Therapeutic Class Overview
Buprenorphine and Buprenorphine/Naloxone

Therapeutic Class

- **Overview/Summary:** Buprenorphine (Subutex®) and buprenorphine/naloxone (Suboxone®) are Food and Drug Administration (FDA)-approved for the treatment of opioid dependence.[1-3] These products are classified as Schedule III controlled substances. 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).[1-3] 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.[4] During buprenorphine administration, opioid-dependent patients experience positive subjective opioid effects which are limited by ceiling effect.[1-3] Naloxone, an antagonist at the μ-opioid receptor, 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.[2,3] Therefore, the addition of naloxone to buprenorphine results in a decreased risk of diversion compared to buprenorphine monotherapy. Buprenorphine and buprenorphine/naloxone sublingual tablets are currently available generically.[5] Reckitt Benckiser Pharmaceuticals discontinued distribution of buprenorphine/naloxone sublingual tablets in March 2013, as a result of concerns over accidental/unsupervised pediatric exposure compared to the film formulation; however, generic formulations will remain available.[5,6]

Table 1. Current Medications Available in Therapeutic Class[1-3]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agent			
Buprenorphine (Subutex®*)	Treatment of opioid dependence	Sublingual tablet: 2 mg 8 mg	✔
Combination Product			
Buprenorphine/naloxone (Suboxone®*)	Treatment of opioid dependence	Sublingual film: 2.0/0.5 mg 4/1 mg 8/2 mg 12/3 mg Sublingual tablet: 2.0/0.5 mg 8/2 mg	✔ †

*Available generically in one dosage form or strength.
† Buprenorphine/naloxone 2.0/0.5 mg and 8/2 mg sublingual tablets only.

Evidence-based Medicine

- Results from one double-blind, placebo- and active-controlled study (N=326) demonstrated 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.[7] A

smaller, randomized controlled trial (N=32) also showed no significant difference in withdrawal symptoms between buprenorphine and buprenorphine/naloxone.[8]

- 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.[9-11]
- In a meta-analysis of 21 randomized controlled trials, treatment with buprenorphine at doses ≥16 mg/day was associated with a greater likelihood of remaining 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.[12]
- 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.[13-15]
- When compared to other agents, one Cochrane review showed that buprenorphine was less effective than methadone in retaining patients in opioid dependence treatment.[16] Another Cochrane review showed that buprenorphine-based therapy was as effective as methadone and more effective than clonidine in the management of opioid withdrawal symptoms.[17]

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.[4]
    - Buprenorphine alone should be used for pregnant patients and for the induction therapy of patients who are transitioning from methadone treatment.[4]
    - Transitioning patients to buprenorphine/naloxone as early as possible to minimize potential diversion associated with buprenorphine monotherapy is also reccomended.[4,18]
- Other Key Facts:
    - Buprenorphine (Subutex®) and buprenorphine/naloxone (Suboxone®) sublingual tablets are available generically.[5]

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Therapeutic Class Review
Buprenorphine and Buprenorphine/Naloxone

Overview/Summary

Buprenorphine (Subutex®) and buprenorphine/naloxone (Suboxone®) are Food and Drug Administration (FDA)-approved for the treatment of opioid dependence.[1-3] Buprenorphine is available as a sublingual tablet, and buprenorphine/naloxone is available as sublingual tablet and film. These products are classified as Schedule III controlled substances. Although buprenorphine and buprenorphine/naloxone have been studied in pain management and depression, neither of these sublingual products holds an FDA-approval for these indications and their use for these indications will not be discussed within this review.[4] In addition, the transdermal formulation of buprenorphine (Butrans®) is FDA-approved for moderate to severe chronic pain management, and will not be discussed within this review.[4] Buprenorphine and buprenorphine/naloxone sublingual tablets are currently available generically.[4] In September 2012, Reckitt Benckiser Pharmaceuticals notified the FDA that it was voluntarily discontinuing production of buprenorphine/naloxone sublingual tablets as a result of increasing concerns over accidental/unsupervised pediatric exposure with the tablets compared to the film formulation. The unique, child-resistant, unit-dose packaging of the film formulation is believed to be a contributing factor to reduced exposure rates in children. Distribution of buprenorphine/naloxone sublingual tablets was discontinued in March 2013; however, generic formulations will remain available.[4,5]

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).[1-3] 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.[6] During buprenorphine administration, opioid-dependent patients experience positive subjective opioid effects which are limited by ceiling effect.[1-3]

