Executive Summary of the Focused Update of the ASAM National Practice Guideline for the Treatment of Opioid Use Disorder

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A Focused Update of the ASAM National Practice Guideline for the Treatment of Opioid Use Disorder is published in the current issue of the Journal of Addiction Medicine. The focused update included a search of Medline's PubMed database from January 1, 2014 to September 27, 2018, as well as a search of the grey literature (archives of the Clinical Guideline Clearinghouse, and key agency and society websites) for new practice guidelines and relevant systematic reviews addressing the use of medications and psychosocial treatments in the treatment of opioid use disorder, including within special populations. The search identified 11 practice guidelines and 35 systematic reviews that informed the subsequent RAND/UCLA Appropriateness Method (RAM) process employed to facilitate the focused update by a National Guideline Committee of addiction experts. New and updated recommendations were included if they were considered: (a) clinically meaningful and applicable to a broad range of clinicians treating addiction involving opioid use; and (b) urgently needed to ensure the Practice Guideline reflects the current state of the science for the existing recommendations, aligns with other relevant practice guidelines, and reflects newly approved medications and formulations.

Key Words: addiction, addiction medicine, addiction treatment, American Society of Addiction Medicine, ASAM, buprenorphine, clinical practice guideline, criminal justice, Methadone, Naloxone, naltrexone, opioid, opioid use disorder, opioid use disorder treatment, opioids, pain, pregnancy, substance use disorder, withdrawal

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RATIONALE

In 2015, The American Society of Addiction Medicine (ASAM) published a National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use.[1] The Practice Guideline contains recommendations for the evaluation and treatment of opioid use disorder, opioid withdrawal management, psychosocial treatment, special populations, and opioid overdose. Between September 2018 and July 2019, ASAM reconvened an independent committee to oversee a focused update of this Practice Guideline. The purpose of the focused update was to develop new and revised recommendations based on a targeted review of new evidence, FDA approval of new buprenorphine formulations (see Table 1) and evolving clinical practice guidance.

GUIDELINE FOCUS

This *Practice Guideline* was developed for the treatment of opioid use disorder and the prevention of opioid overdose-related deaths. The medications covered in this guideline are mainly, but not exclusively, those that have been FDA-approved for the treatment of opioid dependence (DSM-4)[2] or opioid use disorder (DSM-5).[3] The most recent version, DSM-5, combined the criteria for opioid abuse and opioid dependence, from prior versions of the DSM, in its new diagnosis of opioid use disorder. Therefore, pharmacologic treatment may not be appropriate for all patients along the entire opioid use disorder continuum. In a study comparing opioid dependence from DSM-4 and opioid use disorder from DSM-5, optimal concordance occurred when four or more DSM-5 criteria were endorsed (ie, the DSM-5 threshold for moderate opioid use disorder).[3] Other medications have been used off-label to treat opioid use disorder (clearly noted in the text); however, the Guideline Committee has not issued recommendations on the use of those medications.

TARGET POPULATIONS

This *Practice Guideline* is primarily intended for clinicians involved in evaluating patients and providing authorization for pharmacological treatments at any level. The intended audience falls into the broad groups of physicians; other healthcare providers (especially those with prescribing authority); medical educators and faculty

TABLE 1. Buprenorphine Formulations

Generic Name	Route of Administration Dosing	Brand Names	For the Treatment of	Formulation Considerations
Buprenorphine (monoproduct)	Sublingual Tablets Daily	Generic versions available similar to Subutex±	Opioid withdrawal and opioid use disorder	Some risk for diversion or misuse; Requires daily compliance
Buprenorphine and naloxone	Sublingual tablets and film Daily	Generic versions available in addition to Suboxone, Cassipa, Zubsolv, Bunavail	Opioid withdrawal and opioid use disorder	Lower potential for misuse and diversion (compared to monoproduct); Requires daily compliance
Buprenorphine extended-release	Extended-release Injection (Monthly)	Sublocade	Moderate to severe opioid use disorder in patients who have initiated treatment with transmucosal buprenorphine followed by dose adjustment for a minimum of 7 days	No risk for patient diversion or misuse; Requires patients to be on a stable dose of transmucosal buprenorphine for at least 7 days; Monthly instead of daily medication compliance; Less fluctuation in buprenorphine levels (compared to daily doses)
Buprenorphine extended-release	Extended-release Injection (Weekly or Monthly)	Brixadi	Moderate to severe opioid use disorder in patients who have initiated treatment with a single dose of transmucosal buprenorphine or who are already being treated with buprenorphine	Tentative approval from FDA (not currently eligible for marketing in the U.S. because of exclusivity considerations). No risk for patient diversion or misuse; only a single prior dose of transmucosal buprenorphine required prior to initiation; Weekly or Monthly instead of daily medication compliance; Less fluctuation in buprenorphine levels (compared to daily doses)
Buprenorphine hydrochloride	Subcutaneous Implant (Every 6 months)	Probuphine Implant	Treatment of opioid use disorder in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine (i.e., no more than 8 mg per day)	Requires prolonged stability on 8 mg per day or less transmucosal buprenorphine; No risk for patient diversion or misuse; Physician training required for implant insertion and removal; Insertion site should be examined one week after insertion; Implant must be removed after 6 months; Risks associated with improper insertion and removal; Currently only FDA approved for a total treatment duration of one year (one insertion per arm); Less fluctuation in buprenorphine levels (compared to daily doses)

* Some patients may experience withdrawal/cravings when switched to a different formulation.
± Subutex was discontinued.
Table content was derived from FDA labels. Labels and label updates can be accessed at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

for other healthcare professionals in training; and clinical care managers, including those offering utilization management services.

GUIDELINE DEVELOPMENT PROCESS

This *Practice Guideline* was developed using the RAND Corporation (RAND)/University of California, Los Angeles (UCLA) Appropriateness Method (RAM)[4] a process that combines scientific evidence and clinical knowledge to determine the appropriateness of a set of clinical procedures. The RAM Process is a deliberate approach encompassing review of existing guidelines, literature reviews, appropriateness ratings, necessity reviews, and document development. For this project, ASAM selected an independent committee to oversee guideline development, to participate in review of treatment scenarios, and to assist in writing. For the 2019 guideline development process, ASAM's then Quality Improvement Council, chaired by Margaret Jarvis, MD, oversaw the selection process for the independent development committee, referred to as the Guideline Committee.

EVIDENCE REVIEW AND GRADING

For the focused update, a search of Medline's PubMed database from January 1, 2014 to September 27, 2018 was conducted to identify new practice guidelines and relevant systematic reviews addressing the use of medications and psychosocial treatments in the treatment of opioid use disorder, including in special populations. The archives of the Clinical Guideline Clearinghouse, and key agency and society websites were also searched for additional newly published guidelines. The US FDA website was searched for recent relevant drug approvals and mandated label changes. A predefined set of inclusion and exclusion criteria were applied to identify practice guidelines and systematic reviews for inclusion in the Focused Update. Included guidelines and systematic reviews were not independently (ie, outside of what was performed by the publication authors) assessed for risk of bias.

