependent and lived within commuting distance of the clinic</p>	<p>N=405</p> <p>91 day treatment period followed by a 10 year longitudinal follow-up</p>	<p>Primary: Effects of opioid maintenance treatment on mortality rate</p> <p>Secondary: Difference between two treatment groups in exposure to opioid maintenance treatment episodes greater than seven and 14 days, causes of death and effects of race, level of heroin dependence and age on mortality rate</p>	<p>Primary: There were 30 deaths in the follow-up period (16 in the buprenorphine group vs 14 in the methadone group). Each additional treatment episode of methadone or buprenorphine treatment lasting longer than seven days reduced the risk of death on average by 28% (95% CI, 7 to 44).</p> <p>Secondary: There was no significant difference over the follow-up period in percentage time exposure to opioid maintenance treatment episodes greater than seven days between the buprenorphine and methadone groups (P=0.52). The methadone group was significantly more likely to spend greater percentage follow-up time in methadone treatment episodes longer than 14 days (P<0.0001). The buprenorphine group was also significantly more likely to spend longer time in buprenorphine treatment episodes longer than 14 days (P<0.0001).</p> <p>Drug overdose or related complications were the most common causes of death in the 30 deceased participants (40% of the deaths).</p> <p>Aboriginal or Torres Strait Islander patients had 5.32 times the risk of death of non-Aboriginal or Torres Strait Islander participants (95% CI, 1.89 to 14.95).</p> <p>The risk of death among participants using more heroin at baseline during follow-up was 12% lower (95% CI, 5 to 18; P value not reported) than less frequent heroin users at baseline.</p> <p>The risk of death during the follow-up period was 11% lower for older patients (95% CI, 2 to 19) than younger participants who were randomized to methadone.</p>

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<p>Farré et al²⁸</p> <p>Buprenorphine ≥8 mg daily (high dose)</p> <p>vs</p> <p>buprenorphine <8 mg daily (low dose)</p> <p>vs</p> <p>methadone ≥50 mg daily (high dose)</p> <p>vs</p> <p>methadone <50 mg daily (low dose)</p> <p>vs</p> <p>levo-acetylmethadol</p>	<p>MA</p> <p>Patients seeking treatment for opioid dependence</p>	<p>N=1,944 (13 trials)</p> <p>Variable duration</p>	<p>Primary: Retention rate and reduction of opioid use</p> <p>Secondary: Not reported</p>	<p>Primary: High doses of methadone were more effective than low doses of methadone in the reduction of illicit opioid use (OR, 1.72; 95% CI, 1.26 to 2.36).</p> <p>High doses of methadone were significantly more effective than low doses of buprenorphine (<8 mg/day) for retention rates and illicit opioid use, but similar to high doses of buprenorphine (≥8 mg/day).</p> <p>Patients treated with levo-acetylmethadol had more risk of failure of retention than those receiving high doses of methadone (OR, 1.92; 95% CI 1.32 to 2.78).</p> <p>Secondary: Not reported</p>
<p>Gowing et al²⁹</p> <p>Buprenorphine</p> <p>vs</p> <p>methadone (five studies), α₂-adrenergic agonists (12 studies) or different buprenorphine-based regimens (five studies)</p>	<p>MA (22 RCTs)</p> <p>Patients who were withdrawing from heroin and/or methadone</p>	<p>N=1,736</p> <p>5 to 90 days</p>	<p>Primary: Intensity of withdrawal, duration of withdrawal treatment, adverse events and completion of treatment, number of treatment following completion of withdrawal intervention</p>	<p>Primary: Overall, buprenorphine and methadone appeared to be similarly effective in the management of opioid withdrawal. Buprenorphine was shown to be more effective than clonidine in reducing withdrawal symptoms and retaining patients in withdrawal treatment. No significant differences in adverse events were found between buprenorphine and other treatments.</p> <p><i>Buprenorphine vs methadone</i> Studies comparing buprenorphine to methadone reported no significant difference in withdrawal severity between the two groups.</p> <p>Results from two studies showed that duration of withdrawal treatment was 1.38 days shorter with buprenorphine than methadone, but this</p>

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			Secondary: Not reported	<p>difference did not reach statistical significance (95% CI, -4.27 to 1.51; P=0.35).</p> <p>Four studies showed no significant difference in completion of treatment between buprenorphine and methadone (RR, 1.18; 95% CI, 0.93 to 1.49; P=0.18).</p> <p><i>Buprenorphine vs α_2-adrenergic agonists</i> Intensity of withdrawal was significantly lower with buprenorphine compared to clonidine in terms of both mean peak withdrawal score (SMD, -0.45; 95% CI, -0.64 to -0.25; P<0.001) and mean overall withdrawal score (SMD, -0.59; 95% CI, -0.79 to -0.39; P<0.001).</p> <p>In four studies, duration of withdrawal treatment was significantly shorter with buprenorphine by 0.92 day compared to clonidine (95% CI, 0.57 to 1.27; P<0.001).</p> <p>Completion of treatment was shown to be more likely with buprenorphine compared to clonidine in eight studies (RR, 1.64; 95% CI, 1.31 to 2.06; P<0.001; NNT, 4).</p> <p><i>Comparison of different rates of buprenorphine taper</i> Two studies showed no significant difference in withdrawal severity between groups of different rates of buprenorphine dose reduction. One study showed greater patient-rated severity with the rapid taper group but no difference in observers' assessment. Another study showed that patients in the rapid taper group but not the gradual taper group reported muscle aches and insomnia. A third study showed that peak withdrawal occurred earlier with the rapid taper group.</p> <p>Duration of treatment was shown to be shorter with the rapid taper group than the gradual taper group (9 vs 28 days; P value not reported) but not significantly different in the other study (9.5±1.8 vs 9.8±0.9 days; P>0.05).</p> <p>Data were conflicting on the completion of treatment.</p>

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Johnson et al³⁰</p> <p>Buprenorphine 8 mg daily vs methadone 60 mg daily vs methadone 20 mg daily</p>	<p>DB, PG, RCT</p> <p>Adults seeking treatment for opioid dependence</p>	<p>N=162</p> <p>17-week maintenance phase, followed by a 8-week detoxification phase</p>	<p>Primary: Retention time in treatment, urine samples negative for opioids, and failure to maintain abstinence</p> <p>Secondary: Not reported</p>	<p>Secondary: Not reported</p> <p>Primary: During the maintenance phase, the retention rates were significantly greater for buprenorphine (42%) than for methadone 20 mg/day (20%; P<0.04).</p> <p>During the maintenance phase, the percentage of urine samples negative for opioids was significantly greater for buprenorphine (53%; P<0.001) and methadone 60 mg/day (44%; P<0.04), than for methadone 20 mg/day (29%).</p> <p>Failure to maintain abstinence during the maintenance phase was significantly greater for methadone 20 mg/day, than for buprenorphine (P<0.03).</p> <p>During the detoxification phase, there were no differences between the treatment groups with regards to urine samples negative for opioids.</p> <p>During the 25 week study period, retention rates for buprenorphine (30%; P<0.01) and methadone 60 mg/day (20%; P<0.05) were significantly greater than for methadone 20 mg/day (6%).</p> <p>All treatments were well tolerated, with similar profiles of self-reported adverse effects.</p> <p>The percentages of patients who received counseling did not differ between groups.</p> <p>Secondary: Not reported</p>
<p>Kamien et al³¹</p> <p>Buprenorphine/ naloxone 8 mg/2 mg daily</p>	<p>DB, DD, RCT</p> <p>Patients ≥18 years of age who met criteria for opioid</p>	<p>N=268</p> <p>17 weeks</p>	<p>Primary: Amount of opioid abstinence achieved over time</p>	<p>Primary: The percentage of opioid-free urine samples over time did not differ significantly among drug groups (P=0.81) or among drug doses (P=0.46).</p> <p>Secondary:</p>

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs buprenorphine/ naloxone 16 mg/4 mg daily vs methadone 45 to 90 mg daily	dependence and who were using heroin or prescription opioids or receiving methadone maintenance treatment		Secondary: Proportion of patients who achieved 12 consecutive opioid-negative samples, proportion of patients with successful inductions, medication compliance, non-opioid illicit drug use, and treatment retention	<p>The proportion of patients who had at least 12 consecutive opioid-negative urine samples were as follows: 10% (buprenorphine/naloxone 8 mg/2 mg) 17% (buprenorphine/naloxone 16 mg/4 mg), 12% (methadone 45 mg), and 16% (methadone 90 mg). The percentage of patients with at least 12 consecutive opioid-negative urine samples differed by dose (8 vs 16 mg buprenorphine/naloxone; $P<0.001$, 45 vs 90 mg methadone; $P=0.02$), but not by drug (8 mg buprenorphine/naloxone vs 45 mg methadone; $P=0.18$, 16 mg buprenorphine/naloxone vs 90 mg methadone; $P=0.22$). Those receiving higher doses of methadone or buprenorphine/naloxone were more likely to have at least 12 consecutive opioid-negative urine samples than those receiving lower doses.</p> <p>Successful inductions occurred in 80.5, 81.0, 82.7 and 82.9% of the patients receiving buprenorphine/naloxone 8 mg/2 mg, buprenorphine/naloxone 16 mg/4 mg, methadone 45 and 90 mg, respectively. There were no significant differences among the treatment groups ($P=0.22$ to $P=0.98$).</p> <p>Medication compliance did not differ significantly among the treatment groups ($P=0.41$).</p> <p>Non-opioid drug use did not change significantly over time, nor did it differ significantly across groups ($P=0.32$ to $P=0.83$).</p> <p>Treatment retention did not differ significantly in the low dose groups ($P=0.09$) or in the high dose groups ($P=0.28$).</p>
Meader et al ³² Buprenorphine vs methadone (three studies), clonidine (eight studies) or lofexidine* (one study)	MA (23 RCTs) Patients with opioid dependence who were undergoing opioid detoxification	N=2,112 3 to 30 days	Primary: Completion of treatment Secondary: Not reported	Primary: Buprenorphine had the highest probability (85.00%) of being the most effective treatment for opioid detoxification, followed by methadone (12.10%), lofexidine (2.60%) and clonidine (0.01%). There was no significant difference between buprenorphine and methadone (OR, 1.64; 95% CI, 0.68 to 3.79). Based on the mixed treatment comparisons, buprenorphine was more effective than clonidine (OR, 3.95; 95% CI, 2.01 to 7.46) and lofexidine (OR, 2.64; 95% CI, 0.90 to 7.50), though the latter comparison did not

