# *Therapeutic Class Overview*
# *Opioid Dependence Agents*

**Overview/Summary:**
This review will focus on the partial opioid agonists and opioid antagonists. These agents are used alone or in combination in the treatment of opioid use disorder with several agents used for the reversal of opioid overdose.[1-9] 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] Naloxone solution and naloxone auto-injector (Evzio®) are used for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.[8-9] 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. Naloxone is available as a vial for injection, prefilled syringe for injection and auto-injector solution (Evzio®)[1-9] Products which contain buprenorphine are classified as Schedule III controlled substances.[10] 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.[11,12] Buprenorphine and buprenorphine/naloxone sublingual tablets, naltrexone tablets and naloxone vials and prefilled syringes 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.[2-9] 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] Similarly, when naloxone alone is administered to a patient via intravenous, intramuscular or subcutaneous routes, reversal of opioid-related effects is expected. This includes respiratory and/or nevous system depression.[8-9] Evzio® (naloxone injection) is a prefilled autoinjector designed to deliver 0.4 mg of naloxone per injection. The injection can be given intramuscularly or subcutaneously into the outer thigh and may be given through clothing, if necessary. In addition, the device has a retractable needle system that is designed to prevent needlesticks. Evzio® (naloxone injection) is designed to be administered by laypersons in the presence of a patient with an apparent opioid overdose. The autoinjector device gives electronic voice instructions to the caregiver, including instruction to seek emergency medical assistance after a dose is administered.[9]

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.[13] Naloxone is recommended as an appropriate emergency pharmacologic intervention for instances of opioid overdose.[14] Additionally, The Substance Abuse and Mental Health Services Administration and American Medical Association are among some of the prominent medical organizations and advocacy groups that recognize naloxone as standard care for pharmacologic treatment of opioid overdose.[16,17]

**Table 1. Current Medications Available in Therapeutic Class**[1-9]

| 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:<br>2 mg<br>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®):<br>380 mg<br><br>Tablet (ReVia®):<br>50 mg | - |
| Naloxone (Evzio®) | Opioid overdose§ | Auto-injector solution (Evzio®):<br>0.4 mg/0.4 mL<br><br>Prefilled syringe, solution:<br>0.4 mg/mL<br>2 mg/2 mL<br><br>Vial, solution<br>0.4 mg/mL | a |
| **Combination Product** | | | |
| Buprenorphine/naloxone | Opioid dependence, treatment induction† (Suboxone®); opioid dependence, treatment maintenance† | Buccal film (Bunavail®):<br>2.1/0.3 mg<br>4.2/0.7 mg<br>6.3/1 mg<br><br>Sublingual film (Suboxone®):<br>2/0.5 mg<br>4/1 mg<br>8/2 mg<br>12/3 mg<br><br>Sublingual tablet:<br>2/0.5 mg<br>8/2 mg<br><br>Sublingual tablet (Zubsolv®):<br>1.4/0.36 mg<br>5.7/1.4 mg | - |

* According to the manufacturer, buprenorphine sublingual tablets are preferred for use only during induction of treatment for opioid dependance, 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.
§As manifested by respiratory and/or central nervous system depression.

## 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.[20-30, 41-48]

- 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.[22, 31-38]
- 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).[58]
- 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.[59]
- FDA-approval of Evzio® (naloxone injection) was based upon data from a bioavailability trial that compared Evzio® (naloxone injection) to naloxone given through a standard syringe. Subjects were randomized to receive Evzio® (naloxone injection) or standard naloxone injection on day one. On day two, the subjects received the opposite treatment in order to evaluate the comparative bioavailability. The mean peak plasma concentration ($C_{max}$), median times to peak plasma concentrations ($T_{max}$), mean elimination half-life ($T_{1/2}$) and mean area under-the-curve (AUC) mere similar when Evizio® (naloxone injection) was compared to standard naloxone injections (P values not reported).[60]

## 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.[13]
    - 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.[13]
    - Naloxone is recommended as an appropriate emergency pharmacologic intervention for instances of opioid overdose.[14]
    - Naltrexone is generally reserved as an alternative regimen after buprenorphine-containing products and methadone.[15]
- 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.[18]
    - Naltrexone extended-release suspension for injection is injected intramuscularly in the gluteal muscle every 4 weeks by a healthcare provider.[3]

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# *Therapeutic Class Review*
# *Opioid Dependence Agents*

**Overview/Summary**

This review will focus on the partial opioid agonists and opioid antagonists. These agents are used alone or in combination in the treatment of opioid use disorder with several agents used for the reversal of opioid overdose.[1-9] 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] Naloxone solution and naloxone auto-injector (Evzio®) are used for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.[8-9] 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. Naloxone is available as a vial for injection, prefilled syringe for injection and auto-injector solution (Evzio®)[1-9] Products which contain buprenorphine are classified as Schedule III controlled substances.[10] 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.[11,12] Buprenorphine and buprenorphine/naloxone sublingual tablets, naltrexone tablets and naloxone vials and prefilled syringes 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.[13] 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.[2-9] 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] Similarly, when naloxone alone is administered to a patient via intravenous, intramuscular or subcutaneous routes, reversal of opioid-related effects is expected. This includes respiratory and/or nevous system depression.[8-9] Evzio® (naloxone injection) is a prefilled autoinjector designed to deliver 0.4 mg of naloxone per injection. The injection can be given intramuscularly or subcutaneously into the outer thigh. Evzio® (naloxone injection) may be given through clothing, if necessary, and the device has a retractable needle system that is designed to prevent needlesticks. Each carton of Evzio® (naloxone injection) contains two autoinjector devices and a trainer that may be reused for repeat training purposes.[9] Evzio® (naloxone injection) is designed to be administered by laypersons in the presence of a patient with an apparent opioid overdose. The autoinjector device gives electronic voice instructions to the caregiver, including instruction to seek emergency medical assistance after a dose is administered. The electronic voice instructions also instruct caregivers to take the Evzio® (naloxone injection) to the patient's physician for proper disposal and a refill of the medication after a dose is used. Should the electronic voice instructions fail to work, each autoinjector has printed instructions on the label of the device. If used according to the printed instructions on the device label, the Evzio® (naloxone injection) autoinjector will still deliver the necessary dose of naloxone, even if the electronic voice instructions fail to properly function.[9]

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.[13] Transitioning patients to buprenorphine/naloxone as early as possible to minimize potential diversion associated with buprenorphine monotherapy is also reccomended.[13] Veterans Health Administration and American Psychiatric Association guidelines outline a similar strategy with methadone and buprenorphine first line.[14-15] Only the American Psychiatric Association guidelines recommend naltrexone use as an alternative regimen.[15] Naloxone is recommended as an appropriate emergency pharmacologic intervention for instances of opioid overdose.[14] Additionally, The Substance Abuse and Mental Health Services Administration and American Medical Association are among some of the prominent medical organizations and advocacy groups that recognize naloxone as standard care for pharmacologic treatment of opioid overdose.[16,17]

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.[18]

## 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 | - |
| Naloxone (Evzio®) | Opioid antagonist | a |
| **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 Indications**[1-9]

| Indication | Single Entity | | | Combination |
|---|---|---|---|---|
| | Buprenorphine | Naltrexone | Naloxone | 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 ‖ | | |
| Opioid overdose# | | | a | |

* According to the manufacturer, buprenorphine sublingual tablets are preferred for use only during induction of treatment for opioid dependance, 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.
‖Indiction is for Vivitrol® only.
¶Indication is for Suboxone® only.
#As manifested by respiratory and/or central nervous system depression.

