General

# Buprenorphine and its formulations: a comprehensive review

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Buprenorphine, a novel long-acting analgesic, was developed with the intention of two purposes: analgesia and opioid use disorder. Regarding its pharmacodynamics, it is a partial agonist at mu receptors, an inverse agonist at kappa receptors, and an antagonist at delta receptors. For the purpose of analgesia, three formulations of buprenorphine were developed: IV/IM injectable formulation (Buprenex®), transdermal patch formulation (Butrans®), and buccal film formulation (Belbuca®). Related to opioid dependence, the formulations developed were subcutaneous extended release (Sublocade®), subdermal implant (Probuphine®), and sublingual tablets (Subutex®). Lastly, in order to avoid misuse of buprenorphine for opioid dependence, two combination formulations paired with naloxone were developed: film formulation (Suboxone®) and tablet formulation (Zubsolv®). In this review, we present details of each formulation along with their similarities and differences between each other and clinical considerations.

## INTRODUCTION

Buprenorphine was first marketed in 1985 as an opioid analgesic. It was originally a scheduled V-controlled substance in the United States and offered in a low-dose formulation.[1] It was branded as Buprenex® in 0.3mg/ml injectable form. In the early 2000s, two additional buprenorphine products were added to the market following approval by the Food and Drug Administration (FDA).[2] Suboxone® and Subutex® were offered in high dose (2 mg and 8 mg) sublingual tablets. Importantly, Subutex® consisted of pure buprenorphine, and Suboxone® consisted of a 4:1 ratio of buprenorphine to naloxone. The Department of Health and Human Services and the United States Drug Enforcement Administration determined that buprenorphine and any medication containing buprenorphine be classified as a schedule III-controlled substance as of 2002.

By 2010, Butrans® was FDA approved as an extended use opioid analgesic for persistent pain. Since 2000, the Drug Addiction Treatment Act of 2000 has given practitioners the ability to prescribe buprenorphine for opioid use disorder after specific training programs.[3]

Buprenorphine is the mainstay of treatment for opioid use disorder as well as its analgesic potential that stems from the compounds' unique binding profile.[1,4] Buprenorphine binds to all three major opioid receptor classes (mu, kappa, delta) in addition to an orphanin FQ/nociception receptor.[5]

This novel drug is a partial agonist at the mu receptors, an inverse agonist at the kappa receptors, and an antagonist at the delta receptors.[6] The unique analgesic properties of buprenorphine are dependent on the acrylamide receptor in the brain.[5] In terms of its kinetics, buprenorphine has an oral bioavailability of approximately 10-15% based on the massive first-pass hepatic clearance. Sublingual, buccal, and illicit conversion mostly skips the first-pass hepatic clearance. Therefore, sublingual tablet bioavailability is around 50%. A three-compartment model assuming a first-order elimination best defines the pharmacokinetics of buprenorphine. Buprenorphine is metabolized by the CYP3A4 and CYP2C8 to the active metabolite, norbuprenorphine. Glucuronidation is the rate-limiting step in the metabolism of buprenorphine. The byproducts undergo biliary and renal excretion as well as further biliary excretion and enterohepatic recirculation. The ability of the

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buprenorphine to have minimal drug-drug interactions with other opioids is very advantageous in terms of the CYP3A4 metabolism.[7] In this regard, buprenorphine can cause QT prolongation and so drugs that possess similar cardiac effects must be carefully scrutinized when consideration is given to add buprenorphine therapy.

Since 2000, the Drug Addiction Treatment Act has allowed buprenorphine to be used for Opioid Use Disorder as medication-assisted treatment.[8] Buprenorphine should be used in combination with therapy and counseling. The comprehensive approach to treatment provides more opportunities for patients to successfully treat their disease or prevent more withdrawal or relapses in the future. It is important to note that just because buprenorphine is classified as a partial agonist, that does not correlate to its clinical efficacy.[7] Webster et al. concluded that buprenorphine should be used for chronic pain management over other options due to its safety and pharmacokinetic properties. It should be considered before other scheduled II, III, and IV opioids and ultimately has a better metabolic profile and tolerability and requires no weaning period when switching opioid drug classes.[9] Because Suboxone® contains naloxone, patients who on opioids and given a full-agonist opioid can have precipitation of opioid withdrawal symptoms and therefore, specific loading strategies are commonly employed as early withdrawal from the full opioid agonist is clinically seen to ensure the best timing for loading. Buprenorphine preparations can also provide an effective method for the treatment of adolescents and young adults with opioid use disorder. In certain circumstances, buprenorphine can even be used as a fourth-line option for cancer treatment as well.[9]