The literature search identified 210 unique practice guidelines and systematic reviews. Following dual review of titles and abstracts, 67 publications were retrieved for full-text review. Of these, 11 practice guidelines[5–15] and 35

systematic reviews[16–50] met criteria for inclusion in the focused update. Key findings from included guidelines, systematic reviews and newly approved US FDA drugs, formulations and mandated label changes were abstracted and mapped to the existing ASAM recommendation statements. Using the RAM Process, hypothetical statements (ie, draft clinical guidance) were developed and presented, along with supporting evidence, to the focused update Practice Guideline Committee first for appropriateness rating and later, following revision, for necessity rating. Thirty statements were generated for the first round of appropriateness rating. Following round one, statements were revised, and 24 were presented for a second round of appropriateness and then necessity rating. The 24 newly generated statements for the focused update along with a review of the language in existing statements resulted in 35 major revisions; 57 statements underwent minor edits and the addition of 10 new recommendations. In addition, 34 statements underwent minor edits that did not change the substantive meaning of the original recommendation.

For the purposes of this document, a clinician is a health professional involved in the assessment, diagnosis, and treatment of medical problems, such as a physician, psychologist, nurse practitioners (NPs), physician assistants (PA), clinical nurse specialists, certified registered nurse anesthetists, certified nurse midwives (as distinguished from one specializing in research).[5]

Summary of Recommendations *Updated*

Part 1: Assessment and Diagnosis of Opioid Use Disorder

Assessment Recommendations.

1. The first clinical priority should be given to identifying and making appropriate referral for any urgent or emergent medical or psychiatric problem(s), including drug-related impairment or overdose.
2. ***New*** Comprehensive assessment of the patient is critical for treatment planning. However, completion of all assessments should not delay or preclude initiating pharmacotherapy for opioid use disorder. If not completed before initiating treatment, assessments should be completed soon thereafter.
3. ***Minor Revision*** Completion of the patient's medical history should include screening for concomitant medical conditions, including psychiatric disorders, infectious diseases (viral hepatitis, HIV, and tuberculosis [TB]), acute trauma, and pregnancy.
4. ***Minor Revision*** A physical examination should be completed as a component of the comprehensive assessment process. The prescriber (the clinician authorizing the use of a medication for the treatment of opioid use disorder) should ensure that a current physical examination is contained within the patient medical record before (or soon after) a patient is started on pharmacotherapy.
5. ***Minor Revision*** Initial laboratory testing should include a complete blood count, liver enzyme tests, and tests for TB, hepatitis B and C, and HIV. Testing for sexually transmitted infections should be strongly considered. Hepatitis A and B vaccinations should be offered, if appropriate.
6. ***Minor Revision*** Women of childbearing potential should be tested for pregnancy, and all women of childbearing potential should be queried regarding methods of contraception.
7. ***Minor Revision*** Patients being evaluated for opioid use disorder, and/or for possible medication use in the treatment of opioid use disorder, should undergo (or have completed) an assessment of mental health status and possible psychiatric disorders (such as is outlined in *The ASAM Criteria*[51] and The ASAM Standards[52]).
8. ***Minor Revision*** Opioid use disorder is often co-occurring with other substance use disorders. Evaluation of a patient with opioid use disorder should include a detailed history of other past and current substance use and substance use disorders.
9. ***Minor Revision*** The use of cannabis, stimulants, alcohol, and/or other addictive drugs should not be a reason to withhold or suspend opioid use disorder treatment. However, patients who are actively using substances during opioid use disorder treatment may require greater support including a more intensive level of care (see *The ASAM Criteria*[51] and The ASAM Standards[52]).
10. ***Major Revision*** The use of benzodiazepines and other sedative-hypnotics should not be a reason to withhold or suspend treatment with methadone or buprenorphine. While the combined use of these medications increases the risk of serious side effects, the harm caused by untreated opioid use disorder can outweigh these risks. A risk-benefit analysis should be conducted, and greater support should be provided including careful medication management to reduce risks.[53]
11. ***Minor Revision*** A nicotine use query should be completed routinely for all patients and counseling on cessation of the use of tobacco products and electronic nicotine delivery devices (eg, vaping) provided if indicated.
12. ***Minor Revision*** As part of comprehensive care the patient should receive a multidimensional assessment (as described in *The ASAM Criteria*[51]), including an assessment of social and environmental factors to identify facilitators and barriers to addiction treatment and long-term recovery (including pharmacotherapy). Addiction is a complex bio-psycho-social illness, for which the use of medication(s) is only one component of comprehensive treatment.

Diagnosis Recommendations.

1. ***Minor Revision*** Other clinicians may diagnose opioid use disorder, but confirmation of the diagnosis must be obtained by the prescriber before pharmacotherapy for opioid use disorder commences.
2. Opioid use disorder is primarily diagnosed on the basis of the history provided by the patient and a comprehensive assessment that includes a physical examination.
3. ***Minor Revision*** Validated clinical scales that measure withdrawal symptoms may be used to assist in the evaluation of patients with opioid use disorder.

4. ***Minor Revision*** Drug testing is recommended during the comprehensive assessment process, and during treatment to monitor patients for adherence to prescribed medications and use of alcohol, illicit, and controlled substances. The frequency of testing is determined by several factors including stability of the patient, type of treatment, and treatment setting. For additional information see The ASAM Appropriate Use of Drug Testing in Clinical Addiction Medicine[54] guidance document.

Part 2: Treatment Options

1. ***Major Revision*** All FDA approved medications for the treatment of opioid use disorder should be available to all patients. Clinicians should consider the patient's preferences, past treatment history, current state of illness, and treatment setting when deciding between the use of methadone, buprenorphine, and naltrexone.
2. ***New*** There is no recommended time limit for pharmacological treatment.
3. ***Major Revision*** Patients' psychosocial needs should be assessed, and patients should be offered or referred to psychosocial treatment based on their individual needs. However, a patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacotherapy, with appropriate medication management. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing individual needs.
4. ***Minor Revision*** The venue in which treatment is provided should be carefully considered. Methadone can only be provided in opioid treatment programs (OTPs) and acute care settings (under limited circumstances). Buprenorphine can be dispensed in at OTP (in accordance with Federal law [42 CFR Part 8]), or prescribed by waivered clinicians in any setting, including office based opioid treatment (OBOT) in accordance with the Federal law (21 CFR §1301.28).Naltrexone can be prescribed in any setting by any clinician with the authority to prescribe medication. Clinicians should consider a patient's psychosocial situation, co-occurring disorders, and risk of diversion when determining which treatment setting is most appropriate (see The ASAM Criteria[51] for additional guidance).
5. ***Minor Revision*** Patients with active co-occurring alcohol use disorder or sedative, hypnotic, or anxiolytic use disorder (or who are in treatment for a substance use disorder involving use of alcohol or other sedative drugs, including benzodiazepines or benzodiazepine receptor agonists) may need a more intensive level of care than can be provided in an office-based setting. Persons who are regularly using alcohol or other sedatives, but do not meet the criteria for diagnosis of a specific substance use disorder related to that class of drugs, should be carefully monitored.
6. ***Major Revision*** The prescribing of benzodiazepines or other sedative-hypnotics should be used with caution in patients who are prescribed methadone or buprenorphine for the treatment of an opioid use disorder. While the combined use of these drugs increases the risk of serious side effects, the harm caused by untreated opioid use disorder can outweigh these risks. A risk-benefit analysis should be conducted when deciding whether to co-prescribe these medications.
7. Methadone is recommended for patients who may benefit from daily dosing and supervision in an OTP, or for patients for whom buprenorphine for the treatment of opioid use disorder has been used unsuccessfully in an OTP or OBOT setting.
8. ***New*** Opioid dosing guidelines developed for chronic pain, expressed in morphine milligram equivalents (MME), are not applicable to medications for the treatment of opioid use disorders.
9. ***Minor Revision*** Oral naltrexone for the treatment of opioid use disorder is often adversely affected by poor medication adherence and should not be used except under very limited circumstances. Clinicians should reserve its use for patients who would be able to comply with special techniques to enhance their adherence, for example, observed dosing. Extended-release injectable naltrexone reduces, but does not eliminate, issues with medication adherence.
10. ***Minor Revision*** The Prescription Drug Monitoring Program (PDMP) should be checked regularly for the purpose of confirming medication adherence and to monitor for the prescribing of other controlled substances.
11. ***New*** Naloxone, for the reversal of opioid overdose, should be provided to patients being treated for, or with a history of, opioid use disorder. Patients and family members/significant others should be trained in the use of naloxone in overdose.