**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. The median time to peak plasma concentration of naloxone injection is 0.25 hours.[8-9]

**Table 3. Pharmacokinetics**[1-9]

| 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 (oral)† 0.5 to 1.36 (inj)‡ |
| 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-ß-naltrexol is 13 hours.
†Sublingual and buccal formulations only; not reported for naloxone injection.
‡Half-life of naloxone auto-injector reported as 1.36 hours, half-life of other naloxone formulations reported as 0.5 to 1.35 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.[19-59] FDA-approval of Evzio® (naloxone injection) was based upon data from a bioavailability trial that compared Evzio® (naloxone injection) to naloxone 0.4 mg given through a standard syringe. Additionally, an ease of use study was conducted for Evzio® (naloxone injection).[60]

In the study in which approval of Evzio® (naloxone injection) was based upon, bioavailability of Evzio® (naloxone injection) was compared to naloxone 0.4 mg given through a standard syringe in 30 healthy subjects. Subjects were randomized to receive Evzio® (naloxone injection) or standard naloxone injection on day one. On day two, the subjects received the opposite treatment in order to evaluate the comparative bioavailability. The mean peak plasma concentration ($C_{max}$) for Evzio® (naloxone injection) was 1,240 pg/mL, versus a $C_{max}$ of 1,070 pg/mL for standard naloxone injection. Median times to peak plasma concentrations for Evzio® (naloxone injection) and standard naloxone injection were 0.25 hour and 0.33 hour, respectively. The mean elimination half-life ($T_{1/2}$) for Evzio® (naloxone injection) was 1.28 hours, versus a mean $T_{1/2}$ of 1.36 hours for standard naloxone injection. The mean area under-the-curve (AUC) for Evzio® (naloxone injection) was 1,930 pg•hr/mL, and the mean AUC for standard naloxone injection was 1,980 pg•hr/mL.[60]

In addition to the bioavailability study, an ease of use study was conducted for Evzio® (naloxone injection) in order to evaluate the ability of laypersons to administer a successful injection. The study evaluated the ability of 20 English-speaking participants aged 12 to 19 years and 20 English-speaking participants aged 20 to 65 years to administer a simulated dose of Evzio® (naloxone injection). The participants were not previously trained to use the Evzio® (naloxone injection) system, and relied upon the voice commands for use instructions. Of the 40 participants, 36 participants (90%) were able to successfully deliver an effective dose of naloxone from the Evzio® (naloxone injection) device. Of the four participants that failed to deliver the dose, two did not press the base of injector firmly enough to activate the autoinjector. One participant did not hold the autoinjector in place for a full second, and the other participant that failed to deliver an effective naloxone dose used the Evzio® (naloxone injection) training unit, rather than the unit with active medication. The average time to give the injection was 64.0 seconds for the adult cohort and 57.6 seconds for the juvenile (12 to 29 years of age) cohort.[60]

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.[20-21] A smaller, randomized controlled trial (N=32) also showed no significant difference in withdrawal symptoms between buprenorphine and buprenorphine/naloxone.[22]

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.[23-25] 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.[26]

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.[27] 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.[28-31]

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.[22, 231-38] However, when low doses of buprenorphine were studied (≤8 mg/day), high doses of methadone (≥50 mg/day) proved to be more efficacious.[29, 39-41]

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.[58]

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.[59]

**Table 4. Clinical Trials**

| Study and Drug Regimens | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Mattick et al[19]<br><br>Buprenorphine maintenance therapy<br><br>vs<br><br>methadone maintenance therapy (17 studies) or placebo (seven studies) | MA (24 RCTs)<br><br>Patients with opioid dependence | N=4,497<br><br>2 to 52 weeks | Primary:<br>Treatment retention, use of opioids, use of other substances, criminal activity and mortality; physical health, psychological health and adverse events<br><br>Secondary:<br>Not reported | Primary:<br>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.<br><br>*Flexible dose buprenorphine vs flexible dose methadone*<br>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).<br><br>*Low dose buprenorphine vs low dose methadone*<br>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).<br><br>*Low dose buprenorphine vs medium dose methadone*<br>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).<br><br>*Medium dose buprenorphine vs low dose methadone*<br>One study showed lower retention rate with buprenorphine compared to methadone while three studies showed no statistically significant |

| Study and Drug Regimens | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | 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).<br><br>*Medium dose buprenorphine vs medium dose methadone*<br>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).<br><br>*Low dose buprenorphine vs placebo*<br>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).<br><br>*Medium dose buprenorphine vs placebo*<br>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).<br><br>*High dose buprenorphine vs placebo*<br>Results from four studies (N=728) showed higher retention rate with |

| Study and Drug Regimens | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | 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).<br><br>Secondary:<br>Not reported |
| Fudala et al[20]<br><br>Phase 1<br>Buprenorphine 16 mg daily<br><br>vs<br><br>buprenorphine/naloxone 16/4 mg daily<br><br>vs<br><br>placebo<br><br>Phase 2<br>Buprenorphine 8 to12 mg for two days, then buprenorphine/naloxone 24/6 mg daily | MC, PC, RCT with OL phase<br><br>Patients 18 to 59 years of age who met the DMS-IV criteria for opioid dependence and who were seeking opioid-substitution pharmacotherapy | Phase 1<br>N=326<br><br>Phase 2<br>N=472<br><br>52 weeks | Primary:<br>Efficacy measured by percentage of urine samples negative for opioids and the patients' self-reported craving for opioids<br><br>Secondary:<br>Patients' and clinicians' impressions of overall status and adverse events | Primary:<br>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).<br><br>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).<br><br>Secondary:<br>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).<br><br>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).<br><br>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. |

| Study and Drug Regimens | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Daulouede et al[21]<br><br>Buprenorphine at patient's current dosage SL<br><br>vs<br><br>buprenorphine/naloxone at the same buprenorphine dose SL | MC, OL, PRO, XO<br><br>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<br><br>5 days | Primary:<br>Patient-rated global satisfaction with study medication<br><br>Secondary:<br>Well-being in the past 24 hours, tablet taste, tablet size, SL dissolution time, patient preference and adverse events | Primary:<br>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).<br><br>Secondary:<br>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).<br><br>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.<br><br>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.<br><br>Twenty-three adverse events were reported during study period. The most commonly reported adverse events were fatigue, hyperhidrosis, diarrhea and headache. |
| Strain et al[22]<br><br>Buprenorphine soluble film 16 mg SL daily<br><br>vs<br><br>buprenorphine/naloxone soluble film 16 mg SL daily | RCT<br><br>Patients 25 to 56 years of age with opioid dependence | N=34<br><br>5 days | Primary:<br>Change in COWS scores<br><br>Secondary:<br>Pupillometry, VAS and subjective adjective rating scales and adverse | Primary:<br>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).<br><br>Secondary: |