Naloxone, an antagonist at the μ-opioid receptor, 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.[2,3] Therefore, the addition of naloxone to buprenorphine results in a decreased risk of diversion compared to buprenorphine monotherapy.[6]

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.[7] The requirements for this waiver include but are not limited to: specialization in addiction psychiatry, completion of an eight hour certification program and the ability to refer addiction treatment patients for appropriate counseling and other non-pharmacologic therapies.[2]

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.[6] Transitioning patients to buprenorphine/naloxone as early as possible to minimize potential diversion associated with buprenorphine monotherapy is also reccomended.[6,7] Clinical trials comparing buprenorphine, both as monotherapy and in combination with naloxone, have demonstrated a significantly lower rate of positive thrice-weekly urine samples for non-study opioids compared to placebo.[1-3] When compared to opioid

dependence treatment with methadone, treatment with buprenorphine and buprenorphine/naloxone offers the advantage of administration without enrollment in an addiction treatment program at a specialized clinic. This flexibility in administration potentially allows more patients to be treated for opioid addiction than previously possible.[6] However, buprenorphine has been shown to be less effective in retaining patients in treatment compared to methadone and is significantly more costly.[8]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Agent		
Buprenorphine (Subutex®*)	Partial opioid agonist	✔
Combination Product		
Buprenorphine/naloxone (Suboxone®*)	Partial opioid agonist/opioid antagonist	✔ †

*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 Indications[1-3]

Generic Name	Treatment of Opioid Dependence
Single Entity Agent	
Buprenorphine	✔
Combination Product	
Buprenorphine/naloxone	✔

In addition to their Food and Drug Administration approved indications buprenorphine and buprenorphine/naloxone sublingual dosage forms have been used off-label for pain management and depression.[4]

Pharmacokinetics

The inter-patient variability in the sublingual absorption of buprenorphine and naloxone is wide; however, the variability within subjects is low.[1-3]

Table 3. Pharmacokinetics[1-3,4]

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

Clinical Trials

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

One double-blind, placebo- and active-controlled study (N=326) showed 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.[9] A smaller, randomized controlled trial (N=32) also showed no significant difference in withdrawal symptoms between buprenorphine and buprenorphine/naloxone.[10]

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.[11-13] 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.[14]

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.[15]

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.[16-18]

When compared to other agents, one Cochrane review showed that buprenorphine was less effective than methadone in retaining patients in opioid dependence treatment.[8] Another Cochrane review showed that buprenorphine-based therapy was as effective as methadone and more effective than clonidine in the management of opioid withdrawal symptoms.[19]

Table 4. Clinical Trials

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ling et al[20] Buprenorphine 1, 4, 8 or 16 mg/day dissolved in 30% ethyl alcohol	DB, MC Patients with a mean age of 36 who met the DSM-III criteria for opioid dependence and had used opioids daily during the previous six months	N=736 16 weeks	Primary: Safety and efficacy as measured by retention in treatment, illicit opioid use and opioid craving Secondary: Not reported	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 group, 51% for the 4 mg group, 52% for the 8 mg group and 61% for the 16 mg group. 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). 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). Secondary: Not reported
Lintzeris et al[21] 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	OL Patients ≥18 years of age with opioid dependent and an opioid positive urine screen on assessment	N=18 8 days	Primary: Severity of withdrawal experience as measured by VAS 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	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). 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. 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

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			events	"too low" (*P* value not reported). 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 three or more days, and data was unavailable for the remaining three patients (*P* values not reported). 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. 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). Sixteen patients reported adverse events. The most common were headache (50%), sedation (28%), nausea, constipation and anxiety (21%).
Kornor et al[22] Buprenorphine flexible daily dosing to a maximum dose of 16 mg daily	OL Patients ≥22 years of age with opioid dependence who were willing to enroll in a nine-month buprenorphine program	N=75 9 months	Primary: Self reported opioid abstinence in program completers and non-completers 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,	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). 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). 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).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			cannabis, polysubstance and intravenous use, employment, illegal activities, psychiatric problems and medical problems	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 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).
Fareed et al[15] 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
Fareed et al[23] Buprenorphine >16 mg/day (mean dose, 27.5±4.8 mg) vs buprenorphine ≤16 mg/day (mean dose, 11.5±4.8 mg)	OS Patients with opioid dependence who were receiving buprenorphine maintenance treatment	N=77 ≥1 month	Primary: Treatment retention rate and percentage of urine drug screens positive for opioids or cocaine Secondary: Not reported	Primary: Treatment drop-out rate was similar between the high- and moderate-dose groups (37.5 vs 43.0%; *P*=0.67). 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). Secondary: Not reported