Part 3: Treating Opioid Withdrawal

1. ***Minor Revision*** Using methadone or buprenorphine for opioid withdrawal management is recommended over abrupt cessation of opioids. Abrupt cessation of opioids may lead to strong cravings, and/or acute withdrawal syndrome which can put the patient at risk for relapse, overdose, and overdose death.
2. ***Minor Revision*** Opioid withdrawal management (ie, detoxification) on its own, without ongoing treatment for opioid use disorder, is not a treatment method for opioid use disorder and is not recommended. Patients should be advised about the risk of relapse and other safety concerns, including increased risk of overdose and overdose death. Ongoing maintenance medication, in combination with psychosocial treatment appropriate for the patient's needs, is the standard of care for treating opioid use disorder.
3. ***Minor Revision*** Assessment of a patient undergoing opioid withdrawal management should include a thorough medical history and physical examination, focusing on signs and symptoms associated with opioid withdrawal.
4. ***Minor Revision*** By regulation, opioid withdrawal management with methadone must be done in an OTP or an acute care setting (under limited circumstances). For patients withdrawing from short acting opioids the initial dose should typically be 20 to 30 mg per day and the patient may be tapered off in approximately 6 to 10 days.

5. ***Major Revision*** Opioid withdrawal management with buprenorphine should not be initiated until there are objective signs of opioid withdrawal. (See Part 3 for more information on the timing of initiating buprenorphine.) Once signs of withdrawal have been objectively confirmed, a dose of buprenorphine sufficient to suppress withdrawal symptoms is given (an initial dose of 2–4 mg titrated up as needed to suppress withdrawal symptoms).
6. ***Major Revision*** Alpha-2 adrenergic agonists (eg, FDA-approved lofexidine and off-label clonidine) are safe and effective for management of opioid withdrawal. However, methadone and buprenorphine are more effective in reducing the symptoms of opioid withdrawal, in retaining patients in withdrawal management, and in supporting the completion of withdrawal management.[9–11]
7. Opioid withdrawal management using ultra-rapid opioid detoxification (UROD) is not recommended due to high risk for adverse events or death. Naltrexone-facilitated opioid withdrawal management can be safe and effective but should be used only by clinicians experienced with this clinical method, and in cases in which anesthesia or conscious sedation are not employed.

Part 4: Methadone

1. ***Minor Revision*** Methadone is a recommended treatment for patients with opioid use disorder, who are able to give informed consent and have no specific contraindication for this treatment.
2. ***Major Revision*** The recommended initial dose of methadone ranges from 10 to 30 mg, with reassessment as clinically indicated (typically in 2 to 4 hours). Use a lower-than-usual initial dose (2.5 to 10 mg) in individuals with no or low opioid tolerance.
3. ***Major Revision*** Following initial withdrawal stabilization, the usual daily dose of methadone ranges from 60 to 120 mg. Some patients may respond to lower doses and some may need higher doses. Methadone titration should be individualized based on careful assessment of the patient's response and generally the dose should not be increased every day. Typically, methadone can be increased by no more than 10 mg approximately every 5 days based on the patient's symptoms of opioid withdrawal or sedation.
4. The administration of methadone should be monitored because unsupervised administration can lead to misuse and diversion. OTP regulations require monitored medication administration until the patient's clinical response and behavior demonstrates that dispensing non-monitored doses is appropriate.
5. ***Major Revision*** Patients' psychosocial needs should be assessed, and patients should be offered or referred to psychosocial treatment based on their individual needs, in conjunction with methadone in the treatment of opioid use disorder. However, a patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay treatment with methadone, with appropriate medication management. While current federal regulations (42 CFR Part 8) include requirements for psychosocial treatment in OTPs, this can present barriers to access to treatment for some patients and is not consistent with the evidence base. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing their individual needs.
6. ***Minor Revision*** For patients who previously received methadone for the treatment of opioid use disorder, methadone should be reinstituted immediately if relapse occurs or if an assessment determines that the risk of relapse is high (unless contraindicated). Re-initiation of methadone should follow the recommendations above regarding initial dose and titration.
7. ***Minor Revision*** Strategies directed at relapse prevention are an important part of addiction treatment and should be included in any plan of care for a patient receiving opioid use disorder treatment or ongoing monitoring of the status of their disorder.
8. ***Minor Revision*** Transitioning from methadone to another medication for the treatment of opioid use disorder may be appropriate if the patient experiences dangerous or intolerable side effects or is not successful in attaining or maintaining treatment goals through the use of methadone.
9. ***Minor Revision*** Patients transitioning from methadone to buprenorphine in the treatment of opioid use disorder should ideally be on low doses of methadone before making the transition. Patients on low doses of methadone (30–40 mg per day or less) generally tolerate transition to buprenorphine with minimal discomfort, whereas patients on higher doses of methadone may experience significant discomfort in transitioning medications.
10. ***Minor Revision*** Patients transitioning from methadone to naltrexone must be completely withdrawn from methadone and other opioids, before they can receive naltrexone. The only exception would apply when an experienced clinician receives consent from the patient to embark on a plan of naltrexone-facilitated opioid withdrawal management.
11. ***Minor Revision*** There is no recommended time limit for pharmacological treatment with methadone. Patients who discontinue methadone treatment should be made aware of the risks associated with opioid overdose, and especially the increased risk of overdose death if they return to illicit opioid use. Treatment alternatives including buprenorphine (see Part 5) and naltrexone (see Part 6), as well as opioid overdose prevention with naloxone (see part 13), should be discussed with any patient choosing to discontinue treatment.

Part 5: Buprenorphine

1. ***New*** Buprenorphine is a recommended treatment for patients with opioid use disorder, who are able to give informed consent and have no specific contraindication for this treatment.
2. ***Minor Revision*** For patients who are currently opioid dependent, buprenorphine should not be initiated until there are objective signs of opioid withdrawal to reduce the risk of precipitated withdrawal.