| Study and Drug Regimens | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | events | 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).<br><br>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. |
| Kakko et al[23]<br><br>Buprenorphine 16 mg SL daily<br><br>vs<br><br>buprenorphine SL six-day taper (8 mg for two days, 4 mg for two days, 2 mg for two days) followed by placebo | PC, RCT<br><br>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 | N=40<br><br>1 year | Primary:<br>One-year retention in treatment<br><br>Secondary:<br>ASI | Primary:<br>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).<br><br>Secondary:<br>The buprenorphine daily group had a significant reduction in ASI scores over time from baseline (P<0.0001). |
| Woody et al[24]<br><br>Buprenorphine/naloxone up to 14 mg/day of buprenorphine SL for two weeks; dose taper ended by day 14 (detoxification)<br><br>vs<br><br>buprenorphine/naloxone up to 24 mg/day of buprenorphine SL for 12 | MC, RCT<br><br>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<br><br>12 weeks | Primary:<br>Opioid-positive urine test results at weeks four, eight and 12<br><br>Secondary:<br>Treatment retention rate, self-reported use, injecting, enrollment in addiction treatment outside of the study, other drug use and | Primary:<br>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).<br><br>Secondary:<br>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 |

| Study and Drug Regimens | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| weeks; dose taper began at week 9 and ended by week 12<br><br>All patients received 12 weeks of individual and group counseling. | | | adverse events | missing counseling sessions for at least two weeks.<br><br>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).<br><br>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).<br><br>The most commonly reported adverse events were headaches, nausea, insomnia, stomachache, vomiting and anxiety in both groups. |
| Weiss et al[25]<br><br>Phase 1<br>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<br><br>Phase 2<br>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)<br><br>Patients who did not have successful outcome at week 12 proceeded to Phase 2. | MC, RCT<br><br>Patients ≥18 years of age who met DSM-IV criteria for opioid dependence and who were seeking treatment | Phase 1<br>N=653<br><br>12 weeks<br><br>Phase 2<br>N=360<br><br>24 weeks | Primary:<br>Percentage of patients achieving successful outcome<br><br>Secondary:<br>Adverse events | Primary:<br>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.<br><br>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).<br><br>No differences were seen between patients who received standard medical management and those who received additional opioid dependence counseling.<br><br>Secondary:<br>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 |

| Study and Drug Regimens | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| All patients were randomized to receive standard medical management or standard medical management plus opioid dependence counseling prior to entering each study phase. | | | | 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. |
| Polsky et al[26]<br><br>Buprenorphine/naloxone up to 14 mg/day of buprenorphine SL for two weeks; dose taper ended by week 2 (detoxification)<br><br>vs<br><br>buprenorphine/naloxone up to 24 mg/day of buprenorphine SL for 12 weeks; dose taper began at week 9 and ended by week 12<br><br>All patients received 12 weeks of individual and group counseling. | MC, RCT<br><br>Patients 15 to 21 years of age who met DSM-IV criteria for opioid dependence with physiologic features and who sought outpatient treatment | N=152<br><br>12 weeks | Primary:<br>Treatment cost, opioid-free years, QALY, one-year direct medical cost per QALY and one-year direct medical cost per opioid-free years<br><br>Secondary:<br>Net social cost | Primary:<br>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).<br><br>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.<br><br>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.<br><br>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.<br><br>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.<br><br>Secondary:<br>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). |

| Study and Drug Regimens | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Fareed et al[27]<br><br>Buprenorphine ≥16 mg/day<br><br>vs<br><br>buprenorphine <16 mg/day | MA (21 RCTs)<br><br>Patients with opioid dependence who were receiving buprenorphine maintenance treatment | N=2,703<br><br>3 to 48 weeks | Primary:<br>Treatment retention rate and percentage of urine drug screens positive for opioids or cocaine<br><br>Secondary:<br>Not reported | Primary:<br>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).<br><br>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).<br><br>Secondary:<br>Not reported |
| Bickel et al[28]<br><br>Buprenorphine maintenance dose (range from 4 to 8 mg/70 kg) SL every 24 hours<br><br>vs<br><br>double maintenance dose SL every 48 hours<br><br>vs<br><br>triple maintenance dose SL every 72 hours<br><br>Maintenance dose was administered to patients for 13 consecutive days prior to the initiation of the above dosing schedules. | DB, PC<br><br>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<br><br>Approximately 80 days | Primary:<br>Self-report measures (i.e., VAS and adjective rating scales) and observer measures<br><br>Secondary:<br>Not reported | Primary:<br>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).<br><br>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.<br><br>Secondary:<br>Not reported |
| Petry et al[29]<br><br>Buprenorphine maintenance dose (ranged from 4 to 8 | DB, PC, XO<br><br>Patients ≥18 years of age who were in | N=14<br><br>Approximately 43 days | Primary:<br>Subjective opioid agonist and withdrawal effects | Primary:<br>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). |

| Study and Drug Regimens | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| mg/70 kg) SL every 24 hours<br><br>vs<br><br>double maintenance dose SL every 48 hours<br><br>vs<br><br>triple maintenance dose SL every 72 hours<br><br>vs<br><br>quadruple maintenance dose SL every 96 hours<br><br>Patients were administered 10 days of their daily SL maintenance dose to ensure stabilization. | good health and met DSM-III criteria for opioid dependence and FDA qualification criteria for methadone treatment | | Secondary:<br>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).<br><br>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.<br><br>Secondary:<br>Not reported |
| Schottenfeld et al[30]<br><br>Buprenorphine 16 mg/70 kg SL daily<br><br>vs<br><br>buprenorphine 34 mg/70 kg SL on Fridays and Sundays and 44 mg/70 kg SL on Tuesdays<br><br>There was a three-day buprenorphine induction phase prior to randomization. | DB, RCT<br><br>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<br><br>12 weeks | Primary:<br>Retention, three times per week urine toxicology tests and weekly self-reported illicit drug use<br><br>Secondary:<br>Not reported | Primary:<br>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).<br><br>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).<br><br>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 |