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Bickel et al[16] 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[17] Buprenorphine maintenance dose (ranged 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	DB, PC, XO 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=14 Approximately 43 days	Primary: Subjective opioid agonist and withdrawal effects Secondary: Not reported	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). 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). 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. Secondary: Not reported

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs quadruple maintenance dose SL every 96 hours Patients were administered 10 days of their daily SL maintenance dose to ensure stabilization.				
Schottenfeld et al[18] 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 There was a three-day buprenorphine induction phase prior to randomization.	DB, RCT 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	N=92 12 weeks	Primary: Retention, three times per week urine toxicology tests and weekly self-reported illicit drug use Secondary: Not reported	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). 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). 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 daily group vs 1.70±0.22 in the thrice-weekly group; *P*=0.27). Secondary: Not reported
Kakko et al[11] Buprenorphine 16 mg SL daily vs	PC, RCT Patients >20 years of age with opioid dependence who were seeking admission for	N=40 1 year	Primary: One-year retention in treatment Secondary: ASI	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). Secondary: The buprenorphine daily group had a significant reduction in ASI scores

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
buprenorphine SL six-day taper (8 mg for two days, 4 mg for two days, 2 mg for two days) followed by placebo	medically-assisted heroin withdrawal and who had a history of heroin dependence (as defined by the DSM-IV criteria) for at least one year			over time from baseline (*P*<0.0001).
Assadi et al[24] Experimental protocol: Buprenorphine 12 mg IM in 24 hours vs 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) Authors reported that buprenorphine SL is two thirds as potent as IM, so 32 mg SL is equivalent to 18 mg IM.	DB, PG, RCT Patients 18 to 60 years of age who met the DSM-IV criteria for opioid dependence	N=40 10 days	Primary: Days of retention in treatment and rates of successful detoxification Secondary: SOWS and OOWS	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). 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). 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). 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*=0.56).
Fudala et al[9] Phase 1 Buprenorphine 16 mg daily vs buprenorphine/naloxone 16/4	MC, PC, RCT with OL phase Patients 18 to 59 years of age who met the DMS-IV criteria for opioid dependence and	Phase 1 N=326 Phase 2 N=472 52 weeks	Primary: Efficacy measured by percentage of urine samples negative for opioids and the patients' self reported craving for opioids	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). 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

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg daily vs placebo Phase 2 Buprenorphine 8 to12 mg for two days, then buprenorphine/naloxone 24/6 mg daily	who were seeking opioid-substitution pharmacotherapy		Secondary: Patients' and clinicians' impressions of overall status and adverse events	each week). 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). 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). 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*=005 respectively), with the withdrawal syndrome and diarrhea occurring more frequently in the placebo group and constipation occurring more frequently in the treatment groups.
Daulouede et al[25] Buprenorphine at patient's current dosage SL vs buprenorphine/naloxone at the same buprenorphine dose SL	MC, OL, PRO, XO Patients ≥18 years of age who were receiving stable, maintenance treatment with buprenorphine 2 to 16 mg/day for at least six months	N=53 5 days	Primary: Patient-rated global satisfaction with study medication Secondary: Well-being in the past 24 hours, tablet taste, tablet size, SL dissolution time, patient preference and adverse events	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). 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). 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. On day five, 54 and 31% of patients indicated preference to buprenorphine/naloxone and buprenorphine, respectively. Fifteen percent