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>In addition, studies involving the following comparisons were included: methadone vs clonidine (five studies), methadone vs lofexidine* (two studies) and clonidine vs lofexidine* (four studies)</p>				<p>reach statistical significance.</p> <p>Methadone was more effective than clonidine (OR, 2.42; 95% CI, 1.07 to 5.37) and lofexidine (OR, 1.62; 95% CI, 0.58 to 4.57), though the latter comparison did not reach statistical significance.</p> <p>Secondary: Not reported</p>
<p>Petitjean et al³³</p> <p>Buprenorphine sublingual tablets (flexible dosing schedule)</p> <p>vs</p> <p>methadone (flexible dosing schedule)</p>	<p>DB, RCT</p> <p>Patients seeking treatment for opioid dependence</p>	<p>N=58</p> <p>6 weeks</p>	<p>Primary: Treatment retention rate, urine samples positive for opiates, substance use</p> <p>Secondary: Not reported</p>	<p>Primary: The retention rate was significantly better in the methadone group than in the buprenorphine group (90 vs 56%, respectively; P<0.001).</p> <p>There were similar proportions of opioid positive urine samples in both treatment groups (buprenorphine, 62%; methadone, 59%) and positive urine specimens, as well as mean heroin craving scores decreased significantly over time (P=0.035 and P<0.001).</p> <p>The proportion of cocaine-positive toxicology results did not differ between groups.</p> <p>At week six, the mean stabilization doses were 10.5 mg/day for buprenorphine and 69.8 mg/day for methadone.</p> <p>Secondary: Not reported</p>
<p>Soyka et al³⁴</p> <p>Buprenorphine (mean daily dose 9 to 12 mg)</p> <p>vs</p> <p>methadone (mean daily dose 44 to 50 mg)</p>	<p>RCT</p> <p>Opioid-dependent patients who had been without opioid substitution therapy</p>	<p>N=140</p> <p>6 months</p>	<p>Primary: Retention rate; substance use; predictors of outcome</p> <p>Secondary: Not reported</p>	<p>Primary: There was an overall retention rate of 52.1%. There was no significant difference between buprenorphine-treated patients and methadone-treated patients (55.3 vs 48.4%).</p> <p>Substance use decreased significantly over time in both groups and was non-significantly lower in the buprenorphine group.</p> <p>Predictors of outcome were length of continuous opioid use and age at onset of opioid use (significant in the buprenorphine group only). Mean dosage and other parameters were not significant predictors of outcome.</p>

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The intensity of withdrawal symptoms showed the strongest correlation with drop-out. Secondary: Not reported
Ling et al ³⁵ Buprenorphine 8 mg daily vs methadone 30 mg daily vs methadone 80 mg daily	DB, RCT Patients seeking treatment for opioid dependence	N=225 1 year	Primary: Urine toxicology, retention, craving, and withdrawal symptoms Secondary: Not reported	Primary: Patients receiving high-dose methadone maintenance therapy performed significantly better on measures of retention, opioid use, and opioid craving than either the low-dose methadone group or the buprenorphine group. Performance on measures of retention, opioid use, and opioid craving were not significantly different between the low-dose methadone group or the buprenorphine group. Secondary: Not reported
Schottenfeld et al ³⁶ Buprenorphine 4 mg daily vs buprenorphine 12 mg daily vs methadone 20 mg daily vs methadone 65 mg daily	DB, RCT Patients seeking treatment for opioid dependence	N=116 24 weeks	Primary: Retention in treatment and illicit opioid and cocaine use Secondary: Not reported	Primary: There were significant effects of maintenance treatment on rates of illicit opioid use, but no significant differences in treatment retention or the rates of cocaine use. The rates of opioid-positive toxicology tests were lowest for treatment with 65 mg of methadone (45%), followed by 12 mg of buprenorphine (58%), 20 mg of methadone (72%), and 4 mg of buprenorphine (77%), with significant contrasts found between 65 mg of methadone and both lower-dose treatments and between 12 mg of buprenorphine and both lower-dose treatments. Secondary: Not reported
Ling et al ³⁷ Buprenorphine 1, 4, 8 or 16 mg/day dissolved in 30%	DB, MC Patients with a mean age of 36	N=736 16 weeks	Primary: Safety and efficacy as measured by retention in	Primary: Fifty-one percent of the patients completed the 16 week study. Completion rates varied by dosage group as follows: 40% for the 1 mg

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ethyl alcohol	who met the DSM-III criteria for opioid dependence and had used opioids daily during the previous six months		<p>treatment, illicit opioid use and opioid craving</p> <p>Secondary: Not reported</p>	<p>group, 51% for the 4 mg group, 52% for the 8 mg group and 61% for the 16 mg group.</p> <p>The 16 mg group had significantly more patients with 13 consecutive negative urines than both the 1 mg group (P<0.001) and the 4 mg group (P<0.006).</p> <p>Significantly higher craving scores were observed for the 1 mg group compared to the 8 mg group at week four (P<0.01), eight (P<0.01) and 12 (P=0.04), but not at week 16 (P=0.15).</p> <p>Secondary: Not reported</p>
<p>Lintzeris et al³⁸</p> <p>Buprenorphine SL tablets titrated to achieve comfortable withdrawal at the following total daily dose range: 4 to 8 mg on day 1, 0 to 16 mg on days 2 to 4, 0 to 8 mg on day 5 and 0 mg on days 6 to 8</p>	<p>OL</p> <p>Patients ≥18 years of age with opioid dependent and an opioid positive urine screen on assessment</p>	<p>N=18</p> <p>8 days</p>	<p>Primary: Severity of withdrawal experience as measured by VAS</p> <p>Secondary: Measure of patient satisfaction with buprenorphine treatment, satisfaction with dosing regimen by Likert scale, drug use during the withdrawal episode, positive urine drug screen and adverse events</p>	<p>Primary: The mean expected withdrawal severity as measured by VAS was 28 at intake. The mean experienced withdrawal severity was significantly lower compared to baseline (16±12; 95% CI, -26 to -2; P<0.05).</p> <p>Secondary: When asked to identify positive and negative aspects of treatment, 79% of patients reported no, minimal or mild withdrawal symptoms; 57% of patients reported feeling normal and being able to perform daily activities; 36% of patients reported reduced or no cravings for heroin use; 29% of patients reported being psychologically comfortable during withdrawal; 7% of patients reported dissatisfaction with inconvenience of daily dosing; 7% of patients reported that the dosing interval was too short; 7% of patients identified sleep disturbance; 57% of patients reported side effects and 36% did not report any negative aspects of treatment.</p> <p>The majority of patients rated the adequacy of their doses as “about right” on the Likert scale (11 of 14 patients). Three subjects rated their doses as “too low” (P value not reported).</p> <p>Over the eight days of treatment, five patients (28%) reported no drug use, five patients (28%) reported drug use on one day, two patients (11%) reported drug use on two days, three patients (17%) reported drug use on</p>

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>three or more days, and data was unavailable for the remaining three patients (P values not reported).</p> <p>On day five, nine patients (50% of total sample and 60% of patients in treatment) had a negative urine screen for opioids. Five patients had positive urine test results while results for one patient were missing.</p> <p>On days seven and eight, there were an equal number of patients with positive and negative opioid urine screens (four patients, 22% of the sample, 29% of patients in treatment). Four patients were no longer in treatment, and six reported heroin use (P values not reported).</p> <p>Sixteen patients reported adverse events. The most common were headache (50%), sedation (28%), nausea, constipation and anxiety (21%).</p>
<p>Kornor et al³⁹</p> <p>Buprenorphine flexible daily dosing to a maximum dose of 16 mg daily</p>	<p>OL</p> <p>Patients ≥22 years of age with opioid dependence who were willing to enroll in a nine-month buprenorphine program</p>	<p>N=75</p> <p>9 months</p>	<p>Primary: Self reported opioid abstinence in program completers and non-completers</p> <p>Secondary: Difference in number of days within 30 days prior to follow up interview in which the following occurred: heavy drinking, street opioid use, sedative, amphetamine, cannabis, polysubstance and intravenous use, employment, illegal activities, psychiatric</p>	<p>Primary: More program completers compared to non-completers reported abstinence from opioids during the 30 days prior to the follow-up, a difference that was not significant (7 vs 2; P=0.16).</p> <p>Secondary: Completers were employed for a higher number of days than non-completers at follow up (9 vs 2 days, respectively; P=0.012). There were no statistically significant differences between the two groups with regard to other psychosocial variables and substance use (P values not reported).</p> <p>At follow-up, 37 patients received agonist replacement therapy in the past 30 days while 31 patients did not. There was a higher rate of abstinence from street opioids in the patients who received agonist therapy (24 of 37) compared to those who did not (9 of 31; P=0.003).</p> <p>Patients who received agonist therapy within 30 days prior to follow-up had spent fewer days using street opioids (P<0.001), using two or more substances (P<0.038), injecting substances (P<0.007) and engaging in illegal activities (P<0.001) compared to those who did not. Patients who</p>