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| | | | | daily group vs 1.70±0.22 in the thrice-weekly group; P=0.27).<br><br>Secondary:<br>Not reported |
| Gibson et al[31]<br><br>Buprenorphine (dosing not specified)<br><br>vs<br><br>methadone (dosing not specified) | DB, MC, RCT<br><br>Patients ≥18 years of age who were heroin-dependent and lived within commuting distance of the clinic | N=405<br><br>91 day treatment period followed by a 10 year longitudinal follow-up | Primary:<br>Effects of opioid maintenance treatment on mortality rate<br><br>Secondary:<br>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 | Primary:<br>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).<br><br>Secondary:<br>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).<br><br>Drug overdose or related complications were the most common causes of death in the 30 deceased participants (40% of the deaths).<br><br>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).<br><br>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.<br><br>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. |

| Study and Drug Regimens | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Farré et al[32]<br><br>Buprenorphine ≥8 mg daily (high dose<br><br>vs<br><br>buprenorphine <8 mg daily (low dose)<br><br>vs<br><br>methadone ≥50 mg daily (high dose)<br><br>vs<br><br>methadone <50 mg daily (low dose)<br><br>vs<br><br>levo-acetylmethadol | MA<br><br>Patients seeking treatment for opioid dependence | N=1,944 (13 trials)<br><br>Variable duration | Primary:<br>Retention rate and reduction of opioid use<br><br>Secondary:<br>Not reported | Primary:<br>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).<br><br>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).<br><br>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).<br><br>Secondary:<br>Not reported |
| Gowing et al[33]<br><br>Buprenorphine<br><br>vs<br><br>methadone (five studies), $\alpha_2$-adrenergic agonists (12 studies) or different buprenorphine-based regimens (five studies) | MA (22 RCTs)<br><br>Patients who were withdrawing from heroin and/or methadone | N=1,736<br><br>5 to 90 days | Primary:<br>Intensity of withdrawal, duration of withdrawal treatment, adverse events and completion of treatment, number of treatment following completion of withdrawal intervention | Primary:<br>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.<br><br>*Buprenorphine vs methadone*<br>Studies comparing buprenorphine to methadone reported no significant difference in withdrawal severity between the two groups.<br><br>Results from two studies showed that duration of withdrawal treatment was 1.38 days shorter with buprenorphine than methadone, but this |

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| | | | Secondary:<br>Not reported | difference did not reach statistical significance (95% CI, -4.27 to 1.51; P=0.35).<br><br>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).<br><br>*Buprenorphine vs $\alpha_2$-adrenergic agonists*<br>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).<br><br>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).<br><br>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).<br><br>*Comparison of different rates of buprenorphine taper*<br>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.<br><br>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).<br><br>Data were conflicting on the completion of treatment. |

| Study and Drug Regimens | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | Secondary:<br>Not reported |
| Johnson et al[34]<br><br>Buprenorphine 8 mg daily<br><br>vs<br><br>methadone 60 mg daily<br><br>vs<br><br>methadone 20 mg daily | DB, PG, RCT<br><br>Adults seeking treatment for opioid dependence | N=162<br><br>17-week maintenance phase, followed by a 8-week detoxification phase | Primary:<br>Retention time in treatment, urine samples negative for opioids, and failure to maintain abstinence<br><br>Secondary:<br>Not reported | Primary:<br>During the maintenance phase, the retention rates were significantly greater for buprenorphine (42%) than for methadone 20 mg/day (20%; P<0.04).<br><br>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%).<br><br>Failure to maintain abstinence during the maintenance phase was significantly greater for methadone 20 mg/day, than for buprenorphine (P<0.03).<br><br>During the detoxification phase, there were no differences between the treatment groups with regards to urine samples negative for opioids.<br><br>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%).<br><br>All treatments were well tolerated, with similar profiles of self-reported adverse effects.<br><br>The percentages of patients who received counseling did not differ between groups.<br><br>Secondary:<br>Not reported |
| Kamien et al[35]<br><br>Buprenorphine/ naloxone 8 mg/2 mg daily | DB, DD, RCT<br><br>Patients ≥18 years of age who met criteria for opioid | N=268<br><br>17 weeks | Primary:<br>Amount of opioid abstinence achieved over time | Primary:<br>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).<br><br>Secondary: |

| Study and Drug Regimens | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| vs<br><br>buprenorphine/ naloxone 16 mg/4 mg daily<br><br>vs<br><br>methadone 45 to 90 mg daily | dependence and who were using heroin or prescription opioids or receiving methadone maintenance treatment | | Secondary:<br>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 | 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.<br><br>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).<br><br>Medication compliance did not differ significantly among the treatment groups (P=0.41).<br><br>Non-opioid drug use did not change significantly over time, nor did it differ significantly across groups (P=0.32 to P=0.83).<br><br>Treatment retention did not differ significantly in the low dose groups (P=0.09) or in the high dose groups (P=0.28). |
| Meader et al[36]<br><br>Buprenorphine<br><br>vs<br><br>methadone (three studies), clonidine (eight studies) or lofexidine* (one study) | MA (23 RCTs)<br><br>Patients with opioid dependence who were undergoing opioid detoxification | N=2,112<br><br>3 to 30 days | Primary:<br>Completion of treatment<br><br>Secondary:<br>Not reported | Primary:<br>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).<br><br>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 |

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| 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) | | | | reach statistical significance.<br><br>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.<br><br>Secondary:<br>Not reported |
| Petitijean et al[37]<br><br>Buprenorphine sublingual tablets (flexible dosing schedule)<br><br>vs<br><br>methadone (flexible dosing schedule) | DB, RCT<br><br>Patients seeking treatment for opioid dependence | N=58<br><br>6 weeks | Primary:<br>Treatment retention rate, urine samples positive for opiates, substance use<br><br>Secondary:<br>Not reported | Primary:<br>The retention rate was significantly better in the methadone group than in the buprenorphine group (90 vs 56%, respectively; P<0.001).<br><br>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).<br><br>The proportion of cocaine-positive toxicology results did not differ between groups.<br><br>At week six, the mean stabilization doses were 10.5 mg/day for buprenorphine and 69.8 mg/day for methadone.<br><br>Secondary:<br>Not reported |
| Soyka et al[38]<br><br>Buprenorphine (mean daily dose 9 to 12 mg)<br><br>vs<br><br>methadone (mean daily dose 44 to 50 mg) | RCT<br><br>Opioid-dependent patients who had been without opioid substitution therapy | N=140<br><br>6 months | Primary:<br>Retention rate; substance use; predictors of outcome<br><br>Secondary:<br>Not reported | Primary:<br>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%).<br><br>Substance use decreased significantly over time in both groups and was non-significantly lower in the buprenorphine group.<br><br>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. |

| Study and Drug Regimens | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | The intensity of withdrawal symptoms showed the strongest correlation with drop-out.<br><br>Secondary:<br>Not reported |
| Ling et al[39]<br><br>Buprenorphine 8 mg daily<br><br>vs<br><br>methadone 30 mg daily<br><br>vs<br><br>methadone 80 mg daily | DB, RCT<br><br>Patients seeking treatment for opioid dependence | N=225<br><br>1 year | Primary:<br>Urine toxicology, retention, craving, and withdrawal symptoms<br><br>Secondary:<br>Not reported | Primary:<br>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.<br><br>Performance on measures of retention, opioid use, and opioid craving were not significantly different between the low-dose methadone group and the buprenorphine group.<br><br>Secondary:<br>Not reported |
| Schottenfeld et al[40]<br><br>Buprenorphine 4 mg daily<br><br>vs<br><br>buprenorphine 12 mg daily<br><br>vs<br><br>methadone 20 mg daily<br><br>vs<br><br>methadone 65 mg daily | DB, RCT<br><br>Patients seeking treatment for opioid dependence | N=116<br><br>24 weeks | Primary:<br>Retention in treatment and illicit opioid and cocaine use<br><br>Secondary:<br>Not reported | Primary:<br>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.<br><br>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.<br><br>Secondary:<br>Not reported |
| Ling et al[41]<br><br>Buprenorphine 1, 4, 8 or 16 mg/day dissolved in 30% | DB, MC<br><br>Patients with a mean age of 36 | N=736<br><br>16 weeks | Primary:<br>Safety and efficacy as measured by retention in | Primary:<br>Fifty-one percent of the patients completed the 16 week study.<br><br>Completion rates varied by dosage group as follows: 40% for the 1 mg |