3. ***Major Revision*** Once objective signs of withdrawal are observed, initiation of buprenorphine should start with a dose of 2 to 4 mg. Dosages may be increased in increments of 2 to 8 mg.
4. ***Major Revision*** The setting for initiation of buprenorphine should be carefully considered. Both office-based and home-based initiation are considered safe and effective when starting buprenorphine treatment. Clinical judgement should be used to determine the most appropriate setting for a given patient and may include consideration of the patient's past experience with buprenorphine and assessment of their ability to manage initiation at home.
5. ***Major Revision*** Following initiation, buprenorphine dose should be titrated to alleviate symptoms. To be effective, buprenorphine dose should be sufficient to enable patients to discontinue illicit opioid use. Evidence suggests that 16 mg per day or more may be more effective than lower doses. There is limited evidence regarding the relative efficacy of doses higher than 24 mg per day, and the use of higher doses may increase the risk of diversion.[13,14,36]
6. ***New*** The FDA recently approved several new buprenorphine formulations for treatment of opioid use disorder. As data regarding the effectiveness of these products are currently limited, clinicians should use these products as indicated and be mindful of emerging evidence as it becomes available.
7. ***Major Revision*** Patients' psychosocial needs should be assessed, and patients should be offered or referred to psychosocial treatment based on their individual needs, in conjunction with buprenorphine in the treatment of opioid use disorder. However, a patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay buprenorphine treatment, with appropriate medication management. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing their individual needs.
8. ***Minor Revision*** Clinicians should take steps to reduce the chance of buprenorphine diversion. Recommended strategies may include frequent office visits (eg, weekly in early treatment); drug testing, including testing for buprenorphine and metabolites; and recall visits for medication counts. Refer to ASAM's Sample Diversion Control Policy for additional strategies to reduce the risk for diversion.
9. ***Minor Revision*** Drug testing should be used to monitor patients for adherence to buprenorphine and use of illicit and controlled substances. For additional guidance see *The ASAM Appropriate Use of Drug Testing in Clinical Addiction Medicine*.[8]
10. ***Minor Revision*** Patients should be seen frequently at the beginning of treatment until they are determined to be stable.
11. When considering a transition from buprenorphine to naltrexone, providers should note that 7 to 14 days should typically elapse between the last dose of buprenorphine and the start of naltrexone to ensure that the patient is not physically dependent on opioids before starting naltrexone.
12. ***Minor Revision*** When considering a transition from buprenorphine to methadone, there is no required time delay because the transition to a full mu-opioid agonist from a partial agonist does not typically result in an adverse reaction.
13. ***Minor Revision*** There is no recommended time limit for pharmacological treatment with buprenorphine. Patients who discontinue buprenorphine treatment should be made aware of the risks associated with opioid overdose, and especially the increased risk of death if they return to illicit opioid use. Treatment alternatives including methadone (see Part 4) and naltrexone (see Part 6), as well as opioid overdose prevention with naloxone (see part 13) should be discussed with any patient choosing to discontinue treatment.
14. ***Minor Revision*** Buprenorphine taper and discontinuation is a slow process and close monitoring is recommended. Buprenorphine tapering is generally accomplished over several months. Patients should be encouraged to remain in treatment for ongoing monitoring past the point of discontinuation.

Part 6: Naltrexone

1. ***Major Revision*** Extended-release injectable naltrexone is a recommended treatment for preventing relapse to opioid use disorder in patients who are no longer physically dependent on opioids, able to give informed consent, and have no contraindications for this treatment.
2. ***Major Revision*** Extended-release injectable naltrexone should generally be administered every 4 weeks by deep IM injection in the gluteal muscle at the set dosage of 380 mg per injection. Some patients, including those who metabolize naltrexone more rapidly, may benefit from dosing as frequently as every 3 weeks.
3. ***Major Revision*** Oral naltrexone is not recommended except under limited circumstances (see Part 6 for more details).
4. ***Major Revision*** Patients' psychosocial needs should be assessed, and patients should be offered or referred to psychosocial treatment based on their individual needs, in conjunction with extended-release naltrexone. A patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay naltrexone treatment, with appropriate medication management. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing their individual needs.
5. ***Minor Revision*** There is no recommended length of treatment with naltrexone. Duration depends on clinical judgment and the patient's individual circumstances. Because there is no physical dependence associated with naltrexone, it can be stopped abruptly without withdrawal symptoms.
6. ***Minor Revision*** Transitioning from naltrexone to methadone or buprenorphine should be planned, considered, and monitored. Transitioning from an antagonist such as naltrexone to a full agonist (methadone) or a partial agonist (buprenorphine) is generally less complicated than transitioning from a full or partial agonist to an antagonist

because there is no physical dependence associated with antagonist treatment and thus no possibility of precipitated withdrawal. Patients being transitioned from naltrexone to buprenorphine or methadone will not have physical dependence on opioids and thus the initial doses of methadone or buprenorphine should be low. Patients should not be transitioned until a significant amount of the naltrexone is no longer in their system, about 1 day for oral naltrexone or 28 days for extended-release injectable naltrexone.

7. ***Minor Revision*** Patients who discontinue naltrexone treatment should be made aware of the increased risks associated with opioid overdose, and especially the increased risk of overdose death, if they return to illicit opioid use. Treatment alternatives including methadone (see Part 4) and buprenorphine (see Part 5), as well as overdose prevention with naloxone (see part 13) should be discussed with any patient choosing to discontinue treatment.

Part 7: Psychosocial Treatment in Conjunction With Medications for the Treatment of Opioid Use Disorder

1. ***Major Revision*** Patients' psychosocial needs should be assessed, and patients should be offered or referred to psychosocial treatment, based on their individual needs, in conjunction with any pharmacotherapy for the treatment of, or prevention of relapse to, opioid use disorder. However, a patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacological treatment of opioid use disorder, with appropriate medication management. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing their individual needs.
2. Treatment planning should include collaboration with qualified behavioral healthcare providers to determine the optimal type and intensity of psychosocial treatment and for renegotiation of the treatment plan for circumstances in which patients do not adhere to recommended plans for, or referrals to, psychosocial treatment.

Part 8: Special Populations: Pregnant Women

1. ***New*** The first priority in evaluating pregnant women for opioid use disorder should be to identify emergent or urgent medical conditions that require immediate referral for clinical evaluation.
2. ***Minor Revision*** Treatment with methadone or buprenorphine is recommended and should be initiated as early as possible during pregnancy.
3. ***Major Revision*** Pregnant women who are physically dependent on opioids should receive treatment using methadone or buprenorphine rather than withdrawal management or psychosocial treatment alone.
4. ***Major Revision*** A medical examination and psychosocial assessment are recommended when evaluating pregnant women for opioid use disorder. However, completion of all assessments should not delay or preclude initiating pharmacotherapy for opioid use disorder. If not completed before initiating treatment, assessments should be completed as soon as possible thereafter.
5. Obstetricians and gynecologists, and other healthcare providers that care for pregnant women, should be alert to signs and symptoms of opioid use disorder. Pregnant women with opioid use disorder are more likely to seek prenatal care late in pregnancy, miss appointments, experience poor weight gain, or exhibit signs of withdrawal or intoxication.
6. ***Major Revision*** The psychosocial needs of pregnant women being treated for opioid use disorder should be assessed and patients should be offered or referred to psychosocial treatment based on their individual needs. A woman's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacological treatment, with appropriate medication management, during pregnancy. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing their individual needs.
7. Counseling and testing for HIV should be provided (in accordance with state law). Tests for hepatitis B and C and liver enzymes are also suggested. Hepatitis A and B vaccinations is recommended for those whose hepatitis serology is negative.
8. ***Minor Revision*** Drug and alcohol testing should be used to monitor patients for adherence to medication and for use of illicit and controlled substances. This should be done with informed consent from the mother, realizing that there may be adverse legal and social consequences for substance use. State laws differ on reporting substance use during pregnancy. Laws that penalize women for substance use and for obtaining treatment serve to prevent women from obtaining prenatal care and worsen outcomes. For further clarity see The ASAM Appropriate Use of Drug Testing in Clinical Addiction Medicine[8] guidance document.
9. ***Minor Revision*** Care for pregnant women with opioid use disorder should be comanaged by a clinician experienced in obstetrical care and a clinician experienced in the treatment of opioid use disorder.
10. Hospitalization during initiation of methadone or buprenorphine may be advisable due to the potential for adverse events, especially in the third trimester.
11. ***Major Revision*** Methadone should be initiated at a dose range of 10 to 30 mg. Incremental doses of 5 to 10 mg is recommended every 3 to 6 hours, as needed, to treat withdrawal symptoms, to a maximum first day dose of 30 to 40 mg.
12. ***Major Revision*** After initiation, clinicians should increase the methadone dose by no more than 10 mg approximately every 5 days. The goal is to maintain the lowest dose that controls withdrawal symptoms and minimizes the desire to use additional opioids.
13. ***Minor Revision*** Clinicians should be aware that the pharmacokinetics of methadone are affected by pregnancy. With advancing gestational age, plasma levels of methadone progressively decrease and clearance increases. Increased and/or split doses may be needed as pregnancy progresses. Twice-daily dosing is more effective and has fewer side effects than single dosing

but may not be practical because methadone is typically dispensed in an OTP. After childbirth, doses may need to be adjusted (typically reduced) based on changes in weight and metabolism.