The focus of this review, therefore, is to discuss the different formulations of buprenorphine available for opioid dependence and analgesic treatment. For analgesia, buprenorphine can be obtained in an IV/IM injectable form, transdermal patch, and buccal form. For opioid dependence, buprenorphine can be obtained in a subcutaneous extended-release, subdermal implant, and sublingual tablet. Lastly, a combined buprenorphine/naloxone formulation exists for opioid dependence in a film formulation and a sublingual tablet.

## BUPRENORPHINE FORMULATIONS FOR ANALGESIA

### IV/IM INJECTABLE FORMULATION (BUPRENEX®)

Buprenex® is a brand of injectable buprenorphine manufactured by Indivior Inc. It was approved by the FDA in 1982 to treat acute moderate to severe pain and can be given intravenously or intramuscularly.[10] It comes in clear liquid form, with each mL of Buprenex® containing 0.3 mg of buprenorphine. With a peak plasma concentration at 5-15 minutes and effects lasting for 6 hours or longer, this formulation proves to be a good option for managing pain that has comparable efficacy to other opioids.[11] In a literature review conducted by Hale et al., IV buprenorphine was often found to be equally or more efficacious than morphine for treating pain in the postoperative setting.[12] 1 mL of Buprenex® can be given by slow intravenous injection (over 2 minutes) or by deep intramuscular injection every six hours as needed.[10] Times to onset and peak effect is decreased when administered intravenously compared to intramuscularly.

Buprenex®'s common side effects are sedation, respiratory depression, nausea, vomiting, headache, and dizziness.[13] Unlike morphine and fentanyl, which have dose-dependent impacts on respiratory depression, intravenous buprenorphine exhibits a ceiling effect on respiratory depression at higher doses.[14] This ceiling effect is not shown for its analgesic properties, making Buprenex® and buprenorphine, in general, a favorable option when respiratory depression is a concern.

### TRANSDERMAL PATCH FORMULATION (BUTRANS®)

Manufactured by Teva and approved in June 2010 by the FDA, Butrans® is indicated for chronic pain that requires around-the-clock treatment and does not respond well to other treatment options.[15] In the United States, buprenorphine patches are available in 5-, 7.5-, 10-, 15-, and 20-µg/h doses.[12,14] Buprenorphine itself has several properties that make it optimal for the transdermal formulation, including its low molecular weight, high lipophilicity, and high potency.[16] In a systematic review by Hale et al. in 2021, 100% of the clinical studies reviewed showed that transdermal buprenorphine was found to be effective at treating chronic pain.[12,17] It has also been found that transdermal buprenorphine had similar analgesic efficacy to transdermal fentanyl, oral morphine, and oral oxycodone in the treatment of cancer pain.[12,18]

There have been limited studies evaluating efficacy in postoperative pain management, but so far, it is found to be effective and safe.[19,20] Regardless, it is not yet approved by the FDA for short-term analgesia or acute pain management.[15] Since the patch lasts for seven days, it would not be the best option for pain that would not last more than a few days, such as pain following a dental procedure.[19]

In a literature review by Pergolizzi and Raffa in 2019, it was found that the most common adverse events in transdermal buprenorphine clinical trials were nausea, headache, dizziness, constipation, somnolence, vomiting, dry mouth, and application site symptoms like pruritis, erythema, and rash.[14] Due to a risk of prolongation of the QTc interval, it's best to avoid the use of patches in patients with a history of Long QT Syndrome or an immediate family member with this condition, or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide), or other medications that prolong the QTc interval. It was considered safe and well-tolerated in all studies that were examined in their review.[14] Patient compliance with transdermal patch buprenorphine tends to be high, likely because of ease of use.[14] The patch can be worn for a duration of seven days, and it is recommended that the site of the application is rotated to avoid the increased drug absorption that can occur if applied in the same area within 3-4 weeks.[21]

### BUCCAL FILM FORMULATION (BELBUCA®)

Belbuca® is the buccal film formulation of buprenorphine that was Introduced by BioDelivery Sciences International Inc. and approved by the FDA in 2015 for the management of chronic pain.[22] In the United States, Belbuca® is available in the following strengths: 75, 150, 300, 450, 600, 750, and 900µg.[14] This is a wider range of doses compared to the transdermal patch, and it can be administered every twelve hours.[21] Avoid prescribing with a dosing frequency of less than "every 12 hours" due to the potential for QTc interval prolongation.