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| ethyl alcohol | who met the DSM-III criteria for opioid dependence and had used opioids daily during the previous six months | | treatment, illicit opioid use and opioid craving<br><br>Secondary:<br>Not reported | group, 51% for the 4 mg group, 52% for the 8 mg group and 61% for the 16 mg group.<br><br>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).<br><br>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).<br><br>Secondary:<br>Not reported |
| Lintzeris et al[42]<br><br>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<br><br>Patients ≥18 years of age with opioid dependent and an opioid positive urine screen on assessment | N=18<br><br>8 days | Primary:<br>Severity of withdrawal experience as measured by VAS<br><br>Secondary:<br>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 | Primary:<br>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).<br><br>Secondary:<br>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.<br><br>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).<br><br>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 |

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| | | | | three or more days, and data was unavailable for the remaining three patients (P values not reported).<br><br>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.<br><br>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).<br><br>Sixteen patients reported adverse events. The most common were headache (50%), sedation (28%), nausea, constipation and anxiety (21%). |
| Kornor et al[43]<br><br>Buprenorphine flexible daily dosing to a maximum dose of 16 mg daily | OL<br><br>Patients ≥22 years of age with opioid dependence who were willing to enroll in a nine-month buprenorphine program | N=75<br><br>9 months | Primary:<br>Self reported opioid abstinence in program completers and non-completers<br><br>Secondary:<br>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 | Primary:<br>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).<br><br>Secondary:<br>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).<br><br>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).<br><br>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 |

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| | | | 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). |
| Fareed et al[44]<br><br>Buprenorphine >16 mg/day (mean dose, 27.5±4.8 mg)<br><br>vs<br><br>buprenorphine ≤16 mg/day (mean dose, 11.5±4.8 mg) | OS<br><br>Patients with opioid dependence who were receiving buprenorphine maintenance treatment | N=77<br><br>≥1 month | Primary:<br>Treatment retention rate and percentage of urine drug screens positive for opioids or cocaine<br><br>Secondary:<br>Not reported | Primary:<br>Treatment drop-out rate was similar between the high- and moderate-dose groups (37.5 vs 43.0%; P=0.67).<br><br>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).<br><br>Secondary:<br>Not reported |
| Assadi et al[45]<br><br>Experimental protocol:<br>Buprenorphine 12 mg IM in 24 hours<br><br>vs<br><br>Conventional protocol:<br>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)<br><br>Authors reported that buprenorphine SL is two thirds as potent as IM, so 32 | DB, PG, RCT<br><br>Patients 18 to 60 years of age who met the DSM-IV criteria for opioid dependence | N=40<br><br>10 days | Primary:<br>Days of retention in treatment and rates of successful detoxification<br><br>Secondary:<br>SOWS and OOWS | Primary:<br>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).<br><br>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).<br><br>Secondary:<br>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).<br><br>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 |

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| mg SL is equivalent to 18 mg IM. | | | | (P=0.56). |
| Minozzi et al[46]<br><br>Buprenorphine<br><br>vs<br><br>buprenorphine-based treatment (one study) or clonidine (one study) | SR (2 RCTs)<br><br>Patients 13 to 18 years of age with opioid dependence | N=190<br><br>2 to 12 weeks | Primary:<br>Drop-out rate, opioid-positive urine test results or self-reported drug use, tolerability and rate of relapse<br><br>Secondary:<br>Enrollment in other treatment, use of other substances of abuse, overdose, criminal activity and social functioning | Primary:<br>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.<br><br>*Buprenorphine vs clonidine*<br>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).<br><br>*Buprenorphine/naloxone detoxification (two weeks) vs maintenance treatment (12 weeks)*<br>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).<br><br>Secondary:<br>*Buprenorphine vs clonidine*<br>Patients receiving buprenorphine were more likely to receive psychosocial or naltrexone treatment (RR, 11.00; 95% CI, 1.58 to 76.55).<br><br>*Buprenorphine/naloxone detoxification (two weeks) vs maintenance treatment (12 weeks)*<br>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[47]<br><br>Buprenorphine/naloxone SL tablets for a total of 4/1 mg | DB, MC, OL, RCT<br><br>Patients ≥15 years of age with opioid | N=234<br><br>13 days | Primary:<br>Treatment compliance and retention | Primary:<br>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 |
|---|---|---|---|---|
| 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 | dependence who were experiencing withdrawal symptoms and who requested medical treatment for the symptoms | | Secondary:<br>Ancillary medications administration rate and adverse effects | 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).<br><br>Secondary:<br>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%).<br><br>Sixty-one percent of adverse events were expected events associated with drug relapse; however, the specific adverse events were not reported. |
| Correia et al[48]<br><br>Buprenorphine/naloxone 8/2 mg SL daily<br><br>vs<br><br>buprenorphine/naloxone 16 mg/4 mg SL daily<br><br>vs<br><br>buprenorphine/naloxone 32/8 mg SL daily<br><br>After two weeks on each maintenance dose, participants underwent challenge sessions consisting of IM hydromorphone. | DB, RCT<br><br>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<br><br>11 weeks | Primary:<br>Opioid blockade and withdrawal effects<br><br>Secondary:<br>Not reported | Primary:<br>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).<br><br>The 8/2 mg dose produced lower oxygen saturation as compared to the 16/4 mg dose (P≤0.05).<br><br>There were no significant differences regarding symptoms of withdrawal among the study doses (P>0.05).<br><br>As time since the last dose increased, so did the number of mild effects reported (P value not reported).<br><br>Secondary:<br>Not reported |