14. ***Major Revision*** If a woman becomes pregnant while she is receiving naltrexone, it may be appropriate to discontinue the medication if the patient and clinician agree that the risk of relapse is low. A decision to remain on naltrexone during pregnancy should be carefully considered by the patient and her clinician and should include a discussion on the insufficiency of research on risks (if any) of continued use of naltrexone. If the patient chooses to discontinue treatment with naltrexone and is at risk for relapse, treatment with methadone or buprenorphine should be considered.
15. ***Minor Revision*** Use of naloxone challenge to test for opioid dependence and risk of precipitated withdrawal is not recommended for pregnant women with opioid use disorder.
16. ***Minor Revision*** Unless otherwise contraindicated (see Part 8), mothers receiving methadone or buprenorphine for treatment of opioid use disorders should be encouraged to breastfeed.

Part 9: Special Populations: Individuals With Pain

1. ***Minor Revision*** For all patients with pain, it is important that the correct diagnosis is made and that pain is addressed. Alternative treatments including non-opioid medications with pain modulating properties, behavioral approaches, physical therapy, and procedural approaches (eg, regional anesthesia) should be considered before prescribing opioid medications for pain.
2. ***Minor Revision*** If pharmacological treatment is considered, non-opioid analgesics, such as acetaminophen and NSAIDs, and non-opioid medications with pain modulating properties should be tried first.
3. ***Minor Revision*** For patients with pain who have an active opioid use disorder but are not in treatment, methadone or buprenorphine should be considered. The patient's opioid use disorder and pain should be stabilized and managed concurrently.
4. ***Major Revision*** For patients taking methadone or buprenorphine for the treatment of opioid use disorder, temporarily increasing the dose or dosing frequency (ie, split dosing to maximize the analgesic properties of these medications) may be effective for managing pain. (Titration of methadone should follow the guidance in Part 4 of this guideline)
5. ***Major Revision*** For patients taking methadone for the treatment of opioid use disorder who have acute pain refractory to other treatments and require additional opioid-based analgesia, adding a short acting full agonist opioid to their regular dose of methadone can be considered to manage moderate to severe acute pain. The dose of additional full agonist opioid analgesic prescribed is anticipated to be higher than the typical dose necessary to achieve adequate analgesia in opioid-naïve individuals.
6. ***New*** Patients receiving buprenorphine for opioid use disorder who have moderate to severe acute pain refractory to other treatments and require additional opioid-based analgesia may benefit from the addition of as-needed doses of buprenorphine.
7. ***Major Revision*** The addition of a short-acting full agonist opioid to the patient's regular dose of buprenorphine can be effective for the management of severe acute pain in supervised settings, such as during hospitalization. The dose of additional full agonist opioid analgesic prescribed is anticipated to be higher than the typical dose necessary to achieve adequate analgesia in opioid-naïve individuals. Because of a lack of evidence, the committee was unable to come to consensus on whether this adjunct treatment can be safely prescribed in ambulatory care settings.
8. ***Major Revision*** Discontinuation of methadone or buprenorphine before surgery is not required. Higher-potency intravenous full agonists opioids can be used perioperatively for analgesia.
9. ***Minor Revision*** Decisions related to discontinuing or adjusting the dose of buprenorphine prior to a planned surgery should be made on an individual basis, through consultation between the surgical and anesthesia teams and the addiction treatment provider when possible.
10. ***Major Revision*** If it is decided that buprenorphine or methadone should be discontinued before a planned surgery, this may occur the day before or the day of surgery, based on surgical and anesthesia team recommendations. Higher-potency intravenous full agonists opioids can be used perioperatively for analgesia. Methadone or buprenorphine can be resumed postoperatively when the need for full opioid agonist analgesia has resolved, with additional considerations for postoperative pain management as described for acute pain above. The initial dose and titration should typically be determined by the prescriber. In general, pre-surgery daily doses of these medications can be resumed if they were withheld for less than 2 to 3 days.
11. ***Minor Revision*** Patients on naltrexone may not respond to opioid analgesics in the usual manner. Therefore, it is recommended that mild pain be treated with non-opioid analgesics, and moderate to severe pain be treated with higher potency NSAIDs (eg, ketorolac) on a short-term basis.
12. ***Minor Revision*** Oral naltrexone should be discontinued 72 hours before surgery and extended-release injectable naltrexone should be discontinued 30 days before an anticipated surgery. (Reinitiation of naltrexone should follow the guidance in Part 6 of this guideline)
13. ***New*** Naltrexone's blockade of the mu opioid receptor can often be overcome when necessary with high potency full agonist opioids. In these instances, patients should be closely monitored in an emergency department or hospital setting.

Part 10: Special Populations: Adolescents

1. Clinicians should consider treating adolescents who have opioid use disorder using the full range of treatment options, including pharmacotherapy.

2. ***Minor Revision*** Opioid agonists (methadone and buprenorphine) and antagonists (naltrexone) may be considered for treatment of opioid use disorder in adolescents. Federal laws and FDA approvals should be considered when recommending pharmacotherapy for adolescent patients.
3. ***Major Revision*** Psychosocial treatment is recommended in the treatment of adolescents with opioid use disorder. The risk benefit balance of pharmacological treatment without concurrent psychosocial treatment should be carefully considered and discussed with the patient and her or his parent or guardian as appropriate. A patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacological treatment of opioid use disorder, with appropriate medication management. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing their individual needs.
4. ***Minor Revision*** Concurrent practices to reduce infection (eg, risk behavior reduction interventions) are recommended as components of comprehensive treatment for the prevention of blood-borne viruses (infections related to injection practices) and sexually transmitted infections.
5. Adolescents may benefit from treatment in specialized treatment programs that provide multidimensional services (See The ASAM Criteria[5]).

Part 11: Special Populations: Individuals With Co-occurring Psychiatric Disorders

1. ***Minor Revision*** All patients with opioid use disorder should receive a comprehensive assessment including determination of mental health status and suicide risk, including evaluation of whether the patient is stable. Patients with suicidal or homicidal ideation should be referred immediately for treatment and possibly hospitalization.
2. Management of patients at risk for suicide should include reducing immediate risk, managing underlying factors associated with suicidal intent, and monitoring and follow-up.
3. ***Minor Revision*** All patients with psychiatric disorders should be asked about suicidal ideation and behavior. Patients with a history of suicidal ideation or attempts should have adherence for opioid use disorder and psychiatric disorder medications monitored more closely.
4. ***Minor Revision*** Assessment for psychiatric disorder should occur at the onset of agonist or antagonist treatment. However, completion of all assessments should not delay or preclude initiating pharmacotherapy for opioid use disorder. If not completed before initiating treatment, assessments should be completed as soon as possible thereafter. Reassessment using a detailed mental status examination should occur after stabilization with methadone, buprenorphine, or naltrexone.
5. ***Major Revision*** Pharmacotherapy in conjunction with psychosocial treatment should be offered to patients with opioid use disorder and a co-occurring psychiatric disorder. A patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacological treatment of opioid use disorder, with appropriate mediation management. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing their individual needs.
6. Clinicians should be aware of potential interactions between medications used to treat co-occurring psychiatric conditions and opioid use disorder.
7. Assertive community treatment should be considered for patients with co-occurring schizophrenia and opioid use disorder who have a recent history of, or are at risk of, repeated hospitalization or homelessness.