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			problems and medical problems	received agonist therapy had also been employed for a higher number of days (P=0.046). There was no difference between the two groups in health problems, heavy drinking and use of sedatives, amphetamine and cannabis (P values not reported).
<p>Fareed et al⁴⁰</p> <p>Buprenorphine >16 mg/day (mean dose, 27.5±4.8 mg)</p> <p>vs</p> <p>buprenorphine ≤16 mg/day (mean dose, 11.5±4.8 mg)</p>	<p>OS</p> <p>Patients with opioid dependence who were receiving buprenorphine maintenance treatment</p>	<p>N=77</p> <p>≥1 month</p>	<p>Primary: Treatment retention rate and percentage of urine drug screens positive for opioids or cocaine</p> <p>Secondary: Not reported</p>	<p>Primary: Treatment drop-out rate was similar between the high- and moderate-dose groups (37.5 vs 43.0%; P=0.67).</p> <p>The percentage of the first four urine drug screens that were positive for opioids was higher in the high-dose group compared to the moderate-dose group (45, 14, 9 and 5 vs 29, 5, 10 and 5%, respectively; P<0.00001). No significant differences were seen between the two groups in the percentage of the first four urine drug screens positive for cocaine (P=0.74) or the last four urine drug screens positive for opioids or cocaine (P=0.21 and P=0.47, respectively).</p> <p>Secondary: Not reported</p>
<p>Assadi et al⁴¹</p> <p>Experimental protocol: Buprenorphine 12 mg IM in 24 hours</p> <p>vs</p> <p>Conventional protocol: buprenorphine taper IM over five days (3 mg for two days, 2.7 mg for one day, 1.2 mg for one day and 0.6 mg for 1 day)</p> <p>Authors reported that buprenorphine SL is two thirds as potent as IM, so 32</p>	<p>DB, PG, RCT</p> <p>Patients 18 to 60 years of age who met the DSM-IV criteria for opioid dependence</p>	<p>N=40</p> <p>10 days</p>	<p>Primary: Days of retention in treatment and rates of successful detoxification</p> <p>Secondary: SOWS and OOWS</p>	<p>Primary: There were no significant differences among the treatment protocols in the average number of days the patients stayed in the study (experimental group, 9.5±1.8 days vs the conventional group, 9.8±0.9 days; P=0.52).</p> <p>There were no significant differences in the rates of successful detoxification among the treatment protocols; 18 patients (90%) in each group were detoxified successfully (P value not reported).</p> <p>Secondary: There was no significant difference demonstrated in mean overall SOWS scores between the two treatment protocols (experimental group, 9.0±6.6 vs the conventional group, 9.3±5.2; P=0.86).</p> <p>There were no significant differences found between the treatment protocols with regard to OOWS scores of the main effect of treatment (P=0.81), main effect of time (P=0.60) or treatment-time interactions</p>

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg SL is equivalent to 18 mg IM.				(P=0.56).
Minozzi et al ⁴² Buprenorphine vs buprenorphine-based treatment (one study) or clonidine (one study)	SR (2 RCTs) Patients 13 to 18 years of age with opioid dependence	N=190 2 to 12 weeks	Primary: Drop-out rate, opioid-positive urine test results or self-reported drug use, tolerability and rate of relapse Secondary: Enrollment in other treatment, use of other substances of abuse, overdose, criminal activity and social functioning	Primary: The authors stated that more clinical trials, especially ones involving methadone, were needed to draw a conclusion in the detoxification treatment for opioid dependent adolescents. <i>Buprenorphine vs clonidine</i> There were no significant differences between buprenorphine and clonidine in drop-out rate (RR, 0.45; 95% CI, 0.20 to 1.04) or duration and severity of withdrawal symptoms (WMD, 3.97; 95% CI, -1.38 to 9.32). <i>Buprenorphine/naloxone detoxification (two weeks) vs maintenance treatment (12 weeks)</i> Drop-out rate and relapse rate were significantly higher with detoxification compared to maintenance treatment (RR, 2.67; 95% CI, 1.85 to 3.86; RR, 1.36; 95% CI, 1.05 to 1.76, respectively). No significant differences were seen in opioid positive urine test results (RR, 1.03; 95% CI, 0.82 to 1.28). Self-reported drug use was higher with detoxification compared to maintenance treatment (RR, 1.36; 95% CI, 1.05 to 1.76). Secondary: <i>Buprenorphine vs clonidine</i> Patients receiving buprenorphine were more likely to receive psychosocial or naltrexone treatment (RR, 11.00; 95% CI, 1.58 to 76.55). <i>Buprenorphine/naloxone detoxification (two weeks) vs maintenance treatment (12 weeks)</i> Self-reported alcohol and marijuana use were similar between the two groups (RR, 1.13; 95% CI, 0.63 to 2.02; RR, 1.58; 95% CI, 0.83 to 3.00, respectively). More patients in the detoxification group reported use of cocaine (RR, 8.54; 95% CI, 1.11 to 65.75).
Amass et al ⁴³ Buprenorphine/naloxone SL tablets for a total of 4/1 mg	DB, MC, OL, RCT Patients ≥15 years of age with opioid	N=234 13 days	Primary: Treatment compliance and retention	Primary: Of the 234 patients on buprenorphine/naloxone, all of the patients took the first dose, and most patients received the second dose on day one (82.9%), the doses on days two and three (90.1%) and the majority of

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>on day 1 followed by another 4/1 mg on day 1 unless the patient displayed agonist effects; escalated to 16/4 mg on day 3 and tapered by 2 mg buprenorphine/day to 2/0.5 mg by day 13</p>	<p>dependence who were experiencing withdrawal symptoms and who requested medical treatment for the symptoms</p>		<p>Secondary: Ancillary medications administration rate and adverse effects</p>	<p>doses over the entire treatment course (10.5±3.8 of the 13 possible doses; 80.7%). Sixty-eight percent of patients completed the entire detoxification program (P values not reported).</p> <p>Secondary: The majority of patients (80.3%) were treated with ancillary medications for an average of 2.3 withdrawal medications. The most commonly treated symptoms were insomnia (61.5%), anxiety and restlessness (52.1%) and bone pain and arthralgias (53.8%).</p> <p>Sixty-one percent of adverse events were expected events associated with drug relapse; however, the specific adverse events were not reported.</p>
<p>Correia et al⁴⁴</p> <p>Buprenorphine/naloxone 8/2 mg SL daily</p> <p>vs</p> <p>buprenorphine/naloxone 16 mg/4 mg SL daily</p> <p>vs</p> <p>buprenorphine/naloxone 32/8 mg SL daily</p> <p>After two weeks on each maintenance dose, participants underwent challenge sessions consisting of IM hydromorphone.</p>	<p>DB, RCT</p> <p>Patients with active opioid dependence as confirmed through self-report, urinalysis and observation and who met DSM-IV criteria of current opioid (heroin) dependence</p>	<p>N=8</p> <p>11 weeks</p>	<p>Primary: Opioid blockade and withdrawal effects</p> <p>Secondary: Not reported</p>	<p>Primary: Although substantial, all three buprenorphine doses provided incomplete blockade against opioid agonist effects for 98 hours based on the number of subjective (i.e., drug effects) and physiologic (i.e., blood pressure, heart rate) effects measured (P values for most measures were >0.05 with the exception of pupil diameter and oxygen saturation). The 32/8 mg dose produced less constricted pupils compared to the 8/2 mg dose (P≤0.05).</p> <p>The 8/2 mg dose produced lower oxygen saturation as compared to the 16/4 mg dose (P≤0.05).</p> <p>There were no significant differences regarding symptoms of withdrawal among the study doses (P>0.05).</p> <p>As time since the last dose increased, so did the number of mild effects reported (P value not reported).</p> <p>Secondary: Not reported</p>

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Maremmani et al ⁴⁵ Buprenorphine vs methadone	OL Patients involved in a long-term treatment program with buprenorphine or methadone	N=213 12 months	Primary: Opioid use, psychiatric status, quality of life Secondary: Not reported	Primary: There were significant improvements in opioid use, psychiatric status, and quality of life between the 3rd and 12th months for buprenorphine-treated and methadone-treated patients. Secondary: Not reported
Jones et al ⁴⁶ Buprenorphine 2 to 32 mg per day vs methadone 20 to 140 mg per day	DB, DD, MC, RCT Opioid-dependent women 18 to 41 years of age with a singleton pregnancy between 6 and 30 weeks	N=175 ≥10 days	Primary: Neonates requiring neonate abstinence syndrome therapy, total morphine needed, length of hospital stay, and head circumference Secondary: Not reported	Primary: Percentage neonates requiring neonate abstinence syndrome treatment, peak neonate abstinence syndrome scores, or head circumference did not differ significantly between groups. Neonates exposed to buprenorphine required an average 89% less morphine (1.1 and 10.4 mg; P<0.0091) than did neonates exposed to morphine. Neonates exposed to buprenorphine required an average 43% less time in hospital (10.0 vs 17.5 days; P<0.0091). The methadone group had higher rates of nonserious maternal events overall (P=0.003) and of nonserious cardiac events in particular (P=0.01). No differences in serious adverse events were detected in mothers or nonserious adverse events in neonates. Secondary: Not reported
Pinto et al ⁴⁷ Buprenorphine vs methadone	OS, PRO Cohort of opioid-dependent patients new to substitution therapy	N=361 6 months	Primary: Retention in treatment at six months or successful detoxification based on patient selected substitution therapy Secondary:	Primary: A total of 63% of patients chose methadone and 37% chose buprenorphine. At six months, 50% of buprenorphine patients compared to 70% of methadone patients had favorable outcomes (OR, 0.43; 95% CI, 0.20 to 0.59; P<0.001). Methadone patients were more likely to remain on therapy than those on buprenorphine (HR, 2.08; 95% CI, 1.49 to 2.94). Retention was the primary factor in favorable outcomes at six months.