| Study and Drug Regimens | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Maremmani et al[49]<br><br>Buprenorphine<br><br>vs<br><br>methadone | OL<br><br>Patients involved in a long-term treatment program with buprenorphine or methadone | N=213<br><br>12 months | Primary:<br>Opioid use, psychiatric status, quality of life<br><br>Secondary:<br>Not reported | Primary:<br>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.<br><br>Secondary:<br>Not reported |
| Jones et al[50]<br><br>Buprenorphine<br>2 to 32 mg per day<br><br>vs<br><br>methadone<br>20 to 140 mg per day | DB, DD, MC, RCT<br><br>Opioid-dependent women 18 to 41 years of age with a singleton pregnancy between 6 and 30 weeks | N=175<br><br>≥10 days | Primary:<br>Neonates requiring neonate abstinence syndrome therapy, total morphine needed, length of hospital stay, and head circumference<br><br>Secondary:<br>Not reported | Primary:<br>Percentage neonates requiring neonate abstinence syndrome treatment, peak neonate abstinence syndrome scores, or head circumference did not differ significantly between groups.<br><br>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.<br><br>Neonates exposed to buprenorphine required an average 43% less time in hospital (10.0 vs 17.5 days; P<0.0091).<br><br>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.<br><br>Secondary:<br>Not reported |
| Pinto et al[51]<br><br>Buprenorphine<br><br>vs<br><br>methadone | OS, PRO<br><br>Cohort of opioid-dependent patients new to substitution therapy | N=361<br><br>6 months | Primary:<br>Retention in treatment at six months or successful detoxification based on patient selected substitution therapy<br><br>Secondary: | Primary:<br>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).<br><br>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 | 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.<br><br>A total of 28% of patients selecting buprenorphine reported they would not have accessed treatment with methadone therapy.<br><br>Secondary:<br>Not reported |
| Fiellin et al[52]<br><br>Buprenorphine/naloxone | OS<br><br>Patients meeting criteria for opioid dependence | N=166<br><br>2 to 5 years | Primary:<br>Retention in treatment; percentage of opioid-negative urine specimens<br><br>Secondary:<br>Percentage of cocaine-negative urine specimens; buprenorphine dose; patient satisfaction; serum transaminases; adverse events | Primary:<br>During the follow-up period, 40 patients left treatment.<br><br>A total of 91% of urine specimens had no evidence of illicit opioids.<br><br>Secondary:<br>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.<br><br>The mean dose of buprenorphine/naloxone was 17 mg.<br><br>The mean score on the patient satisfaction instruments was 86 out of a possible 95.<br><br>No patients developed elevations in their aspartate aminotransferase or alanine aminotransferase values that required changes in buprenorphine/naloxone dose or discontinuation.<br><br>No serious adverse events directly related to buprenorphine/naloxone treatment occurred over the two to five-year follow-up period. |
| Kakko et al[53]<br><br>Buprenorphine/naloxone (stepped treatment)<br><br>vs | RCT<br><br>Patients >20 years of age with heroin dependence for >1 year | N=96<br><br>24-day induction phase, followed by a 6 month | Primary:<br>Retention in treatment<br><br>Secondary:<br>Completer analyses of problem severity | Primary:<br>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).<br><br>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 |

| 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).<br><br>Secondary:<br>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[54]<br><br>Buprenorphine SL tablets (flexible dosing schedule)<br><br>vs<br><br>methadone (flexible dosing schedule) | DB, DD, RCT<br><br>Patients seeking treatment for opioid dependence | N=164<br><br>26 weeks | Primary:<br>Treatment retention rate¸ medication and counseling compliance, urine samples positive for opiates<br><br>Secondary:<br>Not reported | Primary:<br>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.<br><br>In both groups, 56% of patients remained in the treatment program through the 16-week flexible dosing period.<br><br>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.<br><br>Secondary:<br>Not reported |
| Cornish et al[55]<br><br>Buprenorphine<br><br>vs<br><br>methadone | MC, OS, PRO<br><br>Opioid dependent patients <60 years of age | N=5,577<br><br>585 days | Primary:<br>All cause mortality<br><br>Secondary:<br>Duration of therapy effect on mortality | Primary:<br>Three percent of patients died while receiving treatment, or within a year of receiving the last prescription. Of these, 35% died while on treatment.<br><br>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 to13.1). After adjustment for age, sex, calendar period, and comorbidity, the mortality rate ratio was 2.3 (95% CI, 1.7 to 3.1).<br><br>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 |
|---|---|---|---|---|
| | | | | There was no difference in the overall mortality rate between patients who received methadone and those who received buprenorphine.<br><br>Secondary:<br>Substitution therapy has a greater than 85% chance of reducing overall mortality when average duration of treatment is at least 12 months. |
| Strain et al[56]<br><br>Buprenorphine 4 mg to 16 mg per day<br><br>vs<br><br>buprenorphine/naloxone SL tablets 1/0.25, 2/0.5, 4/1, 8/2, 16/4 mg per day<br><br>vs<br><br>hydromorphone 2 and 4 mg intramuscular<br><br>vs<br><br>placebo | DB, DD, PC<br><br>Adults with active opioid abuse, but not physically dependent | N=7 | Primary:<br>Peak drug effect; physiologic and psychomotor measures<br><br>Secondary:<br>Not reported | Primary:<br>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.<br><br>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).<br><br>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.<br><br>None of the treatments produced significant changes on measures of blood pressure, heart rate, or respiratory rate.<br><br>There were no significant differences in psychomotor effects among the treatments.<br><br>Secondary:<br>Not reported |

| Study and Drug Regimens | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Bell et al[57]<br><br>Buprenorphine/naloxone | RCT<br><br>Heroin users seeking maintenance treatment | N=119<br><br>3 months | Primary:<br>Retention in treatment and heroin use at three months<br><br>Secondary:<br>Not reported | Primary:<br>At three months, 57% randomized to unobserved treatment, and 61% randomized to observed treatment were retained in the heroin treatment program (P=0.84).<br><br>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).<br><br>Secondary:<br>Not reported |
| Minozzi et al[58]<br><br>Naltrexone maintenance treatment<br><br>vs<br><br>placebo maintenance treatment<br><br>or<br><br>no pharmacologic treatment<br><br>or<br><br>psychotherapy<br><br>or<br><br>benzodiazepines | MA (13 RCTs)<br><br>Patients with a diagnosis of opioid dependence | N=1,158<br><br>varies | Primary:<br>Retention in treatment, use of the primary substance of abuse, side effects and/or<br><br>Secondary:<br>Re-incarcerations | Primary:<br>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).<br><br>There was no statically significant difference in the two outcomes considered between naltrexone and psychotherapy (one study).<br><br>Naltrexone was not superior to benzodiazepines and to buprenorphine for retention and abstinence and side effects (one study).<br><br>Secondary:<br>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[59]<br><br>Naltrexone extended-release | DB, MC, PC, RCT<br><br>Patients 18 years | N=250<br><br>24 weeks | Primary:<br>Response profile for confirmed | Primary:<br>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<br><br>vs<br><br>placebo | of age or older with a diagnosis of opioid dependence disorder | | abstinence during weeks 5 to 24<br><br>Secondary:<br>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).<br><br>Secondary:<br>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 Populations**[1-9]

| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Pediatric | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| **Single Entity Agents** | | | | | |
| Buprenorphine | No difference is response was identified between elderly and younger patients; use with caution in elderly patients.<br><br>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.<br><br>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).<br><br>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).<br><br>Use in severe hepatic impairment has not been evaluated. | C | Yes (% unknown). |
| Naloxone | Reported clinical experience has not indicated differences in response to naloxone; however, clinical studies of | Not studied in renal dysfunction. | Not studied in hepatic dysfunction. | B | Unknown. |

| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Pediatric | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| | naloxone have not included sufficient amounts of patients aged 65 years and older to determine whether clinical response in geriatric patients is different from younger patients.<br><br>FDA-approved for use in children <18 years of age. | | | | |
| **Combination Product** | | | | | |
| Buprenorphine/naloxone | 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; use with caution in elderly patients.<br><br>Safety and efficacy in children <16 years of age have not been established. | No dosage adjustment required for buprenorphine.<br><br>Naloxone is not studied in renal dysfunction. | 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). |