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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. Twenty-three adverse events were reported during study period. The most commonly reported adverse events were fatigue, hyperhidrosis, diarrhea and headache.
Strain et al[10] Buprenorphine soluble film 16 mg SL daily vs buprenorphine/naloxone soluble film 16 mg SL daily	RCT Patients 25 to 56 years of age with opioid dependence	N=34 5 days	Primary: Change in COWS scores Secondary: Pupillometry, VAS and subjective adjective rating scales and adverse events	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). Secondary: 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). 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.
Minozzi et al[26] 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	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. *Buprenorphine vs clonidine* 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).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			treatment, use of other substances of abuse, overdose, criminal activity and social functioning	*Buprenorphine/naloxone detoxification (two weeks) vs maintenance treatment (12 weeks)* 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: *Buprenorphine vs clonidine* Patients receiving buprenorphine were more likely to receive psychosocial or naltrexone treatment (RR, 11.00; 95% CI, 1.58 to 76.55). *Buprenorphine/naloxone detoxification (two weeks) vs maintenance treatment (12 weeks)* 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).
Gowing et al[19] Buprenorphine vs methadone (five studies), α_2-adrenergic agonists (12 studies) or different buprenorphine-based regimens (five studies)	MA (22 RCTs) Patients who were withdrawing from heroin and/or methadone	N=1,736 5 to 90 days	Primary: Intensity of withdrawal, duration of withdrawal treatment, adverse events and completion of treatment, number of treatment following completion of withdrawal intervention Secondary: Not reported	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. *Buprenorphine vs methadone* Studies comparing buprenorphine to methadone reported no significant difference in withdrawal severity between the two groups. Results from two studies showed that duration of withdrawal treatment was 1.38 days shorter with buprenorphine than methadone, but this difference did not reach statistical significance (95% CI, -4.27 to 1.51; *P*=0.35).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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). *Buprenorphine vs α_2-adrenergic agonists* 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). 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). 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). *Comparison of different rates of buprenorphine taper* 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. 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). Data were conflicting on the completion of treatment. Secondary: Not reported

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Mattick et al[8] Buprenorphine maintenance therapy vs methadone maintenance therapy (17 studies) or placebo (seven studies)	MA (24 RCTs) Patients with opioid dependence	N=4,497 2 to 52 weeks	Primary: Treatment retention, use of opioids, use of other substances, criminal activity and mortality; physical health, psychological health and adverse events Secondary: Not reported	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. *Flexible dose buprenorphine vs flexible dose methadone* 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). *Low dose buprenorphine vs low dose methadone* 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). *Low dose buprenorphine vs medium dose methadone* 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). *Medium dose buprenorphine vs low dose methadone* One study showed lower retention rate with buprenorphine compared to methadone while three studies showed no statistically significant difference between the two groups. Pooled analysis on treatment

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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). *Medium dose buprenorphine vs medium dose methadone* 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). *Low dose buprenorphine vs placebo* 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). *Medium dose buprenorphine vs placebo* 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). *High dose buprenorphine vs placebo* Results from four studies (N=728) showed higher retention rate with buprenorphine compared to placebo (RR, 1.74; 95% CI, 1.02 to 2.96).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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). Secondary: Not reported
Meader et al[27] Buprenorphine vs methadone (three studies), clonidine (eight studies) or lofexidine* (one study) 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)	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 reach statistical significance. 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. Secondary: Not reported
Gibson et al[28] Buprenorphine (dosing not specified) vs methadone (dosing not specified)	DB, MC, RCT Patients ≥18 years of age who were heroin-dependent and lived within commuting distance of the clinic	N=405 91 day treatment period followed by a 10 year longitudinal follow-up	Primary: Effects of opioid maintenance treatment on mortality rate Secondary: Difference between two treatment groups in exposure to opioid	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). 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

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			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	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). Drug overdose or related complications were the most common causes of death in the 30 deceased participants (40% of the deaths). 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). 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. 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.
Amass et al[29] Buprenorphine/naloxone SL tablets for a total of 4/1 mg 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	DB, MC, OL, RCT Patients ≥15 years of age with opioid dependence who were experiencing withdrawal symptoms and who requested medical treatment for the symptoms	N=234 13 days	Primary: Treatment compliance and retention Secondary: Ancillary medications administration rate and adverse effects	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 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). 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%). Sixty-one percent of adverse events were expected events associated with drug relapse; however, the specific adverse events were not reported.

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Woody et al[12] Buprenorphine/naloxone up to 14 mg/day of buprenorphine SL for two weeks; dose taper ended by day 14 (detoxification) vs buprenorphine/naloxone up to 24 mg/day of buprenorphine SL for 12 weeks; dose taper began at week 9 and ended by week 12 All patients received 12 weeks of individual and group counseling.	MC, RCT Patients 14 to 21 years of age who met DSM-IV criteria for opioid dependence with physiologic features and who sought outpatient treatment	N=152 12 weeks	Primary: Opioid-positive urine test results at weeks four, eight and 12 Secondary: Treatment retention rate, self-reported use, injecting, enrollment in addiction treatment outside of the study, other drug use and adverse events	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). 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 missing counseling sessions for at least two weeks. 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). 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). The most commonly reported adverse events were headaches, nausea, insomnia, stomachache, vomiting and anxiety in both groups.
Polsky et al[14] Buprenorphine/naloxone up to 14 mg/day of buprenorphine SL for two weeks; dose taper ended by week 2 (detoxification) vs	MC, RCT Patients 15 to 21 years of age who met DSM-IV criteria for opioid dependence with physiologic features and who sought outpatient	N=152 12 weeks	Primary: Treatment cost, opioid-free years, QALY, one-year direct medical cost per QALY and one-year direct medical cost per opioid-free years	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). 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.