Part 12: Special Populations: Individuals in the Criminal Justice System

1. ***New*** All FDA approved medications for the treatment of opioid use disorder should be available to individuals receiving healthcare within the criminal justice system. The treatment plan, including choice of medication, should be based on the patient's individual clinical needs.
2. ***Minor Revision*** Continuation of treatment after release results in a substantial reduction in all-cause and overdose mortality. Treatment should be individualized, and patients should receive complete information to make informed decisions in consultation with a medical and treatment team.
3. ***New*** Individuals entering the criminal justice system should not be subject to forced opioid withdrawal. Patients being treated for opioid use disorder at the time of entrance into the criminal justice system should continue their treatment. Patients with opioid use disorder who are not in treatment should be assessed and offered individualized pharmacotherapy and psychosocial treatment as appropriate.
4. ***Major Revision*** Initiation or maintenance of pharmacotherapy for the treatment of opioid use disorder is recommended for individuals within the criminal justice system (including both jails and prisons). Criminal justice staff should coordinate care and access to pharmacotherapy to avoid interruption in treatment. Patients should not be forced to transition from agonist (methadone or buprenorphine) to antagonist (naltrexone) treatment.
5. ***Major Revision*** Individuals in the criminal justice system who have opioid use disorder or who are experiencing opioid withdrawal should be offered a combination of pharmacotherapy and psychosocial treatment (based on an assessment of their individual psychosocial needs). A patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacological treatment of opioid use disorder, with appropriate medication management. Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing their individual needs.
6. ***New*** If an OTP is not accessible, providers may need to transition individuals from methadone to buprenorphine. Effectively transitioning from methadone to buprenorphine can be challenging but can be achieved safely if managed by a provider experienced in the procedure.

7. ***Major Revision*** Risk for relapse and overdose is particularly high in the weeks immediately following release from prison and jails. Patients being treated for opioid use disorder while in prison or jail should be stabilized on pharmacotherapy (methadone, buprenorphine or naltrexone) and continue in treatment after their release. Patient care on reentry to the community should be individualized and coordinated with treatment providers in the community.
8. ***New*** Naloxone kits should be available within correctional facilities. Individuals with opioid use disorder should receive a naloxone kit prior to release, and individuals and families should be educated in how to administer naloxone.

Part 13: Naloxone for the Treatment of Opioid Overdose

1. ***Major Revision*** Naloxone should be administered in the event of a suspected opioid overdose.
2. ***Minor Revision*** Naloxone may be administered to pregnant women in cases of overdose to save the mother's life.
3. ***Minor Revision*** Patients who are being treated for opioid use disorder (as well as people with a history of opioid use disorder leaving incarceration) and their family members/significant others should be given naloxone kits or prescriptions for naloxone. Patients and family members/significant others should be trained in the use of naloxone in overdose.
4. The Guideline Committee, based on consensus opinion, recommends that first responders such as emergency medical services personnel, police officers, and firefighters be trained in and authorized to carry and administer naloxone.

SUMMARY OF FINDINGS

Grounded in findings from a focused literature search, the RAM Process resulted in new recommendations to Part 1 (Assessment Recommendations), Part 2 (Treatment Options), Part 5 (Buprenorphine), Part 9 (Part 9: Special Populations: Individuals With Pain), and Part 12 (Special Populations: Individuals in the Criminal Justice System) of the Practice Guideline. At least one major or one minor revision was made in every part of the Practice Guideline.

Among the new and updated recommendation statements, the following represent significant shifts in recommended clinical practices from the 2015 publication. ASAM recommends that psychosocial treatment should be offered in conjunction with pharmacotherapy. However, a patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacotherapy. Opioid withdrawal management with buprenorphine should not be initiated until there are objective signs of opioid withdrawal. The U.S. FDA recently approved several new buprenorphine formulations for treatment of opioid use disorder. As the data regarding the effectiveness of these products are currently limited, clinicians should use these products as labeled and be mindful of emerging evidence as it becomes available. Both office-based and home-based buprenorphine inductions are considered safe and effective. Oral naltrexone is not recommended except under limited circumstances. Buprenorphine is a reasonable and recommended alternative to methadone for pregnant women. Naloxone should be administered for suspected overdose by those who have received overdose response education.

With respect to criminal justice settings. The focused update recommends several key changes to the previous clinical guidance. For example, all U.S. FDA approved medications for the treatment of opioid use disorder, should be available to patients within the criminal justice system, and the treatment plan, including choice of medication, should be based on the patient's individual clinical needs. Individuals entering the criminal justice system should not be subject to forced opioid withdrawal. Patients being treated for opioid use disorder at the time of entrance into the criminal justice system should continue their treatment. Patients with opioid use disorder not in treatment at the time of entrance into the criminal justice system should be assessed and offered individualized pharmacotherapy and psychosocial treatment as appropriate. Risk for relapse and overdose is particularly high in the weeks immediately following release from prison and jails. Patients being treated for opioid use disorder while in prison or jail should be stabilized on pharmacotherapy (eg, methadone, buprenorphine or naltrexone) and continued on treatment after their release. Patient care on reentry to the community should be individualized and coordinated with treatment providers in the community. Naloxone kits should be available within correctional facilities. Individuals with opioid use disorder, those with a history of opioid use disorder at risk for relapse, and potential bystanders should receive naloxone kits and training in how to administer naloxone.

CONCLUSION

Since 2015, important new developments (in the form of newly available formulations and medications), published evidence, and clinical guidance related to the treatment of addiction involving opioid use have emerged. As a result, ASAM has made several important updates and is publishing the Focused Update for the ASAM National Practice Guideline for Treatment of Opioid Use Disorder.

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Appendix A: 2019 Guideline Committee Member Relationships with Industry and Other Entities

The ASAM Criteria is a copyrighted by ASAM and ASAM has a financial interest in these guidelines. However, none of the members of the guideline committee or ASAM's Quality Improvement Council who participated in or oversaw development of these guidelines has a direct financial stake in The ASAM Criteria.