**Adverse Drug Events**

The adverse events of buprenorphine, buprenorphine/naloxone (tablets, film), naloxone and naltrexone are summarized in Table 6. Adverse effects for naloxone have generally been voluntarily reported. As such, there is no accurate method to provide their frequency, or to determine if naloxone can be implicated as a causative agent for the events reported. Adverse reactions that have been reported in the post-operative setting are listed below. Additionally, excessive doses of naloxone have been reported to cause agitation, nausea and vomiting.[61,62]

**Table 6. Adverse Drug Events**[1-7]

| Adverse Event (%) | Single Entity Agents | | | Combination Product | |
|---|---|---|---|---|---|
| | Buprenorphine | Naltrexone | Naloxone | Buprenorphine/ Naloxone Tablet | Buprenorphine/ Naloxone Film |

| Adverse Event (%) | Single Entity Agents | | | Combination Product | |
|---|---|---|---|---|---|
| | Buprenorphine | Naltrexone | Naloxone | Buprenorphine/ Naloxone Tablet | Buprenorphine/ Naloxone Film |
| **Body as a Whole** | | | | | |
| Agitation | - | - | a | - | - |
| Anxiety | - | >10% | | - | - |
| Appetite loss | - | <10% | | - | - |
| Asthenia | 4.9 | - | | 6.5 | - |
| Attention disturbances | - | - | - | - | a |
| Chills | 7.8 | <10% | | 7.5 | - |
| Coma | - | - | a | - | - |
| Death | - | - | a | - | - |
| Delayed ejaculation | - | <10% | | - | - |
| 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** | | | | | |
| Cardiac arrest | - | - | a | - | - |
| Hypertension | - | - | a | - | - |
| Hypotension | - | - | a | - | - |
| Palpitation | - | - | | - | a |
| Vasodilation | 3.9 | - | | 9.3 | - |
| Ventricular fibrillation | - | - | a | - | - |
| Ventricular tachycardia | - | - | a | - | - |
| **Digestive System** | | | | | |
| Constipation | 7.8 | <10% | | 12.1 | a |
| Diarrhea | 4.9 | <10% | | 3.7 | - |
| Nausea | 13.6 | a | a | 15 | - |
| Vomiting | 7.8 | >10% | a | 7.5 | a |
| **Local Administration Site** | | | | | |
| Glossodynia | - | - | | - | a |
| Oral hypoesthesia | - | - | | - | ≥1 |
| Oral mucosal erythema | - | - | | - | a |
| **Nervous System** | | | | | |
| Blurry vision | - | - | | - | a |
| Encephalopathy | - | - | a | - | - |
| Insomnia | 21.4 | >10% | | 14 | a |
| Seizure | - | - | a | - | - |
| **Respiratory System** | | | | | |

| Adverse Event (%) | Single Entity Agents | | | Combination Product | |
|---|---|---|---|---|---|
| | Buprenorphine | Naltrexone | Naloxone | Buprenorphine/ Naloxone Tablet | Buprenorphine/ Naloxone Film |
| Dyspnea | - | - | a | - | - |
| Rhinitis | 9.7 | - | | 4.7 | - |
| Pulmonary edema | - | - | a | - | - |
| **Skin & Appendages** | | | | | |
| Skin rash | - | <10% | | - | - |
| Sweating | 12.6 | - | | 14 | a |

a Percent not specified.
- Event not reported.

## Contraindications

**Table 7. Contraindications**[1-9]

| Contraindication | Single Entity Agents | | | Combination Product |
|---|---|---|---|---|
| | Buprenorphine | Naltrexone | Naloxone | Buprenorphine/ Naloxone |
| Hypersensitivity to the active ingredient or to any component. | a | 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 Precautions**[1-9]

| Warning or Precaution | Single Entity Agents | | | Combination Product |
|---|---|---|---|---|
| | Buprenorphine | Naltrexone | Naloxone | 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®) | | |
| Allergic reactions; bronchospasm, angioneurotic edema, and aphylactic shock has been associated with use. | a | | | a |
| Central nervous system depression; concurrent use other central nervous | a | | | a |

| Warning or Precaution | Single Entity Agents | | | Combination Product |
|---|---|---|---|---|
| | Buprenorphine | Naltrexone | Naloxone | Buprenorphine/Naloxone |
| system depressants may exhibit increased central nervous system depression; consider dose reduction of one or both in situations of concomitant prescription. | | | | |
| 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 | | |
| Duration of action of most opioids is likely to exceed that of naloxone resulting in a return of respiratory and/or central nervous system depression after initial improvement. | | | a | |
| Eosinophilic pneumonia has been associated with use; consider when processive 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 |
| Limited efficacy with reversal of respiratory depression by partial agonists or mixed agonist/antagonists such as; reversal may be incomplete. | | | 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 | | |

| Warning or Precaution | Single Entity Agents | | | Combination Product |
|---|---|---|---|---|
| | Buprenorphine | Naltrexone | Naloxone | Buprenorphine/Naloxone |
| 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 then 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 has subsided. | a | a | a | a |
| 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 Interactions**[1-9]

| 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. | Decreased effects of buprenorphine |

| Generic Name | Interacting Medication or Disease | Potential Result |
|---|---|---|
| | phenobarbital, carbamazepine, phenytoin, rifampicin) | |
| 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. |
| Naloxone | Clonidine | Hypotensive and bradycardic effects of clonidine may be reduced; monitor for hypertension. |
| Naloxone | Yohimbine | An increase in adverse effects such as anxiety, hot and cold flashes, increased plasma cortisol levels, nausea, nervousness, and palpitations may result. |

## Dosage and Administration

**Table 10. Dosing and Administration**[1-9]

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| **Single Entity Agents** | | | |
| Buprenorphine | Opioid dependence, treatment induction†:<br>Sublingual tablet: initial, 8 mg on day one followed by 16 mg on day two<br><br>Opioid dependence, treatment maintenance†:<br>Sublingual tablet: maintenance progressive dose adjustment of 2 to 4 mg, general range of 4 to 24 mg per day | Safety and efficacy in children <16 years of age have not been established. | Sublingual tablet:<br>2 mg<br>8 mg |
| Naltrexone | Alcohol dependence:<br>Extended-release suspension for injection: 380 mg via intramuscular injection in the gluteal muscle every four weeks by a healthcare provider<br><br>Tablet: 50 mg once daily for up to 12 weeks<br><br>Opioid dependence‡:<br>Tablet: initial, 25 mg once daily; if no withdrawal symptoms occur, increase to 50 mg once daily thereafter<br><br>Opioid dependence, prevention of relapse following opioid detoxification:<br>Extended-release suspension for injection: 380 mg via intramuscular injection in the gluteal muscle every four weeks by a healthcare provider | Safety and efficacy in children <18 years of age have not been established. | Suspension for injection, extended-release:<br>380 mg<br><br>Tablet:<br>50 mg |