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Not reported	<p>Buprenorphine patients were more likely to not use illicit opiates (OR, 2.13; 95% CI, 1.509 to 3.027; P<0.001) and to achieve detoxification.</p> <p>A total of 28% of patients selecting buprenorphine reported they would not have accessed treatment with methadone therapy.</p> <p>Secondary: Not reported</p>
<p>Fiellin et al⁴⁸</p> <p>Buprenorphine/naloxone</p>	<p>OS</p> <p>Patients meeting criteria for opioid dependence</p>	<p>N=166</p> <p>2 to 5 years</p>	<p>Primary: Retention in treatment; percentage of opioid-negative urine specimens</p> <p>Secondary: Percentage of cocaine-negative urine specimens; buprenorphine dose; patient satisfaction; serum transaminases; adverse events</p>	<p>Primary: During the follow-up period, 40 patients left treatment.</p> <p>A total of 91% of urine specimens had no evidence of illicit opioids.</p> <p>Secondary: Overall, 96% had no evidence of cocaine; 98% of tested urines had no evidence of benzodiazepines; 99% of tested urines had no evidence of methadone.</p> <p>The mean dose of buprenorphine/naloxone was 17 mg.</p> <p>The mean score on the patient satisfaction instruments was 86 out of a possible 95.</p> <p>No patients developed elevations in their aspartate aminotransferase or alanine aminotransferase values that required changes in buprenorphine/naloxone dose or discontinuation.</p> <p>No serious adverse events directly related to buprenorphine/naloxone treatment occurred over the two to five-year follow-up period.</p>
<p>Kakko et al⁴⁹</p> <p>Buprenorphine/naloxone (stepped treatment)</p> <p>vs</p>	<p>RCT</p> <p>Patients >20 years of age with heroin dependence for >1 year</p>	<p>N=96</p> <p>24-day induction phase, followed by a 6 month</p>	<p>Primary: Retention in treatment</p> <p>Secondary: Completer analyses of problem severity</p>	<p>Primary: The 6-month retention was 78% with buprenorphine/naloxone stepped treatment and methadone maintenance therapy being virtually identical (adjusted OR, 1.02; 95% CI, 0.65 to 1.60).</p> <p>The proportion of urine samples free of illicit opiates over time increased and ultimately reached approximately 80% in both arms at the end of the</p>

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
methadone (maintenance treatment)		follow-up phase	(Addiction Severity Index); proportion of urine samples free of illicit drugs	study (P=0.00003). No difference between the two groups was found (P=0.87). Secondary: Problem severity as measured by the Addiction Severity Index decreased over time (P<0.000001). No difference between the treatment arms was found (P=0.90).
Strain et al ⁵⁰ Buprenorphine SL tablets (flexible dosing schedule) vs methadone (flexible dosing schedule)	DB, DD, RCT Patients seeking treatment for opioid dependence	N=164 26 weeks	Primary: Treatment retention rate, medication and counseling compliance, urine samples positive for opiates Secondary: Not reported	Primary: Buprenorphine (mean dose ~9 mg/day) and methadone (mean dose 54 mg/day) were equally effective in sustaining retention in treatment, compliance with medication, and counseling regimens. In both groups, 56% of patients remained in the treatment program through the 16-week flexible dosing period. Opioid-positive urine sample rates were 55 and 47% for buprenorphine and methadone groups, respectively. Cocaine-positive urine sample rates were 70 and 58%, respectively. Secondary: Not reported
Cornish et al ⁵¹ Buprenorphine vs methadone	MC, OS, PRO Opioid dependent patients <60 years of age	N=5,577 585 days	Primary: All cause mortality Secondary: Duration of therapy effect on mortality	Primary: Three percent of patients died while receiving treatment, or within a year of receiving the last prescription. Of these, 35% died while on treatment. Overall, the risk of death during opiate substitution treatment was lower than the risk of death while off treatment. Crude mortality rates off therapy nearly doubled (1.3 vs 0.7 per 100-person years). Standardized mortality rates were 5.3 (95% CI, 4.0 to 6.8) on treatment vs 10.9 (95% CI, 9.0 to 13.1). After adjustment for age, sex, calendar period, and comorbidity, the mortality rate ratio was 2.3 (95% CI, 1.7 to 3.1). The risk of death increased 8 to 9-fold in the month immediately after the end of opiate substitution therapy, which did not vary according to medication, dosing within standard thresholds, or planned cessation.

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>There was no difference in the overall mortality rate between patients who received methadone and those who received buprenorphine.</p> <p>Secondary: Substitution therapy has a greater than 85% chance of reducing overall mortality when average duration of treatment is at least 12 months.</p>
<p>Strain et al⁵²</p> <p>Buprenorphine 4 mg to 16 mg per day</p> <p>vs</p> <p>buprenorphine/naloxone SL tablets 1/0.25, 2/0.5, 4/1, 8/2, 16/4 mg per day</p> <p>vs</p> <p>hydromorphone 2 and 4 mg intramuscular</p> <p>vs</p> <p>placebo</p>	<p>DB, DD, PC</p> <p>Adults with active opioid abuse, but not physically dependent</p>	<p>N=7</p>	<p>Primary: Peak drug effect; physiologic and psychomotor measures</p> <p>Secondary: Not reported</p>	<p>Primary: Dose-related increases in ratings of Drug Effects, High, Good Effects, and Liking were seen for hydromorphone, for buprenorphine, and for the combination of buprenorphine/naloxone. The predominant effects were seen with the highest doses tested (hydromorphone 4 mg, buprenorphine/naloxone 8/2 and 16/4 mg, and buprenorphine 8 and 16 mg). None of the treatments produced significant changes in ratings of Bad Effects or Sick.</p> <p>For ratings of Drug Effects, only the two higher doses of buprenorphine alone (8 and 16 mg) produced significantly increased ratings compared to placebo (P<0.05 and P<0.01, respectively).</p> <p>The combination dose of 8-2 mg and 16-4 produced ratings of drug effects that were lower than those produced by the buprenorphine dose of 8 mg. The differences between buprenorphine alone and buprenorphine/naloxone doses were not statistically significant for these or any other measures.</p> <p>None of the treatments produced significant changes on measures of blood pressure, heart rate, or respiratory rate.</p> <p>There were no significant differences in psychomotor effects among the treatments.</p> <p>Secondary: Not reported</p>

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Bell et al ⁵³ Buprenorphine/naloxone	RCT Heroin users seeking maintenance treatment	N=119 3 months	Primary: Retention in treatment and heroin use at three months Secondary: Not reported	Primary: At three months, 57% randomized to unobserved treatment, and 61% randomized to observed treatment were retained in the heroin treatment program (P=0.84). On an intention-to-treat analysis, reductions in days of heroin use in the preceding month, from baseline to three months, did not differ significantly; 18.5 days (95% CI, 21.8 to 15.3) and 22 days (95% CI, 24.3 to 19.7), respectively (P=0.13). Secondary: Not reported
Minozzi et al ⁵⁴ Naltrexone maintenance treatment vs placebo maintenance treatment or no pharmacologic treatment or psychotherapy or benzodiazepines	MA (13 RCTs) Patients with a diagnosis of opioid dependence	N=1,158 varies	Primary: Retention in treatment, use of the primary substance of abuse, side effects and/or Secondary: Re-incarcerations	Primary: Naltrexone maintenance therapy was not statistically different for all the primary outcomes considered when compared to no pharmacological treatment. Considering only studies in which patient's adherence were strictly enforced, there was a statistically significant difference in retention and abstinence with naltrexone over non therapy (RR, 2.93; 95% CI, 1.66 to 5.18). There was no statically significant difference in the two outcomes considered between naltrexone and psychotherapy (one study). Naltrexone was not superior to benzodiazepines and to buprenorphine for retention and abstinence and side effects (one study). Secondary: There was a significant difference in re-incarceration between the naltrexone maintenance group and no pharmacological treatment, RR 0.47 (95% CI, 0.26 to 0.84).
Krupitsky et al ⁵⁵ Naltrexone extended-release	DB, MC, PC, RCT Patients 18 years	N=250 24 weeks	Primary: Response profile for confirmed	Primary: The median proportion of weeks of confirmed abstinence was 90.0% (95% CI, 69.9 to 92.4) in the naltrexone extended-release group

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
injection once monthly vs placebo	of age or older with a diagnosis of opioid dependence disorder		abstinence during weeks 5 to 24 Secondary: Self-reported opioid-free days, opioid craving scores, number of days of retention, and relapse to physiological opioid dependence	compared with 35.0% (11.4 to 63.8) in the placebo group (P=0.0002). Secondary: Patients in the naltrexone extended-release group self-reported a median of 99.2% (range 89.1 to 99.4) opioid-free days compared with 60.4% (46.2 to 94.0) for the placebo group (P=0.0004). The mean change in craving was -10.1 (95% CI, -12.3 to -7.8) in the naltrexone extended-release group compared with 0.7 (95% CI, -3.1 to 4.4) in the placebo group (P<0.0001). Median retention was over 168 days in the naltrexone extended-release group compared with 96 days (95% CI, 63 to 165) in the placebo group (P=0.0042). Naloxone challenge confirmed relapse to physiological opioid dependence in 17 patients in the placebo group compared with one in the naltrexone extended-release group (P<0.0001). Naltrexone extended-release was well tolerated. Two patients in each group discontinued owing to adverse events. No naltrexone extended-release-treated patients died, overdosed, or discontinued owing to severe adverse events.