The buccal film formulation of buprenorphine has a higher bioavailability than other formulations, making it the most effective delivery method besides intravenous.[23,24] Both the buccal and transdermal formulations bypass first-pass gastrointestinal and hepatic metabolism, which could make these good analgesic options, especially for patients who are having gastrointestinal issues.[23] The frequency of constipation with buccal film buprenorphine is 4%, compared to 8-31% with full µ-opioid receptor agonists.[14] Some patients may experience adhesion issues with buprenorphine buccal film.[14]

In a literature review by Hale et al. in 2021, all published studies at that time showed that buccal film formulations were successful in producing analgesia for chronic low back pain.[12] Several studies have demonstrated that the efficacy of the buccal film formulation of Belbuca® is comparable to the efficacy of other extended-release opioids, even in opioid-experienced patients.[25–28] When searching the literature, no studies were found that evaluated the use of buccal buprenorphine for acute or postoperative pain. Compared to the transdermal formulation of buprenorphine, Belbuca® has a higher dose range, higher bioavailability, and strong clinical data supporting its safety and efficacy for chronic pain management.[14,24]

## BUPRENORPHINE FORMULATIONS FOR OPIOID DEPENDENCE

### SUBCUTANEOUS EXTENDED RELEASE (SUBLOCADE®)

A relatively novel formulation of buprenorphine in the use of treating opioid use dependence is the subcutaneous extended-release injection (Sublocade®), which received FDA approval in 2017 for patients who had already initiated treatment with a buprenorphine product for a minimum of seven days. Comprised of a pre-filled syringe that is injected via the Atrigel® system in the abdominal subcutaneous tissue by a healthcare provider on a monthly basis, (with at least 26 days between doses) patients are initiated on a 300 mg dose for the first two months followed by a maintenance dose of 100 mg. For those patients with inadequate response, the maintenance dose may be increased to 300mg.[29]

Developed to expand access to buprenorphine and reduce the burden of medical adherence, Sublocade® offers patients a long-acting alternative to previous formulations, including sublingual tablets. Reduction in these barriers to access and utilization may lead to greater efficacy in abstinence from non-prescribed opioid use, as prior studies have noted positive results with extended-use medication-assisted treatment.[30–34] Furthermore, this extended-release formulation has been shown to provide prolonged, therapeutic levels of buprenorphine up to eight weeks after subsequent injections, minimizing risks associated with missed doses and potentially improving treatment adherence. A comparison of the efficacy of the subcutaneous versus sublingual formulation revealed statistically significantly greater rates of opioid-negative urine samples in weeks 4-24.[35] The efficacy of this formulation is also well supported as drug-liking VAS scores were significantly reduced when comparing baseline, pre-Sublocade® scores to post-Sublocade® scores in patients who received IM hydromorphone injections.[36,37]

Despite these benefits, utilization remains dependent upon patient engagement. Numerous studies have been conducted to gauge the perceptions of opioid users on extended-release buprenorphine modalities, with an overall positive response rate regarding these formulations across multiple countries. Of note, the most perceived benefits were related to decreased facility visits, greater autonomy to engage in trips and travel, and reducing the need for willpower to adhere to daily formulations.[38–40] These findings echo the well-established stigma associated with seeking treatment for opioid dependence and how it functions as a barrier to continued adherence.[31,41,42]

While this study by Larance et al. obtained favorable results regarding extended-release formulations, another survey conducted by Kenney et al. found that the majority of patients still preferred daily sublingual tablets versus weekly and monthly injections.[43] This preference may, in part, be related to a host of questions pertaining to the delivery system, efficacy, additional ingredients, dosing, and how the treatment is terminated. Additionally, the context of a patient's willingness to initiate or continue extended-release formulations cannot be considered in a vacuum as multiple variables have been shown to influence these decisions.[44,45] Caution is required when using in patients at risk for arrhythmia. Buprenorphine has been observed to prolong the QTc interval in some patients participating in clinical trials. There should be consideration for risk versus benefits when prescribing buprenorphine to patients with hypokalemia, hypomagnesemia, or clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia.