Guideline Committee Member	Salary	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Institutional, Organizational or other financial benefit	Research	Expert Witness
Chinazo O. Cunningham, MD, MS, FASAM	Albert Einstein College of Medicine – Professor of Medicine Quest Diagnostics	None	None	General Electric Health[*] Data Safety Monitoring Board - Spouse	None	None	None
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(*Continued*)

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Sandra A. Springer, MD, FASAM	Yale School of Medicine – Associate Professor of Medicine	Alkermes[*,*]	None	Infectious Diseases Society of America and HIV Medical Association – Member of Working Group at the Intersection of OUD and Infectious Disease Epidemics	National Center for Advancing Translational Sciences	National Institutes of Health – Research Grant	None
	Veterans Administration Healthcare System			National Academy of Sciences – Appointed Committee Member of Engineering and Medicine Working Group on Evaluating Community Programs Integrating Infectious disease and OUD Treatments	Veterans Administration Cooperative Studies	National Institute on Drug Abuse – Research Grant	
						National Institute on Alcohol Abuse and Alcoholism – Research Grant	
George E. Woody, MD	University of Pennsylvania Perelman School of Medicine Department of Psychiatry - Professor	None	None	None	None	Alkermes – Research Grant	Diagnosis of Substance Use Disorder[*,*]
						American Society of Addiction Medicine – Research Grant	Presence/Absence of substance use disorder or other health problem that could impair practice of licensed professional[*,*]
						National Institute on Drug Abuse[*,*] - Clinical Trial on improving outcomes of opioid addicted prisoners with extended release injectable naltrexone given before or after reentry	
Tricia E. Wright, MD, MS, FACOG, DFASAM	University of California San Francisco – Professor of Clinical Medicine University Health Partners, University of Hawaii	Cambridge University Press[*]	American College of Obstetrics and Gynecology[*] American Society of Addiction Medicine[*]	None	State of Hawaii	None	None
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REVIEW

Benefit-Risk Analysis of Buprenorphine for Pain Management

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Abstract: Health care providers in the United States are facing challenges in selecting appropriate medication for patients with acute and chronic pain in the midst of the current opioid crisis and COVID-19 pandemic. When compared with conventional opioids, the partial μ-opioid receptor agonist buprenorphine has unique pharmacologic properties that may be more desirable for pain management. The formulations of buprenorphine approved by the US Food and Drug Administration for pain management include intravenous injection, transdermal patch, and buccal film. A comparison of efficacy and safety data from studies of buprenorphine and conventional opioids suggests that buprenorphine may be a better-tolerated treatment option for many patients that provides similar or superior analgesia. Our benefit-risk assessment in this narrative review suggests that health care providers should consider that buprenorphine may be an appropriate alternative for pain management over other opioids.

Keywords: buprenorphine, buprenorphine buccal film, analgesia, pain, opioids

Introduction

As a result of the current opioid crisis, the United States is having difficulty providing adequate care for patients with acute and chronic pain.[1] Statistics from 2016 indicate that acute pain is reported by approximately 55% of hospitalized patients, and 50 million (20.4%) adults in the United States have chronic daily pain, with 19.6 million (8%) experiencing high-impact chronic pain that interferes with daily life or work activities.[2] Immediate-release/short-acting or extended-release (ER)/long-acting opioids are often prescribed for pain, as they elicit analgesia by acting on opioid receptors to inhibit nociceptive stimulation.[3] Increased prescribing rates coupled with the diversion of prescription opioids have contributed to the national crisis of opioid use disorder (addiction) and overdose deaths, signifying the need for safer alternatives.[4] Although abuse-deterrent opioid formulations were designed to deter altered routes of administration (eg, snorting, inhalation, chewing, injection) that increase the risk of overdose, these formulations are not abuse-proof.[5] With advancing better practices in response to the opioid crisis, 17 of the 38 states with prescription opioid overdose death data saw a decline between 2017 and 2018, and no states experienced a significant increase.[4] However, opioid abuse rates have increased with the COVID-19 pandemic.[6]

Opioids can be divided into conventional opioids (full μ-opioid receptor agonists such as fentanyl, hydrocodone, morphine, oxycodone)[7] and mixed-action or atypical

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opioids (such as buprenorphine, butorphanol, tramadol, tapentadol).[3] When compared with other opioids currently on the market, the atypical opioid buprenorphine has a unique pharmacologic profile.[8]

Buprenorphine is a partial agonist with very high binding affinity at μ-opioid receptors, an agonist with low binding affinity at the nociceptin opioid receptor (NOP, formerly known as opioid receptor like-1), and an antagonist with high binding affinity at κ- and δ-opioid receptors (Figure 1).[9] The term "partial agonist" was applied owing to a partial effect on stimulating the receptor with in vitro assays.[10] This does not necessarily translate to partial analgesic efficacy in vivo or in clinical practice, as the analgesic signaling pathway may be sufficiently activated by a partial agonist. Partial agonism at the μ-opioid receptor by buprenorphine yields potent analgesia and a ceiling effect on respiratory depression and euphoria and reduces other adverse events commonly observed with conventional opioid use.[10–16] Buprenorphine does not occupy all μ-opioid receptors, which allows for efficacy of concomitant full μ-opioid receptor agonists.[9] Antagonism at the δ- and κ-opioid receptors may limit constipation, respiratory depression, dysphoria, and substance abuse.[9] Kappa-opioid receptor antagonists are currently being considered as promising therapeutics for psychiatric conditions such as depression, anxiety, and substance abuse disorders.[17] Agonism at NOP contributes to spinal analgesia and may limit the potential for substance abuse and tolerance commonly observed with full μ-opioid receptor agonists.

Conventional opioids bind to μ-opioid receptors, which activate signaling pathways that depress neural functions and are associated with adverse events. However, the partial agonistic effects of buprenorphine limit μ-opioid receptor activity, which elicits analgesia pathways but may restrict pathways associated with adverse events, contributing to a more favorable safety profile and patient satisfaction.

Buprenorphine is approved by the US Food and Drug Administration (FDA) for acute pain, chronic pain, opioid use disorder, or opioid dependence, depending on the formulation (Table 1).[7,18] Buprenorphine formulations exist as either a combination therapy with naloxone (eg, Suboxone and similar products) or as stand-alone products. The stand-alone buprenorphine products and their indications are listed in Table 1.[19–26] Buprenorphine also exists as a suppository, but this formulation is not FDA-approved for use in the US.[27]

The purpose of this review is to present the literature assessing the efficacy of buprenorphine products for the treatment of pain and compare the risks and benefits of buprenorphine to conventional opioids. The information presented here can be used to aid health care professionals in medication selection for patients who are experiencing pain and for whom opioid treatment is deemed appropriate.

Methods

This narrative review is based on the authors' knowledge of the literature, their clinical experience, and literature searches including the terms buprenorphine and pain.

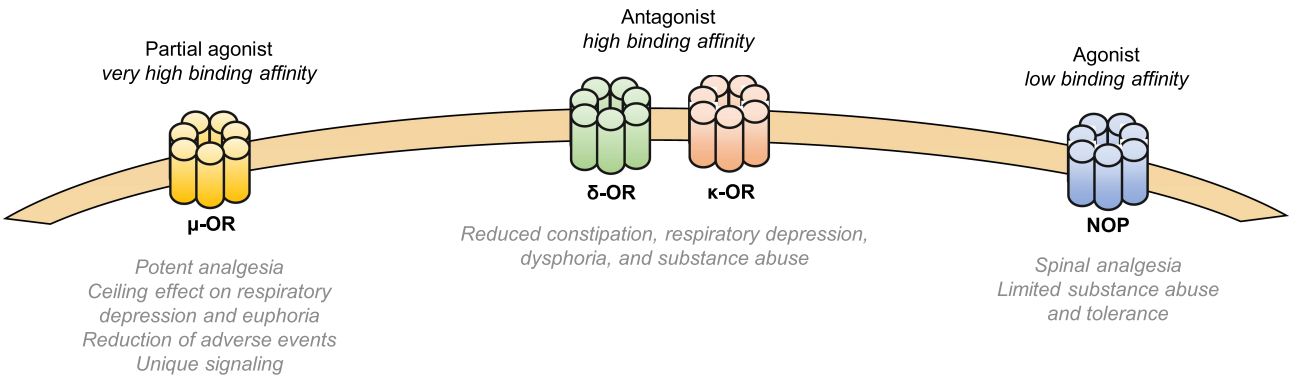

Figure 1 Mechanism of Action of Buprenorphine at Opioid and NOP Receptors. At μ-opioid receptors, buprenorphine is a partial agonist with very high binding affinity, which results in potent analgesia, contributes to a ceiling effect on respiratory depression and euphoria, and reduces other adverse events commonly observed with opioid use owing to unique phosphorylation and signaling activity. Buprenorphine has antagonistic activity with high binding affinity at κ- and δ-opioid receptors, which may limit constipation, respiratory depression, dysphoria, and substance abuse. The agonistic activity and low binding affinity at the NOP receptor contribute to spinal analgesia and may limit the substance abuse potential and tolerance commonly observed with full μ-opioid receptor agonists.
Abbreviations: NOP, nociceptin; OR, opioid receptor.