*Agent not available in the United States.

Drug regimen abbreviations: IM=intramuscular, SL=sublingual

Study abbreviations: CI=confidence interval, DB=double-blind, DD=double dummy, HR=hazard ratio, MA=meta-analysis, MC=multi-center, NNT=number needed to treat, OL=open label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SMD=standard mean difference, SR=systematic review, WMD=weighted mean difference, XO=crossover

Miscellaneous abbreviations: ARCI=Addiction Research Center Inventory, ASI=addiction severity index, COWS=Clinical Opiate Withdrawal Scale, DSM=Diagnostic and Statistical Manual of Mental Disorders, FDA=Food and Drug Administration, OOWS=Objective Opiate Withdrawal Scale, QALY=quality-adjusted life year, SOWS=Subjective Opiate Withdrawal Scale, VAS=visual analog scale

Special Populations**Table 5. Special Populations¹⁻⁷**

Generic Name	Population and Precaution				
	Elderly/ Pediatric	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Entity Agents					
Buprenorphine	No difference in response was identified between elderly and younger patients; use with caution in elderly patients. Safety and efficacy in pediatric patients <16 years of age have not been established.	No dosage adjustment required.	Hepatic dose adjustment may be required; effects of hepatic impairment is unknown; due to extensive metabolism, plasma levels are expected to be higher in patients with moderate and severe hepatic impairment	C	Yes (% unknown).
Naltrexone	Clinical trials for the treatment of alcohol dependence did not include significant numbers of elderly patients in order to determine whether they respond differently than younger subjects; no elderly subjects were included in clinical trials for the treatment of opioid dependence; use with caution in elderly patients. Safety and efficacy in pediatric patients <18 years of age have not been established.	Dose adjustment is not required in patients with mild renal impairment (creatinine clearance 50 to 80 mL/min). Use in moderate or severe renal impairment or those on hemodialysis has not been evaluated; use caution as the primary mode of excretion is via the urine.	Dose adjustment is not required in patients with mild to moderate hepatic impairment (Child-Pugh groups A and B). Use in severe hepatic impairment has not been evaluated.	C	Yes (% unknown).
Combination Product					
Buprenorphine/naloxone	Clinical trials for the treatment of alcohol dependence did not include significant numbers of elderly	No dosage adjustment required for buprenorphine.	Hepatic dose adjustment may be required; effects of	C	Yes (% unknown).

Generic Name	Population and Precaution				
	Elderly/ Pediatric	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	<p>patients in order to determine whether they respond differently than younger subjects; use with caution in elderly patients.</p> <p>Safety and efficacy in children <16 years of age have not been established.</p>	Naloxone is not studied in renal dysfunction.	hepatic impairment is unknown; due to extensive metabolism, plasma levels are expected to be higher in patients with moderate and severe hepatic impairment		

Adverse Drug Events

Table 6. Adverse Drug Events¹⁻⁷

Adverse Event (%)	Single Entity Agents		Combination Product	
	Buprenorphine	Naltrexone	Buprenorphine/ Naloxone Tablet	Buprenorphine/ Naloxone Film
Body as a Whole				
Anxiety	-	>10%	-	-
Appetite loss	-	<10%	-	-
Asthenia	4.9	-	6.5	-
Chills	7.8	<10%	7.5	-
Delayed ejaculation	-	<10%	-	-
Disturbance in attention	-	-	-	a
Energy decreased	-	>10%	-	-
Energy increased	-	<10%	-	-
Depression	-	<10%	-	-
Headache	29.1	>10%	36.4	-
Infection	11.7	-	5.6	-
Intoxication	-	-	-	a
Irritability	-	<10%	-	-
Pain	18.4	-	22.4	-
Pain, abdomen	11.7	>10%	11.2	-
Pain, back	7.8	-	3.7	-
Pain, joint	-	>10%	-	-
Pain, muscle	-	>10%	-	-
Thirst increased	-	<10%	-	-
Withdrawal syndrome	18.4	a	25.2	a
Cardiovascular System				
Palpitation	-	-	-	a
Vasodilation	3.9	-	9.3	-
Digestive System				
Constipation	7.8	<10%	12.1	a
Diarrhea	4.9	<10%	3.7	-

Adverse Event (%)	Single Entity Agents		Combination Product	
	Buprenorphine	Naltrexone	Buprenorphine/ Naloxone Tablet	Buprenorphine/ Naloxone Film
Nausea	13.6	a	15	-
Vomiting	7.8	>10%	7.5	a
Local Administration Site				
Glossodynia	-	-	-	a
Oral hypoesthesia	-	-	-	≥1
Oral mucosal erythema	-	-	-	a
Nervous System				
Blurry vision	-	-	-	a
Insomnia	21.4	>10%	14	a
Respiratory System				
Rhinitis	9.7	-	4.7	-
Skin & Appendages				
Skin rash	-	<10%	-	-
Sweating	12.6	-	14	a

a Percent not specified.
- Event not reported.

Contraindications

Table 7. Contraindications¹⁻⁷

Contraindication	Single Entity Agents		Combination Product
	Buprenorphine	Naltrexone	Buprenorphine/Naloxone
Hypersensitivity to the active ingredient or to any component.	a	a	a
Patients currently dependent on opioids (physiologic), including patients who are receiving maintenance therapy with opiate agonists or partial agonists		a	
Patients that has failed the naloxone challenge test		a	
Patients that has a positive urine drug screen for opioids		a	
Patients in acute opioid withdrawal		a	
Patients receiving opioid analgesics		a	

Warnings/Precautions

Table 8. Warnings and Precautions¹⁻⁷

Warning or Precaution	Single Entity Agents		Combination Product
	Buprenorphine	Naltrexone	Buprenorphine/Naloxone
Abdominal conditions, acute; diagnosis or clinical course of acute abdominal conditions may be obscured with use.	a	a (Vivitrol®)	a
Abuse potential; can be abused similar to opioids, use precautions to minimize risk of misuse, abuse or diversion; do not prescribe multiple refills during early treatment.	a		a
Alcohol withdrawal symptoms are not eliminated or diminished with use.		a (Vivitrol®)	

Warning or Precaution	Single Entity Agents		Combination Product
	Buprenorphine	Naltrexone	Buprenorphine/Naloxone
Allergic reactions; bronchospasm, angioneurotic edema, and anaphylactic shock has been associated with use.	a		a
Central nervous system depression; concurrent use other central nervous system depressants may exhibit increased central nervous system depression; consider dose reduction of one or both in situations of concomitant prescription.	a		a
Cerebrospinal fluid pressure elevated; use caution in patients with head injury, intracranial lesions or when cerebrospinal pressure may be elevated.	a		a
Dependence; chronic administration produces physical dependence, characterized by withdrawal upon abrupt discontinuation or rapid taper.	a		a
Depression and suicide has been reported when used for opioid dependence.		a	
Eosinophilic pneumonia has been associated with use; consider when progressive dyspnea and hypoxemia develop.		a (Vivitrol®)	
Hepatitis, hepatic events; cases of cytolytic hepatitis with jaundice have been reported; baseline and periodic monitoring of liver function during treatment is recommended.	a	a	a
Impairment of ability to drive or operate machinery; use caution in driving or operating hazardous machinery until stabilized.	a		a
Injection site reactions (mild to very severe); accidental subcutaneous injection may increase the risk for severe reactions.		a (Vivitrol®)	
Intracholedochal pressure increased; use with caution with biliary tract dysfunction.	a		a
Neonatal withdrawal has been reported in infants of women treated during pregnancy, often occurs from day one to eight of life.	a		a
Opioid detoxification (ultra-rapid); safety has not been established.		a	
Opioid naïve patients; deaths have been reported when used for analgesia; do not use as an analgesic.	a		a
Opioid overdose vulnerability; use likely to have reduced tolerance to opioids after use and thus respond to lower doses than previously; use caution if restarting opioid therapy.		a	
Opioid withdrawal; may occur in individuals physically dependent on full opioid agonists before the effects of the full opioid agonist	a	a	a