### SUBDERMAL IMPLANT (PROBUPHINE®)

Developed by Total Pharmaceuticals and approved by the FDA in May 2016, Probuphine® is a subdermal implant with a dose equivalent to approximately 80 mg, delivering 1-1.3 mg/day from four to five implants. This regimen is equivalent to plasma concentrations observed in patients taking 8 mg sublingual buprenorphine. Some patients may require an additional one to two implants pending their response. Delivered via applicator in the office setting, these implants remain in place for six months, reaching their steady-state plasma concentrations at approximately four weeks.[46–48]

Developed with the intent of addressing the aforementioned barriers and concerns with daily sublingual

buprenorphine opioid antagonist treatment (OAT), the Probuphine® subdermal implant functioned to fill the same niche as Sublocade®: long-term OAT with a buprenorphine delivery system that reduced patient burden while providing a consistent daily dose that would ensure adequate antagonism and opioid abstinence.[49–52]

In a double-blind, randomized clinical trial comparing sublingual versus subdermal buprenorphine formulations over a period of six months, it was shown that not only was subdermal buprenorphine non-inferior, but it also had a statistically significantly higher rate of opioid abstinence.[53] These findings are especially important in the adolescent population, where prior trials have identified these patients to have significantly higher opioid abstinence rates when on prolonged OAT.[54,55] However, despite these promising studies and clear benefits, Probuphine® was discontinued on 10/15/2020 due to multiple factors, including the delivery system, reimbursements, and inability to commercialize. The insertion and removal of the buprenorphine implants may cause serious implant-site reactions (pain, itching, redness, and swelling).

### SUBLINGUAL TABLETS (SUBUTEX®)

Developed by Reckitt Benckiser Pharmaceuticals Inc. and approved by the FDA in 2002, Subutex® is a 2mg or 8mg sublingual tablet intended for the treatment of opioid dependence and ideally suited for induction of treatment. However, Subutex® is a viable option for maintenance in those patients who cannot tolerate naloxone with a daily dose ranging from 4mg to 24mg, as no clinical benefit was demonstrated beyond 24mg.[56] Although suitable as a means of tapering patients off OAT, the risk of relapse remains high.[57–59] Therefore, the main indication for any formulation of buprenorphine is long-term opioid maintenance treatment, given its partial mu-agonist activity.[60,61] In a Cochrane meta-analysis, buprenorphine was found to have lower retention rates but similar efficacy for patients who remained adherent to the treatment regimen when compared with methadone. With increased doses of sublingual buprenorphine, adherence was improved. These findings support the efficacy of buprenorphine in long-term opioid maintenance therapy but also highlight the importance of adequate dosing.[62]

As previously noted in discussions regarding depot and subdermal implants of buprenorphine, despite positive perceptions of alternative formulations to sublingual buprenorphine, several studies continue to identify sublingual buprenorphine formulations as the most preferred route of delivery.[39,40,42,43] However, regardless of the popularity of sublingual variations, Subutex® was discontinued in 2011 related to reports by the company that the monotherapy formulation creates greater risks for diversion and abuse than combined therapy buprenorphine/naloxone. While more recent studies have yielded conflicting results regarding these claims, this may be confounded by the timing of buprenorphine/naloxone introduction in the United States and distribution patterns amongst geographic locations.[63,64] In international locations where the prevalence of buprenorphine monotherapy use was greater, there is clear evidence of the risk of misuse, abuse, and diversion of daily sublingual formulations of buprenorphine.[65–67] A study conducted in Australia comparing rates of abuse of buprenorphine, buprenorphine/naloxone, and methadone formulations found significantly lower rates of abuse for the combined buprenorphine/naloxone formulation compared to the monotherapy buprenorphine or methadone.[68] In a Finnish study where rates of buprenorphine abuse and diversion were exceptionally high, the introduction of buprenorphine/naloxone formulation was noted to decrease use. However, buprenorphine abuse remained high due to an influx from sources outside the country.[69]

Furthermore, an additional area of benefit in alternatives to sublingual formulations is the reduction of inadvertent access and overdose in pediatric patients. Corresponding with the rising trend of early sublingual buprenorphine OAT prescribing practices were pediatric opioid toxicities and adverse events.[70,71] In a single-center study, rates of hospitalizations for opioid overdoses secondary to inadvertent exposure to methadone or buprenorphine tablets had a statistically significant increase that correlated with prescribing patterns in the immediate geographic location.[72] With alternative long-acting injectables or implants, the risk of pediatric exposure is significantly decreased.

