Therapeutic Class Overview
Opioid Dependence Agents

Overview/Summary:
This review will focus on the agents used for the treatment of opioid dependence, which includes both partial opioid agonists and opioid antagonists. These agents are used alone or in combination for the treatment of opioid use disorder with several agents used for the reversal of opioid overdose.[1-10] Buprenorphine, buprenorphine/naloxone (Bunavail®, Suboxone®, Zubsolv®) and naltrexone (ReVia®, Vivitrol®) are all 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 (Evzio®, Narcan®) is used for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.[8-10] Products which contain buprenorphine are classified as Schedule III controlled substances.[11] Other formulations of buprenorphine, buccal film (Belbuca®), injectable (Buprenex®) and transdermal patch (Butrans®) are FDA-approved for use in the management of pain and will not be discussed within this review.[12-14] Buprenorphine, buprenorphine/naloxone sublingual tablets, naltrexone tablets and naloxone prefilled syringes are currently available as generic products.

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.[15] During buprenorphine administration, opioid-dependent patients experience positive subjective opioid effects which are limited by ceiling effect.[4-7]

Naloxone and naltrexone are μ-opioid receptor antagonists.[2-10] 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.[11] Similarly, when naloxone alone is administered to a patient via intravenous, intramuscular, nasal or subcutaneous routes, reversal of opioid-related effects is expected. This includes respiratory and/or nevous system depression.[8-10]

The United States Substance Abuse and Mental Service Clinical Guideline for the Use of Buprenorphine in the Treatment of Opioid Addiction recommends the use of buprenorphine/naloxone for the induction, stabilization and maintenance phases of opioid addiction treatment for most patients. This guideline also notes that buprenorphine alone should be used for pregnant patients and for the induction therapy of patients who are transitioning from methadone treatment.[15] Transitioning patients to buprenorphine/naloxone as early as possible to minimize potential diversion associated with buprenorphine monotherapy is also reccomended.[15] Veterans Health Administration and American Psychiatric Association guidelines outline a similar strategy with methadone and buprenorphine first line.[16-17] Only the American Psychiatric Association guidelines recommend naltrexone use as an alternative regimen.[17] Naloxone is recommended as an appropriate emergency pharmacologic intervention for instances of opioid overdose.[16] 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.[18,19]

Table 1. Current Medications Available in Therapeutic Class[1-10]

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Buprenorphine‖	Opioid dependence, treatment induction*,†; opioid dependence, treatment maintenance*,†	Sublingual tablet: 2 mg 8 mg	✔
Naltrexone (ReVia®‖, Vivitrol®)	Alcohol dependence; opioid dependence‡ (ReVia®); opioid dependence, prevention of relapse following opioid detoxification (Vivitrol®)	Suspension for injection, extended-release (Vivitrol®): 380 mg Tablet (ReVia®): 50 mg	✔
Naloxone (Evzio®, Narcan®)	Opioid overdose§	Auto-injector solution (Evzio®): 0.4 mg/0.4 mL Nasal Spray (Narcan®) Prefilled syringe: 0.4 mg/mL 2 mg/2 mL	✔
Combination Product			
Buprenorphine/naloxone‖ (Bunavail®, Suboxone®, Zubsolv®)	Opioid dependence, treatment induction† (Suboxone® film); opioid dependence, treatment maintenance†	Buccal film (Bunavail®): 2.1/0.3 mg 4.2/0.7 mg 6.3/1 mg Sublingual film (Suboxone®): 2/0.5 mg 4/1 mg 8/2 mg 12/3 mg Sublingual tablet: 2/0.5 mg 8/2 mg Sublingual tablet (Zubsolv®): 1.4/0.36 mg 5.7/1.4 mg	✔

* According to the manufacturer, buprenorphine sublingual tablets are preferred for use only during induction of treatment for opioid 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.
‖Generic available in at least one dosage form or strength.

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.[22-32,43-50]
- 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.[24,33-40]
- 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).[60]
- 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.[61]
- Evzio® (naloxone injection), Narcan® (naloxone nasal spray), buprenorphine buccal film (Bunavail®) and buprenorphine/naloxone tablet (Zubsolv®) were FDA-approved 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 reference products.[5,7,9,10,62]

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.[15]
    - 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.[15]
    - Naloxone is recommended as an appropriate emergency pharmacologic intervention for instances of opioid overdose.[16]
    - Naltrexone is generally reserved as an alternative regimen after buprenorphine-containing products and methadone.[17]
- Other Key Facts:
    - Buprenorphine is available as a sublingual tablet; buprenorphine/naloxone is available as a sublingual tablet (Zubsolv®), sublingual film (Suboxone®) and buccal film (Bunavail®); naltrexone is available as a tablet (ReVia®) and extended-release suspension for injection (Vivitrol®); and naloxone is available as a prefilled syringe, nasal spray (Narcan®) and auto-injector (Evzio®)[1-10]
    - 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.[20]
    - 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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