Warning or Precaution	Single Entity Agents		Combination Product
	Buprenorphine	Naltrexone	Buprenorphine/Naloxone
has subsided.			
Orthostatic hypotension may occur.	a		a
Pediatric exposure; accidental exposure can cause severe, life-threatening respiratory depression.	a		a
Respiratory depression and death has been associated with use when used with central nervous system depressants; use caution in patients with compromised respiratory function.	a		a
Special populations; administer with caution in debilitated patients, patients with myxedema or hypothyroidism, adrenal cortical insufficiency, central nervous system depression or coma, toxic psychosis, prostatic hypertrophy or urethral stricture, acute alcoholism, delirium tremens or kyphoscoliosis	a		a
Surmountable effect of antagonistic effects when a large dose of opioids are administered.		a	
Use with caution in patients with thrombocytopenia or any coagulation disorder (due to intramuscular injection).		a	

Drug Interactions

Table 9. Drug Interactions¹⁻⁷

Generic Name	Interacting Medication or Disease	Potential Result
Buprenorphine	Barbiturate anesthetics (methohexital, thiamylal, thiopental)	The dose of anesthetic required to induce anesthesia may be reduced, increasing the likelihood of apnea.
Buprenorphine	Benzodiazepines	Concomitant administration results in an increased risk of sedation and life-threatening respiratory depression, especially with over dosage.
Buprenorphine	CYP3A4 Inhibitors (e.g. azole antifungals, macrolide antibiotics, HIV protease inhibitors)	Increased effects of buprenorphine
Buprenorphine	CYP3A4 Inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin)	Decreased effects of buprenorphine
Buprenorphine	Non-nucleotide reverse transcriptase inhibitors	Significant reactions involving CYP3A4 inducers (efavirenz, nevirapine, etravirine) and CYP3A4 inhibitors (delavirdine) have been shown, however there was no significant pharmacodynamic effect.
Naltrexone	Opioid-continuing products (analgesics, antidiarrheals, cough and cold remedies)	Antagonistic effect decreases effectiveness of opioid containing products.

Dosage and Administration**Table 10. Dosing and Administration**¹⁻⁷

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Entity Agents			
Buprenorphine	<p><u>Opioid dependence, treatment induction</u>[†]: Sublingual tablet: initial, 8 mg on day one followed by 16 mg on day two</p> <p><u>Opioid dependence, treatment maintenance</u>[†]: Sublingual tablet: maintenance progressive dose adjustment of 2 to 4 mg, general range of 4 to 24 mg per day</p>	Safety and efficacy in children <16 years of age have not been established.	Sublingual tablet: 2 mg 8 mg
Naltrexone	<p><u>Alcohol dependence</u>: Extended-release suspension for injection: 380 mg via intramuscular injection in the gluteal muscle every four weeks by a healthcare provider</p> <p>Tablet: 50 mg once daily for up to 12 weeks</p> <p><u>Opioid dependence</u>[†]: Tablet: initial, 25 mg once daily; if no withdrawal symptoms occur, increase to 50 mg once daily thereafter</p> <p><u>Opioid dependence, prevention of relapse following opioid detoxification</u>: Extended-release suspension for injection: 380 mg via intramuscular injection in the gluteal muscle every four weeks by a healthcare provider</p>	Safety and efficacy in children <18 years of age have not been established.	Suspension for injection, extended-release: 380 mg Tablet: 50 mg
Combination Product			
Buprenorphine/naloxone	<p><u>Opioid dependence, treatment induction</u>[†]: Sublingual film (Suboxone[®]): 8/2 mg sublingually on day one, followed by 16/4 mg sublingually on day two</p> <p><u>Opioid dependence, treatment maintenance</u>[†]: Buccal film (Bunavail[®]): maintenance (after induction with buprenorphine sublingual tablets), target dose of 8.4/1.4 mg buccally once daily dose adjusted by 2.1/0.3 mg at a time to adequate response, normal range is 2.1/0.3 mg to 12.6/2.1 mg once daily</p> <p>Sublingual film (Suboxone[®]): maintenance, target dose of 16/4 mg sublingually once daily dose adjusted by 2/0.5 mg or 4/1 mg at a time</p>	Safety and efficacy in children <16 years of age have not been established.	Buccal film (Bunavail [®]): 2.1/0.3 mg 4.2/0.7 mg 6.3/1 mg Sublingual film (Suboxone [®]): 2/0.5 mg 4/1 mg 8/2 mg 12/3 mg Sublingual tablet: 2/0.5 mg 8/2 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	<p>to adequate response, normal range is 4/1 mg to 24/6 mg once daily</p> <p>Sublingual tablet: maintenance, target dose of 16/4 mg sublingually once daily dose adjusted by 2/0.5 mg or 4/1 mg at a time to adequate response, normal range is 4/1 to 24/6 mg once daily</p> <p>Sublingual tablet (Zubsolv®): maintenance (after induction with buprenorphine sublingual tablets), target dose of 11.4/2.8 mg sublingually once daily dose adjusted by 1.4/0.36 mg or 2.8/0.72 mg at a time to adequate response, normal range is 2.8/0.72 mg to 17.1/4.2 mg once daily</p>		<p>Sublingual tablet (Zubsolv®): 1.4/0.36 mg 5.7/1.4 mg</p>

† As part of a complete treatment plan to include counseling and psychosocial support.

‡ As part of a comprehensive plan of management that includes some measure to ensure the patient takes the medication.

§ Indication is for ReVia® only.

|| Indication is for Vivitrol® only.

¶ Indication is for Suboxone® only.

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
<p>United States Substance Abuse and Mental Services Center for Substance Abuse Treatment: Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction (2004)¹¹</p>	<ul style="list-style-type: none"> • Buprenorphine/naloxone should be used for the induction, stabilization and maintenance phases of treatment for most patients. • Induction doses should be administered as observed treatment; however, subsequent doses may be obtained with a prescription. • In most patients, buprenorphine/naloxone can be used for induction. If buprenorphine monotherapy is used, patients should be transitioned to buprenorphine/naloxone after no more than two days of treatment. If buprenorphine monotherapy is to be used for extended periods, the number of doses to be prescribed should be limited, and the use of the monotherapy formulation should be justified in the medical record. • Buprenorphine/naloxone or buprenorphine should only be used in patients dependent on long-acting opioids who have evidence of sustained medical and psychosocial stability in conjunction with opioid treatment programs. In these patients, buprenorphine monotherapy should be utilized during the induction phase to avoid precipitation of withdrawal. • For patients taking methadone, the methadone dose should be tapered to £30 mg/day for at least one week and patients should have taken their last dose of methadone ³ 24 hours prior to initiating buprenorphine induction. The first dose of buprenorphine should be 2 mg of the monotherapy formulation. If a patient develops signs or symptoms of withdrawal after the first dose, a second dose of 2 mg should be administered and repeated as needed to a maximum of 8 mg of buprenorphine on day one. The decision to transfer a patient, exhibiting withdrawal symptoms, from methadone at doses >30 mg/day to buprenorphine should be based on a physician's judgment as there is