## COMBINED BUPRENORPHINE/NALOXONE FORMULATIONS FOR OPIOID DEPENDENCE

In current practice, the medical treatment allows for a combination of options for patients struggling with addiction, withdrawals, anxiety, and chronic pain. Partial opioid antagonists can help in the process of addiction when added in combination with an opioid agonist.[5] Individuals may undergo numerous trials and tribulations in getting clean and relapsing. Medication-assisted therapy delivers a means of relief for those suffering from opioid addiction in combination with behavioral therapies.[7] Ultimately, when opioids or illicit drugs are prescribed or used, such as codeine, heroin, methadone, morphine, and oxycodone, individuals become accustomed to dealing with pain by becoming dependent. These medications adversely affect the neural synapse in the body and in the brain.[5] Our system becomes tolerant to having opioids around. When opioids are then abruptly stopped, or someone runs out, extremely uncomfortable and debilitating withdrawals can occur.

Important to note that the formulations of buprenorphine such as Probuphine® and Subutex® have been discontinued for some time. Probuphine® is an implantable form of buprenorphine that consists of four rods that are inserted subcutaneously in the upper arm.[73] They are intended to remain in the upper arm for approximately six months before removal or reinsertion by a licensed healthcare provider.[73] In October 2020, Titan Pharmaceuticals stated that they were no longer manufacturing Probuphine®. They claimed to remove Probuphine® from the U.S. Market in order to focus their efforts on new development and cut business costs. Conversely, Subutex® was discontinued for other reasons. Subutex® was an FDA-approved form of buprenorphine in 2002 for the use in opioid use disorder.[74] Subutex was discontinued in 2011 by Reckitt Benckiser Pharmaceuticals Inc. due to growing con-

cerns about individuals crushing, snorting, and injecting their sublingual tablet formulations. Companies like Reckitt Benckiser began adjusting their formulations of opioid use disorder by adding a deterrent such as a naloxone, an opioid antagonist.[74] Naloxone has limited effects when taken in combination with a partial opioid agonist such as buprenorphine. Due to the poor absorption of naloxone in the gastrointestinal tract, it has very little effect when properly taken. In contrast, it has to ability to block the effects of the buprenorphine when crushed to be snorted and for injection abuse.

## FILM FORMULATION (SUBOXONE®) AND TABLET FORMULATION (ZUBSOLV®)

Suboxone® and Zubsolv® are both used to treat opioid addiction and to be used in combination with behavioral therapy or counseling. The medications contain a combination of both an opioid agonist, buprenorphine, as well as an opioid antagonist, naloxone. The combination of buprenorphine to naloxone in a 4:1 ratio decreases the potential of either being used for opioid abuse or injection use.[75]

Suboxone® was FDA-approved in 2002 for the use of medication-assisted therapy.[75] It comes in a film formulation of four different strengths and is very affordable for patients. Zubsolv® was FDA approved in 2013 for medication-assisted therapy and came in a sublingual tablet of six strengths that are much more expensive for patients than Suboxone.[76] It is important to realize that these medications do have side effects and are very dangerous in combination with other drugs and alcohol.[77] Opioids can cause an overall pain reduction and improvement of well-being but can cause severe respiratory depression. These two formulations mentioned above can cause cravings, muscle cramps, insomnia, and irritability. It is of the utmost importance to pair these treatments with cognitive behavioral therapy or dialectical therapies for overall success.[77]

Lintzeris et al. compared the buprenorphine-naloxone sublingual film to the tablet formulation. It assessed the dose-effect through plasma levels, adverse events, satisfaction, and treatment outcomes.[78] The outpatient double-blind trial randomized patients to either tablets or film over a month period. Treatment outcomes and results were not significantly different. There were comparable outcomes and dose equivalence between the formulations, but more patients were satisfied with the film formulation.[78]