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| Naloxone | Opioid overdose:<br>Auto-injector: 0.4 via intramuscular or subcutaneous injection into the anterolateral aspect of the thigh once, repeat 0.4 mg after two to three minutes, if necessary<br><br>Prefilled syringe, vial: 0.4 to 2 mg intravenously or via intramuscular or subcutaneous injection once, may repeat after two to three minutes, if necessary | Opioid overdose:<br>Auto-injector: 0.4 mg via intramuscular or subcutaneous injection once, may repeat after two to three minutes<br><br>Prefilled syringe, vial: 0.1 mg/kg intravenously (age <5 years) once, 2 mg (age 5 to 18 years) intravenously once, may repeat after two to three minutes | Auto-injector solution (Evzio®):<br>0.4 mg/0.4 mL<br><br>Prefilled syringe, solution:<br>0.4 mg/mL<br>2 mg/2 mL<br><br>Vial, solution<br>0.4 mg/mL |
| **Combination Product** | | | |
| Buprenorphine/ naloxone | Opioid dependence, treatment induction†:<br>Sublingual film (Suboxone®): 8/2 mg sublingually on day one, followed by 16/4 mg sublingually on day two<br><br>Opioid dependence, treatment maintenance†:<br>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<br><br>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 to adequate response, normal range is 4/1 mg to 24/6 mg once daily<br><br>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<br><br>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 | Safety and efficacy in children <16 years of age have not been established. | Buccal film (Bunavail®):<br>2.1/0.3 mg<br>4.2/0.7 mg<br>6.3/1 mg<br><br>Sublingual film (Suboxone®):<br>2/0.5 mg<br>4/1 mg<br>8/2 mg<br>12/3 mg<br><br>Sublingual tablet:<br>2/0.5 mg<br>8/2 mg<br><br>Sublingual tablet (Zubsolv®):<br>1.4/0.36 mg<br>5.7/1.4 mg |

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| | time to adequate response, normal range is 2.8/0.72 mg to 17.1/4.2 mg once daily | | |

† 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.
‖Indiction is for Vivitrol® only.
¶ Indication is for Suboxone® only.

## 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)**[13] | · Buprenorphine/naloxone should be used for the induction, stabilization and maintenance phases of treatment for most patients.<br>· Induction doses should be administered as observed treatment; however, subsequent doses may be obtained with a prescription.<br>· 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.<br>· 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.<br>· 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 insufficient data in this patient population.<br>· 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.<br>· 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 |

| Clinical Guideline | Recommendations |
|---|---|
| | 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.<br>· 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.<br>· 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.<br>· 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.<br>· 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.<br>· 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.<br>· Buprenorphine monotherapy may be used for medically supervised withdrawal.<br>· 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.<br>· 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.<br>· In adolescents and young adults, buprenorphine is a useful option; however, the practitioner should be familiar with the state laws regarding parental consent.<br>· In geriatric patients, the literature is lacking; however, due to differences in metabolism and absorption, additional care should be exercised when treating these patients.<br>· 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.<br>· 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 |

| Clinical Guideline | Recommendations |
|---|---|
| | treatment.<br>· 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.<br>· 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).<br>· Opioid addiction in health care professionals requires specialized, extended care since opioid addiction is an occupational hazard. |
| Veterans Health Administration, Department of Defense: **Clinical Practice Guideline for Management of Substance Use Disorders (2009)**[14] | <u>General considerations</u><br>· Opioid agonist treatment is the first-line treatment for chronic opioid dependence.<br>· Provide access to opioid agonist treatment for all opioid dependent patients, under appropriate medical supervision and with concurrent addition-focused psychosocial treatment.<br>· Strongly recommend methadone or sublingual buprenorphine/naloxone maintenance as first-line therapy. Buprenorphine monotherapy is preferred in pregnancy.<br>· 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.<br><br><u>Opioid agonist treatment program and office-based opioid treatment</u><br>· Opioid agonist treatment should be administered in an opioid agonist treatment program or office-based opioid treatment.<br>· Doses should be adjusted to maintain a therapeutic range between signs/symptoms of overmedication and opioid withdrawal.<br>· The usual dosage range for optimal effects is 60 to 120 mg/day.<br>· Buprenorphine target dose is generally up to 16 mg/day; doses >32 mg are rarely indicated.<br>· In all cases (except pregnancy), the combination product of buprenorphine/naloxone should be used.<br><br><u>Methadone therapy</u><br>· 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.<br>· 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<br>· 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. |

| Clinical Guideline | Recommendations |
|---|---|
| | Buprenorphine therapy<br>· 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.<br>· Buprenorphine induction (~1 week) involves helping a patient in the process of switching from the opioids of abuse to buprenorphine.<br>· In all cases (except pregnancy), the combination product of buprenorphine/naloxone should be used.<br>· 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.<br>· 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. |
| American Psychiatric Association: **Practice Guideline for Treatment of Patients with Substance Use Disorders (2006)**[15] | Treating dependence and abuse<br>· Goals of therapy are to identify stable maintenance dose of opioid agonist and facilitate rehabilitation.<br>· 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.<br>· 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.<br>· Methadone is a full mu agonist opioid, and is the most thoroughly studied and widely used agent for opioid dependence.<br>· Methadone maintenance treatment for opioid-dependent individuals has generally been shown to be effective in:<br>o Decreasing illicit opioid use.<br>o Decreasing psychosocial and medical morbidity.<br>o Improving overall health status.<br>o Decreasing mortality.<br>o Decreasing criminal activity.<br>o Improving social functioning.<br>o Reducing the spread of Human Immunodeficiency Virus infection among intravenous drug users.<br>· 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.<br>· Methadone can be diverted for abuse, as can other opiates that have agonist effects at the mu receptor.<br>· Buprenorphine produces a partial agonist effect at the mu receptor and an antagonistic effect at the kappa receptor.<br>· 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.<br>· The combination of buprenorphine and naloxone significantly reduces the risk of diversion because naloxone will exert a potent opioid |

| Clinical Guideline | Recommendations |
|---|---|
| | antagonist effect if the combination tablet is crushed and administered intravenous by an opioid-dependent person. Naloxone has poor sublingual bioavailability.<br>· Buprenorphine is generally safe. Overdose with buprenorphine generally does not produce significant respiratory depression<br><br>Treating intoxication<br>· Mild to moderate opioid intoxication usually does not require specific therapy.<br>· Severe opioid toxicity, marked by respiratory depression, is a medical emergency. Naloxone will reverse respiratory depression and other overdose manifestations.<br><br>Treating withdrawal<br>· Treatment of withdrawal is directed at safely decreasing acute symptoms and easing transition into a long-term treatment program.<br>· Effective strategies include:<br>o Substitution of opioid with methadone or buprenorphine.<br>o Abrupt discontinuation of opioids, with use of clonidine to suppress withdrawal symptoms.<br>o 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. Naloxone alone is used for the treatment of opioid overdose. 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. Naloxone alone is available as a solution in vials or prefilled syringes and also in an auto-injector device. Buprenorphine and buprenorphine/naloxone sublingual tablets naltrexone tablets, and naloxone vials and syringes are currently available generically.[1-9] 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.[18] Evzio® (naloxone injection) is designed to be administered by laypersons in the presence of a patient with an apparent opioid overdose. Two injections are provided in each package of Evzio® (naloxone injection), should the patient require a second injection before emergency medical services arrive.

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.[20-30,341-48] 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).[58] 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.[59]

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