Clinical Guideline	Recommendations
	<p>insufficient data in this patient population.</p> <ul style="list-style-type: none"> • Patients who are experiencing objective signs of opioid withdrawal and whose last use of a short-acting opioid were at least 12 to 24 hours prior, should be inducted using buprenorphine/naloxone. Patients should receive a first dose of 4/1 to 8/2 mg of the buprenorphine/naloxone combination. If the initial dose of the combination treatment is 4/1 mg and opioid withdrawal symptoms subside but then return (or are still present) after two hours, a second dose of 4/1 mg may be administered. The total amount of buprenorphine administered in the first day should not exceed 8 mg. • If patients do not exhibit withdrawal symptoms after the first day of induction, the patient's daily dose should be equivalent to the total amount of buprenorphine/naloxone (or buprenorphine) that was administered on day one. Doses may be subsequently increased in 2g/0.5 to 4 /1 mg increments daily, if needed for symptomatic relief, with a target dose of 12/3 to 16/4 mg per day within the first week. • Patients experiencing withdrawal symptoms on day two should receive an initial dose of buprenorphine/naloxone equivalent to the total amount of buprenorphine administered on day one plus 4/1 mg (maximum initial dose of 12/3 mg). If withdrawal symptoms are still present two hours after the dose, an additional 4 mg/1 mg dose can be administered. The total dose on day two should not exceed 16/4 mg. Continue dose increases on subsequent days as needed. • The stabilization phase begins when patients are free of withdrawal symptoms and cravings. Most patients will stabilize on daily doses of 16/4 to 24/6 mg; however, doses up to a maximum of 32/8 mg daily may be required in some patients. • During stabilization, patients receiving maintenance treatment should be seen at least weekly. Once a stable buprenorphine dose is reached and toxicologic samples are free of illicit opioids, less frequent visits (biweekly or monthly) may be an option. Toxicology tests for illicit drugs should be administered at least monthly. • The longest phase of treatment is the maintenance phase which may be indefinite. Decisions to decrease or discontinue buprenorphine should be based on a patient commitment to being medication-free and on physician judgment. • Patients treated for opioid withdrawal should receive psychosocial therapy (e.g., individual or group counseling, self-help programs, and patient monitoring) and have their medical comorbidities managed effectively. • Buprenorphine monotherapy may be used for medically supervised withdrawal. • Detoxification in short-acting opioid addiction can be rapid (three days), moderate (10 to 14 days) or long term (indefinite). Buprenorphine long term therapy may be more effective than rapid detoxification from short-acting opioid abuse. • In pregnant women, methadone is currently the standard of care; however, if this option is unavailable or refused by the patient, buprenorphine may be considered as an alternative. Although the Suboxone[®] and Subutex[®] product information advises against use in breast-feeding, the effects on the child would be minimal and buprenorphine use in breast-feeding is not contraindicated in this patient population.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • In adolescents and young adults, buprenorphine is a useful option; however, the practitioner should be familiar with the state laws regarding parental consent. • In geriatric patients, the literature is lacking; however, due to differences in metabolism and absorption, additional care should be exercised when treating these patients. • In instances of polysubstance abuse, buprenorphine may not have a beneficial effect on the use of other drugs. Extra care should be employed in patients who abuse alcohol or benzodiazepines due to the potentially fatal interactions with buprenorphine. • Patients who need treatment for pain but not for addiction should be treated within the context of a medical or surgical setting and should not be transferred to an opioid maintenance program just because they have become physically dependant throughout the course of medical treatment. • Pain, in patients receiving buprenorphine for opioid addiction, should be treated with short-acting opioid pain relievers and buprenorphine should be held. Sufficient time for these medications to be cleared must be allowed before restarting the buprenorphine. Patients with chronic severe pain may not be good candidates for buprenorphine because of the ceiling effect. • In patients recently discharged from controlled environments, intensive monitoring is required, and treating physicians may be called upon to verify and explain treatment regimens, to document patient compliance and to interact with the legal system, employers, and others. These patients may be candidates for buprenorphine treatment even if there is no current opioid abuse. The lowest dose possible of buprenorphine/naloxone should be used (2/0.5 mg). • Opioid addiction in health care professionals requires specialized, extended care since opioid addiction is an occupational hazard.
<p>Veterans Health Administration, Department of Defense: Clinical Practice Guideline for Management of Substance Use Disorders (2009)¹²</p>	<p><u>General considerations</u></p> <ul style="list-style-type: none"> • Opioid agonist treatment is the first-line treatment for chronic opioid dependence. • Provide access to opioid agonist treatment for all opioid dependent patients, under appropriate medical supervision and with concurrent addition-focused psychosocial treatment. • Strongly recommend methadone or sublingual buprenorphine/naloxone maintenance as first-line therapy. Buprenorphine monotherapy is preferred in pregnancy. • By administering an opioid to prevent withdrawal, reduce craving, and reduce the effects of illicit opioids, the opioid-dependent patient is able to focus more readily on recovery activities. <p><u>Opioid agonist treatment program and office-based opioid treatment</u></p> <ul style="list-style-type: none"> • Opioid agonist treatment should be administered in an opioid agonist treatment program or office-based opioid treatment. • Doses should be adjusted to maintain a therapeutic range between signs/symptoms of overmedication and opioid withdrawal. • The usual dosage range for optimal effects is 60 to 120 mg/day. • Buprenorphine target dose is generally up to 16 mg/day; doses >32 mg are rarely indicated. • In all cases (except pregnancy), the combination product of buprenorphine/naloxone should be used.

Clinical Guideline	Recommendations
	<p><u>Methadone therapy</u></p> <ul style="list-style-type: none"> • Methadone for the treatment of opioid dependence may only be prescribed out of an accredited opioid agonist treatment program as it is a schedule II agent. It is illegal to prescribe methadone for the treatment of opioid dependence out of an office-based practice. • For newly admitted patients, the initial dose of methadone should not exceed 30 mg and the total dose for the first day should not exceed 40 mg, without provider documentation that 40 mg didn't reduce withdrawal • Under usual practices, a stable, target dose is greater than 60 mg/day and most patients will require considerably higher doses in order to achieve a pharmacological blockade of reinforcing effects of exogenously administered opioids. <p><u>Buprenorphine therapy</u></p> <ul style="list-style-type: none"> • Office-based treatment with sublingual buprenorphine for opioid dependence can only be provided by physicians who have received a waiver from the Substance Abuse and Mental Health Services Administration (SAMHSA) and have a special Drug Enforcement Agency (DEA) number. • Buprenorphine induction (~1 week) involves helping a patient in the process of switching from the opioids of abuse to buprenorphine. • In all cases (except pregnancy), the combination product of buprenorphine/naloxone should be used. • The initial dose of buprenorphine/naloxone combination is between 2/0.5 mg to 4/1 mg, which can be repeated after two hours. The amount of buprenorphine administered in the first day should not exceed 8 mg. • The daily buprenorphine/naloxone dose is the equivalent to the total amount of buprenorphine/naloxone (or buprenorphine) that was administered on day one. Doses may be increased as needed for symptomatic relief, with a target dose of 12/3 mg to 16/4 mg per day to be achieved within the first week.
<p>American Psychiatric Association: Practice Guideline for Treatment of Patients with Substance Use Disorders (2006)¹³</p>	<p><u>Treating dependence and abuse</u></p> <ul style="list-style-type: none"> • Goals of therapy are to identify stable maintenance dose of opioid agonist and facilitate rehabilitation. • The choice of treatment for opioid dependence is based on patient preference, past response to treatment, probability of achieving and maintaining abstinence, and assessment of the short- and long-term effects of continued use of illicit opioids on the patient's life adjustment and overall health status. • Maintenance treatment with methadone or buprenorphine is appropriate for patients with ³ 1 year history of opioid dependence. Maintenance therapy with naltrexone is an alternative strategy. • Methadone is a full mu agonist opioid, and is the most thoroughly studied and widely used agent for opioid dependence. • Methadone maintenance treatment for opioid-dependent individuals has generally been shown to be effective in: <ul style="list-style-type: none"> ○ Decreasing illicit opioid use. ○ Decreasing psychosocial and medical morbidity. ○ Improving overall health status. ○ Decreasing mortality. ○ Decreasing criminal activity. ○ Improving social functioning.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> ○ Reducing the spread of Human Immunodeficiency Virus infection among intravenous drug users. • Maintenance on methadone is generally safe; however, one key issue is determining a dose sufficient to suppress the patient's opioid withdrawal and craving, as no single dose is optimal for all patients. • Methadone can be diverted for abuse, as can other opiates that have agonist effects at the mu receptor. • Buprenorphine produces a partial agonist effect at the mu receptor and an antagonistic effect at the kappa receptor. • Buprenorphine enters the systemic circulation more slowly through the sublingual route than with parenteral administration and has less abuse potential compared to the parenterally delivered form. • The combination of buprenorphine and naloxone significantly reduces the risk of diversion because naloxone will exert a potent opioid antagonist effect if the combination tablet is crushed and administered intravenous by an opioid-dependent person. Naloxone has poor sublingual bioavailability. • Buprenorphine is generally safe. Overdose with buprenorphine generally does not produce significant respiratory depression <p><u>Treating intoxication</u></p> <ul style="list-style-type: none"> • Mild to moderate opioid intoxication usually does not require specific therapy. • Severe opioid toxicity, marked by respiratory depression, is a medical emergency. Naloxone will reverse respiratory depression and other overdose manifestations. <p><u>Treating withdrawal</u></p> <ul style="list-style-type: none"> • Treatment of withdrawal is directed at safely decreasing acute symptoms and easing transition into a long-term treatment program. • Effective strategies include: <ul style="list-style-type: none"> ○ Substitution of opioid with methadone or buprenorphine. ○ Abrupt discontinuation of opioids, with use of clonidine to suppress withdrawal symptoms. ○ Clonidine-naltrexone detoxification.

Conclusions

Buprenorphine, buprenorphine/naloxone and naltrexone are treatment options for opioid dependent patients who are unable or unwilling to receive clinic-based methadone treatment. Buprenorphine is available as a sublingual tablet, and buprenorphine/naloxone is available as sublingual tablet and film. Naltrexone is available as a tablet or extended-release suspension for injection. Buprenorphine and buprenorphine/naloxone sublingual tablets and naltrexone tablets are currently available generically.¹⁻⁷ Physicians prescribing buprenorphine for opioid dependency in an office-based treatment setting are required to complete a training program as outlined in the Drug Addiction Treatment Act of 2000.¹⁴ Results of clinical trials vary, but generally buprenorphine and buprenorphine/naloxone are considered equally effective and significantly improve outcomes compared to placebo when used for opioid withdrawal.^{16-26,37-44} A meta-analysis evaluated naltrexone compared to non-therapy, and found no significant difference in outcomes. However, when considering only studies in which patient's adherence were strictly enforced, there was a statistically significant difference in retention and abstinence with RR of 2.93 (95% CI, 1.66 to 5.18).⁵⁴ The percentage of subjects achieving each observed percentage of opioid-free weeks was greater in the naltrexone extended release group compared to the placebo group.⁵⁵