Fudala et al. demonstrated the safety and efficacy of the sublingual-tablet formation of buprenorphine and naloxone. The double-blind trial found greater efficacy of buprenorphine/naloxone in combination and buprenorphine alone than placebo.[79] The urine samples that were negative for opiates were significantly greater in both treatment groups at 17.8% and 20.7% compared to the placebo group of 5.8% ($P<.0001$). Importantly, the rate of adverse events was not significantly different in either treatment group compared with the placebo.[79] The results indicated that the treatment was safe and well-tolerated by participants. The combination of buprenorphine/naloxone in combination and buprenorphine alone reduces the use of opiates as well as the cravings for addicted persons in clinic-based settings.[79]

Gunderson et al. compared the higher bioavailability (Buprenorphine/Naloxone) BNX sublingual tablet to generic buprenorphine or BNX sublingual film, specifically the treatment retention during induction and stabilization of the formulation. The multicenter, parallel-group noninferiority trial across the United States found that the higher bioavailability of BNX was non-inferior to both generic buprenorphine for induction and BNX film for stabilization.[80] The high bioavailability of sublingual tablets is efficacious and a well-tolerated option for either form of opioid dependence treatment therapy.

Roux et al. demonstrated that buprenorphine/naloxone (B/N) could be used as a therapeutic option for opioid abusers, chronic pain users, opioid withdrawal patients, and oxycodone users. The 7-week inpatient study assesses the oral administration of oxycodone self-administration by patients suffering from chronic pain and a history of opioid abuse. Once the patients were transitioned from their pro-administration opioids to B/N, they were tested with four different maintenance doses. The pain was found to be significantly reduced on maintenance B/N compared to pro-administration doses.[81] Those patients favoring oxycodone use over B/N experienced more withdrawal and high pain levels. B/N is adequate for the management of pain and withdrawal symptoms of opioid abuse but can also aid in reducing oxycodone preferences.[81]

The novel sublingual B/N rapidly dissolving tablet for opioid addiction treatment demonstrated improved bioavailability, rapid disintegration, and improved taste masking than conventional sublingual tablets. The rapidly dividing tablets showed shorter dissolve times, improved mouthfeel and taste, and ultimately a better patient satisfaction than the conventional formulation.[82]

Dealing with addiction is a struggle, and patients benefit from medication-assisted therapies. The main reason that people relapse is due to painful withdrawals, anxiety, and pain attacks. With that being said, the addition of a partial opioid antagonist to buprenorphine has proven safe and efficacious in the treatment of opioid addiction. In conclusion, the film formulation of Suboxone® is generally harder for patients to take and more of an unpleasant tangy taste in the mouth. In contrast, Zubsolv has better bioavailability and is offered in wider doses. The additional options allow for increased adherence and better overall satisfaction.

## SEROTONIN SYNDROME

Buprenorphine has been reported to cause serotonin syndrome if used concomitantly with other serotonergic drugs. Higher doses or most commonly in combination with serotonergic medications can increase this risk. Consideration should be made when adding buprenorphine to any regimen that includes antidepressants of the SSRI, SNRI, or TCA class. Tramadol, dextromethorphan, linezolid, cyclobenzaprine and many other medications should also be used cautiously if at all in a buprenorphine dependent patient.

## ABILITY TO REVERSE OVERDOSE (OD)

Naloxone has been to go to medication when an antidote is needed to reverse an episode of opioid-induced respiratory depression. One shortcoming of Naloxone is its short half-life and sudden and unpleasant precipitated withdrawal in those dependent or under the acute effects of opioids. Additionally, naloxone re-administration is often required due to renarcotization due to long-acting opioids. Buprenorphine not only is more portable and easier to carry, but also has a superior duration of action and less pronounced withdrawal response compared to naloxone.

Due to buprenorphine lack of respiratory depression, and ability to reverse or precipitate withdrawal, it should be considered as an option for those acutely overdosing or suffering from respiratory depression induced by full agonist opioids. The film can be placed in the mouth while waiting for emergency services or naloxone rescue. Consideration and education of opioid users should include buprenorphine's potential as a substitute for naloxone in opioid-induced respiratory depression.

## CONCLUSION

The development of buprenorphine has helped physicians treat a variety of conditions, especially acute and chronic pain conditions and opioid dependence. Patient tolerability, lower risk of constipation, excellent half-life, and minimal respiratory depression are all superior to most other opioid class members. In this comprehensive review, a wide variety of buprenorphine formulations were elicited and described. Some formulations were specific for purposes of analgesia and others for opioid use disorder. It is the hope that, over time, more physicians become comfortable with the use of this medication in their armamentarium for treating these conditions.

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