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
buprenorphine/naloxone up to 24 mg/day of buprenorphine SL for 12 weeks; dose taper began at week 9 and ended by week 12 All patients received 12 weeks of individual and group counseling.	treatment		Secondary: Net social cost	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. 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. 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. 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).
Weiss et al[13] 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 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)	MC, RCT Patients ≥18 years of age who met DSM-IV criteria for opioid dependence and who were seeking treatment	Phase 1 N=653 12 weeks Phase 2 N=360 24 weeks	Primary: Percentage of patients achieving successful outcome Secondary: Adverse events	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. 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). No differences were seen between patients who received standard medical management and those who received additional opioid dependence counseling.

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Patients who did not have successful outcome at week 12 proceeded to Phase 2. All patients were randomized to receive standard medical management or standard medical management plus opioid dependence counseling prior to entering each study phase.				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 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.
Correia et al[30] Buprenorphine/naloxone 8/2 mg SL daily vs buprenorphine/naloxone 16 mg/4 mg SL daily vs buprenorphine/naloxone 32/8 mg SL daily After two weeks on each maintenance dose, participants underwent challenge sessions consisting of IM hydromorphone.	DB, RCT Patients with active opioid dependence as confirmed through self-report, urinalysis and observation and who met DSM-IV criteria of current opioid (heroin) dependence	N=8 11 weeks	Primary: Opioid blockade and withdrawal effects Secondary: Not reported	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). The 8/2 mg dose produced lower oxygen saturation as compared to the 16/4 mg dose (*P*≤0.05). There were no significant differences regarding symptoms of withdrawal among the study doses (*P*>0.05). As time since the last dose increased, so did the number of mild effects reported (*P* value not reported). Secondary: Not reported

*Agent not available in the United States.
Drug regimen abbreviations: IM=intramuscular, SL=sublingual
Study abbreviations: CI=confidence interval, DB=double-blind, 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=risk ratio, 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 Populations[1]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Entity Agent					
Buprenorphine	Use with caution in elderly patients. Safety and efficacy in children <16 years of age have not been established.	No dosage adjustment required.	Hepatic dose adjustment required.	C	Yes (% unknown).
Combination Product					
Buprenorphine/ naloxone	Use with caution in elderly patients. Safety and efficacy in children <16 years of age have not been established.	No dosage adjustment required for buprenorphine. Naloxone is not studied in renal dysfunction.	Hepatic dose adjustment required.	C	Yes (% unknown).

Adverse Drug Events

Clinical trials have examined the safety of buprenorphine/naloxone and buprenorphine in opioid-dependent patients. In a comparative four-week study, few differences in adverse events between buprenorphine and buprenorphine/naloxone were observed.[1-3] Adverse events that were reported by at least 5% of the patients in the study are outlined in Table 6.

Table 6. Adverse Drug Events[1-3]

Adverse Event (%)	Single Entity Agent	Combination Product	
	Buprenorphine	Buprenorphine/Naloxone Sublingual Tablet	Buprenorphine/Naloxone Sublingual Film
Body as a Whole			
Asthenia	4.9	6.5	-
Chills	7.8	7.5	-
Disturbance in attention	-	-	✔
Headache	29.1	36.4	-
Infection	11.7	5.6	-
Intoxication	-	-	✔
Pain	18.4	22.4	-
Pain, abdomen	11.7	11.2	-
Pain, back	7.8	3.7	-
Withdrawal syndrome	18.4	25.2	✔
Cardiovascular System			
Palpitation	-	-	✔
Vasodilation	3.9	9.3	-
Digestive System			
Constipation	7.8	12.1	✔
Diarrhea	4.9	3.7	-

Adverse Event (%)	Single Entity Agent	Combination Product	
	Buprenorphine	Buprenorphine/Naloxone Sublingual Tablet	Buprenorphine/Naloxone Sublingual Film
Nausea	13.6	15	-
Vomiting	7.8	7.5	✔
Local Administration Site			
Glossodynia	-	-	✔
Oral hypoesthesia	-	-	≥1
Oral mucosal erythema	-	-	✔
Nervous System			
Blurred vision	-	-	✔
Insomnia	21.4	14	✔
Respiratory System			
Rhinitis	9.7	4.7	-
Skin & Appendages			
Sweating	12.6	14	✔

✔ Percent not specified.
- Event not reported.