References

1. Buprenorphine tablet [package insert]. Columbus (OH): Roxane Laboratories, Inc.; 2012 Sep.
2. ReVia[®] [package insert]. Horsham (PA): Teva Select Brands; 2013 Oct.
3. Vivitrol[®] [package insert]. Waltham (MA): Alkermes, Inc.; 2013 Jul.
4. Buprenorphine and naloxone sublingual tablet [package insert]. Columbus (OH): Roxane Laboratories, Inc.; 2013 Nov.
5. Bunavail[®] [package insert]. Raleigh (NC): BioDelivery Sciences International, Inc.; 2014 Jun.
6. Suboxone[®] [package insert]. Richmond (VA). Reckitt Benckiser Pharmaceuticals Inc.; 2014 Apr.
7. Zubsolv[®] [package insert]. New York (NY). Orexo US, Inc.; 2013 Jul.
8. Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2013 [cited 2014 Dec 10]. Available from: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.
9. Butrans[®] [package insert]. Stamford (CT). Purdue Pharma L.P.; 2014 Jun.
10. Buprenex[®] [package insert]. New York (NY). Richmond (VA). Reckitt Benckiser Pharmaceuticals Inc.; 2015 Apr.
11. Center for Substance Abuse Treatment. Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction: a treatment improvement protocol TIP 40. Rockville (MD): Substance Abuse and Mental Health Services Administration (SAMHSA); DHHS Publication No. (SMA) 04-3939. 2004.
12. Veterans Health Administration, Department of Defense. VA/DoD clinical practice guideline for the management of substance use disorders (SUD). Washington (DC): Veterans Health Administration, Department of Defense; 2009 Aug [cited 2014 Dec 10]. Available at: http://www.guideline.gov/summary/summary.aspx?doc_id=4812&nbr=3474.
13. American Psychiatric Association Workgroup on Substance Use Disorders, Kleber HD, Weiss RD, Anton RF, Rounsaville BJ, George TP, et al. Treatment of patients with substance use disorders, second edition. American Psychiatric Association. *Am J Psychiatry*. 2006;163(8 Suppl):5-82.
14. U.S. Department of Health and Human Services: Substance Abuse and Mental Health Services. Drug addiction treatment act of 2000 [guideline on the internet] Washington (DC): U.S. Department of Health and Human Services [cited 2014 Dec 10] Available from: <http://buprenorphine.samhsa.gov/data.html>.
15. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance vs placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2008 Apr;(2):CD002207.
16. Fudala PJ, Bridge TP, Herbert S, Williford WO, Chiang CN, Jones K, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med*. 2003 Sep;349(10):949-58.
17. Daulouède JP, Caer Y, Galland P, Villegier P, Brunelle E, Bachellier J, et al. Preference for buprenorphine/naloxone and buprenorphine among patients receiving buprenorphine maintenance therapy in France: a prospective, multicenter study. *J Subst Abuse Treat*. 2010 Jan;38(1):83-9.
18. Strain EC, Harrison JA, Bigelow GE. Induction of opioid-dependent individuals onto buprenorphine and buprenorphine/naloxone soluble-films. *Clin Pharmacol Ther*. 2011 Mar;89(3):443-9.
19. Kakko J, Svanborg KD, Kreek MJ, Heilig M. One-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomized, placebo-controlled trial. *Lancet*. 2003 Feb;361(9358):662-8.
20. Woody GE, Poole SA, Subramaniam G, Dugosh K, Bogenschutz M, Abbott P, et al. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. *JAMA*. 2008 Nov;300(17):2003-11.
21. Weiss RD, Potter JS, Fiellin DA, Byrne M, Connery HS, Dickinson W, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a two-phase randomized controlled trial. *Arch Gen Psychiatry*. 2011 Dec;68(12):1238-46.
22. Polsky D, Glick HA, Yang J, Subramaniam GA, Poole SA, Woody GE. Cost-effectiveness of extended buprenorphine-naloxone treatment for opioid-dependent youth: data from a randomized trial. *Addiction*. 2010 Sep;105(9):1616-24.
23. Fareed A, Vayalapalli S, Casarella J, Drexler K. Effect of buprenorphine dose on treatment outcome. *J Addict Dis*. 2012;31(1):8-18.
24. Bickel WK, Amass L, Crean JP, Badger GJ. Buprenorphine dosing every one, two or three days in opioid-dependant patients. *Psychopharmacology (Berl)*. 1999 Sep;146(2):111-8.

25. Petry NM, Bickel WK, Badger GJ. A comparison of four buprenorphine dosing regimens in the treatment of opioid dependence. *Clin Pharmacol Ther.* 1999 Sep;66(3):306-14.
26. Schottenfeld RS, Pakes J, O'Connor P, Chawarski M, Oliveto A, Kosten TR. Thrice-weekly vs daily buprenorphine maintenance. *Biol Psychiatry.* 2000 Jun;47(12):1072-9.
27. Gibson A, Degemhardt L, Mattick RP, Ali R, White J O'Brien S. Exposure to opioid maintenance treatment reduces long term mortality. *Addiction.* 2008; 103(3):462-468.
28. Farré M, Mas A, Torrens M, Moreno V, Cami J. Retention rate and illicit opioid use during methadone maintenance interventions: a meta-analysis. *Drug Alcohol Depend.* 2002;65:283-90.
29. Gowing L, Ali R, White JM. Buprenorphine for the management of opioid withdrawal. *Cochrane Database Syst Rev.* 2009 Jul 8;(3):CD002025.
30. Johnson RE, Jaffe JH, Fudala PJ: A controlled trial of buprenorphine treatment for opioid dependence. *JAMA.* 1992;267:2750-5.
31. Kamien J, Branstetter S, Amass L. Buprenorphine-naloxone vs methadone maintenance therapy: a randomized double-blind trial with opioid-dependent patients. *Heroin Addict Relat Clin. Probl* 2008;10:5-18.
32. Meader N. A comparison of methadone, buprenorphine and alpha(2) adrenergic agonists for opioid detoxification: a mixed treatment comparison meta-analysis. *Drug Alcohol Depend.* 2010 Apr;108(1-2):110-4.
33. Petitjean S, Stohler R, Deglon J, Livoti S, Waldvogel D, Uehlinger C. Double-blind randomized trial of buprenorphine and methadone in opiate dependence. *Drug Alcohol Depend.* 2001;62:97-104.
34. Soyka M, Zingg C, Koller G, Kuefner H. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: results from a randomized study. *Int J Neuropsychopharmacol.* 2008;11:641-53.
35. Ling W, Wesson D, Charuvastra C, Klett C. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. *Arch Gen Psychiatry.* 1996;53:401-7.
36. Schottenfeld R, Pakes J, Oliveto A, et al. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Arch Gen Psychiatry.* 1997;54:713-20.
37. Ling W, Charuvastra C, Collins JF, Batki S, Brown LS Jr, Kintaudi P, et al. Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. *Addiction.* 1998;93(4):475-86.
38. Lintzeris N. Buprenorphine dosing regime in the management of out-patient heroin withdrawal. *Drug Alcohol Rev.* 2002 Mar;21(1):39-45.
39. Kornor H, Waal H, Sandvik L. Time-limited buprenorphine replacement therapy for opioid dependence: two-year follow-up outcomes in relation to program completion and current agonist therapy status. *Drug Alcohol Rev.* 2007 Mar;26(2):135-41.
40. Fareed A, Vayalapalli S, Casarella J, Drexler K. Treatment outcome for flexible dosing buprenorphine maintenance treatment. *Am J Drug Alcohol Abuse.* 2012 Mar;38(2):155-60.
41. Assadi SM, Hafezi M, Mokri A, Razzaghi EM, Ghaelo P. Opioid detoxification using high doses of buprenorphine in 24 hours: A randomized, double blind, controlled clinical trial. *J Subst Abuse Treat.* 2004 Jul;27(1):75-82.
42. Minozzi S, Amato L, Davoli M. Detoxification treatments for opiate dependent adolescents. *Cochrane Database Syst Rev.* 2009 Apr 15;(2):CD006749.
43. Amass L, Ling W, Freese TE, Reiber C, Annon JJ, Cohen AH, et al. Bringing buprenorphine-naloxone to community treatment providers: the NIDA clinical trials network field experience. *Am J Addict.* 2004;13 Suppl 1:S42-66.
44. Correia CJ, Walsh SL, Bigelow GE, Strain EC. Effects associated with double-blind omission of buprenorphine/naloxone over a 98-h period. *Psychopharmacology (Berl).* 2006 Dec;189(3):297-306.
45. Maremmani I, Pani P, Pacini M, et al. Substance use and quality of life over 12 months among buprenorphine maintenance-treated and methadone maintenance-treated heroin-addicted patients. *J Subst Abuse Treat.* 2007 Jul;33(1):91-8.
46. Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *NEJM.* 2010;363:2320-31.
47. Pinto H, Maskrey V, Swift L, et al. The SUMMIT trial: a field comparison of buprenorphine vs methadone maintenance treatment. *J Subst Abuse Treat.* 2010;394:340-52.
48. Fiellin D, Moore B, Sullivan L, et al. Long-term treatment with buprenorphine/naloxone in primary care: results at 2-5 years. *Am J Addict.* 2008;17:116-20.

49. Kakko J, Grönbladh L, Svanborg K, et al. A stepped care strategy using buprenorphine and methadone vs conventional methadone maintenance in heroin dependence: a randomized controlled trial. *Am J Psychiatry*. 2007;164:797-803.
50. Strain E, Stitzer M, Liebson I, Bigelow G. Comparison of buprenorphine and methadone in the treatment of opioid dependence. *Am J Psychiatry*. 1994;151:1025-30.
51. Cornish R, Macleod J, Strang J, et al. Risk of death during and after opiate substitution in primary care: prospective observational study in UK General Practice Research Database. *BMJ*. 2010;341:c5475.
52. Strain E, Stoller K, Walsh S, et al. Effects of buprenorphine vs buprenorphine/naloxone tablets in non-dependent opioid abusers. *Psychopharmacology*. 2000;148:374-83.
53. Bell J, Shanahan M, Mutch C, et al. A randomized trial of effectiveness and cost-effectiveness of observed vs unobserved administration of buprenorphine-naloxone for heroin dependence. *Addiction*. 2007;102:1899-907.
54. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev*. 2011 Apr 13;(4):CD001333.
55. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomized trial. *Lancet* 2011; 377:1506-1513.