Contraindications

Table 7. Contraindications[1-3]

Contraindication	Single Entity Agent	Combination Product
	Buprenorphine	Buprenorphine/Naloxone
Hypersensitivity to active ingredient	✔	✔

Warnings/Precautions

Table 8. Warnings and Precautions[1-3]

Warning(s)/Precaution(s)	Single Entity Agent	Combination Product
	Buprenorphine	Buprenorphine/Naloxone
Abuse potential; buprenorphine can be abused in a manner similar to other opioids, legal or illicit; prescribe with appropriate precautions to minimize risks of misuse, abuse or diversion; monitor patient's level of stability, and do not prescribe multiple refills early in treatment or without appropriate follow-up visits	✔	✔
Acute abdominal conditions; similar to other opioids, buprenorphine may obscure the diagnosis or clinical course of acute abdominal conditions	✔	✔
Central nervous system depression; patients receiving buprenorphine and concurrent opioid analgesics or other central nervous system depressants may exhibit increased central nervous system depression	✔	✔
Dependence; buprenorphine is a partial opioid agonist and chronic administration produces physical dependence, characterized by withdrawal symptoms upon abrupt discontinuation or rapid taper	✔	✔
Elevation of cerebrospinal fluid pressure; similar	✔	✔

Warning(s)/Precaution(s)	Single Entity Agent	Combination Product
	Buprenorphine	Buprenorphine/Naloxone
to other opioids, use with caution in patients with head injury, intracranial lesions and other circumstances when cerebrospinal pressure may be increased		
Elevation of intracholedochal pressure; similar to other opioids, use with caution in patients with biliary tract dysfunction	✔	✔
Hepatitis, hepatic events; cases of cytolytic hepatitis with jaundice have been reported; baseline and periodic monitoring of liver function during treatment is recommended	✔	✔
Impairment of ability to drive or operate machinery; use caution in driving or operating hazardous machinery during treatment induction and dose adjustment	✔	✔
Neonatal withdrawal; neonatal withdrawal has been reported in infants of women treated with buprenorphine during pregnancy and most often occur from first to eighth day of life	✔	✔
Orthostatic hypotension; buprenorphine may produce orthostatic hypotension in ambulatory patients like other opioids	✔	✔
Precipitation of opioid withdrawal; due to its partial agonist properties, buprenorphine may precipitate opioid withdrawal signs and symptoms in patients physically dependent on full opioid agonists if administered before the agonist effects of other opioids have subsided	✔	✔
Respiratory depression; buprenorphine, especially when taken by the intravenous route, in combination with benzodiazepines or other central nervous system depressants has been associated with significant respiratory depression and death; use with caution in patients with compromised respiratory function	✔	✔
Special populations; similar to other opioids, administer with caution in debilitated patients and those 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	✔	✔
Use in opioid naïve patients; deaths have been reported in opioid naïve patients receiving buprenorphine sublingual tablet for analgesia; do not use as an analgesic	✔	✔

Drug Interactions

Dosage adjustments of buprenorphine may be necessary in patients receiving cytochrome P450 3A4 inhibitors, such as azole antifungals, macrolide antibiotics and protease inhibitors. There have been reports of coma and death associated with the concomitant intravenous misuse of buprenorphine and benzodiazepines by addicts.[1-3,31,32]

Table 9. Drug Interactions[1-3,31,32]

Generic Name	Interacting Medication or Disease	Potential Result
Buprenorphine	Barbiturate anesthetics (methohexital, thiamylal and thiopental)	The dose of thiopental required to induce anesthesia may be reduced in the presence of buprenorphine. Although apnea may be more common with this combination and drug actions may be additive, no additional precautions other than those routinely used in anesthesia appear necessary.
Buprenorphine	Benzodiazepines (alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, quazepam, temazepam and triazolam)	Concomitant administration results in an increased risk of sedation and life-threatening respiratory depression, especially with over dosage. Subjective and performance responses may also be altered; caution patients against driving or operating machinery while taking these agents.
Buprenorphine	Protease Inhibitors (amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir and tipranavir)	Buprenorphine plasma concentrations may be increased and the half-life prolonged, increasing the risk of adverse reactions. Closely monitor respiratory function during buprenorphine administration and for a longer period than usual after stopping buprenorphine in patients receiving protease Inhibitors. If the buprenorphine is administered continuously, it may be necessary to reduce the buprenorphine dose.

Dosage and Administration

Buprenorphine and buprenorphine/naloxone have a typical dosage range of 12 to 16 mg/day and are administered sublingually once daily. In situations where multiple tablets are administered at the same time, either all tablets may be placed at once or two tablets at a time may be placed under the tongue. In all cases the tablets should remain under the tongue until fully dissolved. If tablets are swallowed, the bioavailability of the drug is reduced. When used as indicated, these agents have similar clinical effects and are interchangeable.[1-3]

Currently there are no adequate, well-controlled studies using buprenorphine/naloxone as the initial medication. During induction, buprenorphine may be preferred since it does not contain naloxone. This is especially true for patients that are in withdrawal from long-acting opioids. The initiation of buprenorphine in the induction phase should occur at least four hours after the patient last used opioids or when the patient begins presenting with early signs of withdrawal. Although there is limited evidence regarding buprenorphine administration with methadone and long-acting opioids, the available evidence suggests the possibility of withdrawal symptoms during the induction phase. These symptoms are more likely to occur in patients maintained on high doses of methadone or when the first buprenorphine dose is administered shortly after the last methadone dose.[1]

Buprenorphine/naloxone can be used for induction in patients dependent on short acting opioids and is the preferred agent for maintenance and in situations where administration is unsupervised. The maintenance phase usually averages one to two months.[1-3] During this time, the recommended target dose of buprenorphine is 16 mg per day with a range between 4 to 24 mg/day, although some patients may require up to a maximum of 32 mg/day.[2,3,6] Doses should be adjusted in increments of 2 to 4 mg to suppress withdrawal symptoms. Although both gradual and abrupt discontinuation methods have been used, there have been no studies to evaluate the best method of dose taper at the end of treatment.[2,3]

Table 10. Dosing and Administration[1-3]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Entity Agent			
Buprenorphine	Treatment of opioid dependence: Sublingual tablet, initial, 12 to 16 mg/day as a single daily dose during induction	Safety and efficacy in children <16 years of age have not been established.	Sublingual tablet: 2 mg 8 mg
Combination Product			
Buprenorphine/ naloxone	Treatment of opioid dependence: Sublingual film and tablet, initial, 12 to 16 mg/day as a single daily dose during maintenance	Safety and efficacy in children <16 years of age have not been established.	Sublingual film: 2/0.5 mg 4/1 mg 8/2 mg 12/3 mg Sublingual tablet: 2/0.5 mg 8/2 mg

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
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)[6]**	• 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 ≥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 insufficient data in this patient population. • 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

Clinical Guideline	Recommendations
	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 to14 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. • 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.

Clinical Guideline	Recommendations
	• 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.

Conclusions

Buprenorphine and buprenorphine/naloxone 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. Buprenorphine and buprenorphine/naloxone sublingual tablets are currently available generically.[1-4] Compared to methadone treatment, the partial agonist buprenorphine has the advantages of providing the positive subjective effects associated with opiate abuse and preventing withdrawal symptoms while removing the euphoria associated with further opioid abuse. Buprenorphine is associated with a risk of respiratory depression, especially if injected or given concomitantly with benzodiazepines or alcohol; however, these risks are less than that of traditional full opioid agonists due to the ceiling effect associated with partial agonist therapy. Naloxone is an opioid antagonist and, when used in combination with buprenorphine, may help to prevent abuse by precipitating withdrawal and dysphoria when this combination product is inappropriately administered via injection.[1-3,6]

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.[7] According to The United States Substance Abuse and Mental Services guidelines, physicians should be aware of the potential for abuse and diversion of buprenorphine monotherapy and reserve maintenance buprenorphine monotherapy for patients who are pregnant or who have a documented allergy to naloxone. Physicians should include buprenorphine as part of a total treatment plan including: counseling services, toxicologic evaluations for opioid abuse, management of comorbidities and close patient monitoring.[6]

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