Table 1 Buprenorphine Products

FDA-Approved Indication	Pain Management			Addiction Medicine				
	Acute Pain	Chronic Pain		OUD		Opioid Dependence		
Trade name	Buprenex	Belbuca	Butrans	Brixadi[a]	Sublocade	Probuphine	Generic Subutex	
Route of administration	Injection	Buccal	Transdermal	Injection	Injection	Implant	Sublingual	
Available dose range	300 µg/mL	75, 150, 300, 450, 600, 750, or 900 µg	5, 7.5, 10, 15, or 20 µg/h	8, 16, 24, or 32 mg weekly; 64, 96, or 128 mg monthly	100 and 300 mg/month	74.2 mg/6 months	2 or 8 mg	
Bioavailability	100%	46%-65%	15%	100%	100%	N/A	15%-30%	

Notes: Combination products are not included. Please see package inserts for full indication, dosing, and REMS requirements for each product. [a]Tentative FDA approval.
Abbreviations: FDA, US Food and Drug Administration; OUD, opioid use disorder; REMS, Risk Evaluation and Mitigation Strategies.

Efficacy of Buprenorphine in Pain Management

Intravenous (IV) Formulation

Although IV buprenorphine has not been studied in chronic pain, this formulation has been shown to have a dose-dependent analgesic effect in patients with acute pain.[28] IV buprenorphine had equal or superior analgesic efficacy to IV morphine for postoperative pain following abdominal, cardiac, lung, and spinal surgery or lateral thoracotomy.[29–36] Bradley et al. found that 4 to 6 µg/kg IV buprenorphine following abdominal surgery (hysterectomy or cholecystectomy) provided more potent analgesia for a longer duration than morphine.[29] In a separate study, administration of intrathecal morphine and IV buprenorphine together alleviated pain and minimized sedation more effectively than either drug separately, with IV buprenorphine reducing the number of side effects when compared with morphine.[37] IV buprenorphine was also more effective than procaine for pain relief in patients with acute pancreatitis.[38] In addition to providing effective pain relief, a low-dose infusion (25 µg/h for 24 hours) of buprenorphine prevented the short-term development of secondary hyperalgesia around postoperative surgical incisions.[33]

Sublingual (SL) Formulation

Although SL buprenorphine is not indicated for chronic pain, a systematic review of 10 chronic pain trials (6 studies used ≤400 µg/dose; 4 studies used ≥400 µg/dose; the dose range across all studies was 0.1–32 mg), including for the treatment of general, osteoarthritic, sickle-cell disease, nociceptive, and cancer chronic pain in the general, elderly, or pediatric populations, found this formulation to be efficacious in 100% of the studies.[39] For example, Malinoff et al. examined patients with chronic pain syndrome and found that pain decreased in 86% of patients following SL buprenorphine administration, and many patients reported improved mood, decreased sleep disturbance, and an improved sense of well-being after treatment.[40] For acute pain, SL buprenorphine had similar or greater postoperative analgesic efficacy when compared with IV patient-controlled analgesia (morphine) or intramuscular morphine following surgery (Figure 2); however, significant relief was not observed until after 2 hours postdose, suggesting that IV buprenorphine may be more appropriate for immediate relief from severe acute pain.[41,42] SL buprenorphine (0.4 mg) also produced

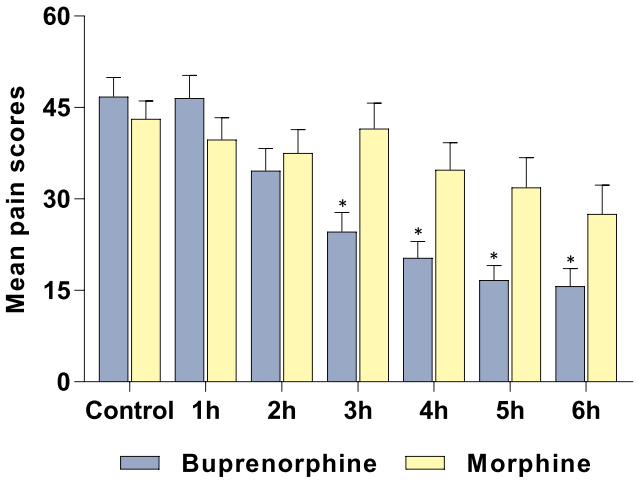

Figure 2 Pain Relief Induced by Intramuscular Morphine or Sublingual Buprenorphine Following Surgery. Pain scores were determined using a VAS after the administration of 0.4 mg SL buprenorphine or an injection of 10 mg/mL morphine. *p<0.05 for comparisons between groups at that time.
Notes: Data from Edge et al (1979).[41]
Abbreviations: h, hour(s); SL, sublingual; VAS, visual analog scale.

analgesia equal to or greater than that produced by oral dihydrocodeine (60 mg) in patients with postoperative pain.[43]

Transdermal Formulation

In a systematic review, transdermal buprenorphine was found to be efficacious in 29 (100%) clinical studies that examined chronic pain (general, low back, osteoarthritis, malignant, and musculoskeletal pain).[7] The dosages of transdermal buprenorphine used in these chronic pain studies ranged from 5 to 140 µg/h (the highest available dosage strength in the United States is 20 µg/h). Steiner et al. found that 12 weeks of treatment with transdermal buprenorphine resulted in significantly lower pain scores than placebo in opioid-naive patients with chronic low back pain.[44] A multicenter randomized phase 4 trial by Corli et al. showed that transdermal buprenorphine had analgesic efficacy similar to that of transdermal fentanyl, oral morphine, and oral oxycodone in patients with cancer pain (Figure 3).[45] In addition, transdermal buprenorphine has demonstrated efficacy in the treatment of postsurgical acute pain to a similar or greater extent than oral tramadol or tramadol/acetaminophen.[46–48]

Buccal Film Formulation

Buprenorphine buccal film (75 µg to 900 µg) has demonstrated analgesic efficacy in all currently published studies examining its effect on chronic low back pain (Figure 4).[49–51] A retrospective analysis found that converting from a long-acting full µ-opioid receptor agonist to buprenorphine buccal film provided continued analgesia in most patients despite a reduction in daily morphine milligram equivalent (MME) factor, which could lead to improved patient safety outcomes.[52] To date, no studies have examined the effects of buprenorphine buccal film for acute pain, presenting a valuable opportunity for future research.

Transdermal vs Buccal Film for Chronic Pain Management

Among the formulations FDA-approved for chronic pain, buprenorphine buccal film has a higher bioavailability. Although buprenorphine has poor oral bioavailability and transdermal bioavailability is limited, the mucosa allows for higher bioavailability via the buccal route.[9] Buprenorphine buccal film also has a larger available dose range compared to the transdermal patch, which may be preferable for some patients (Table 1). The 20 µg/h patch may not provide

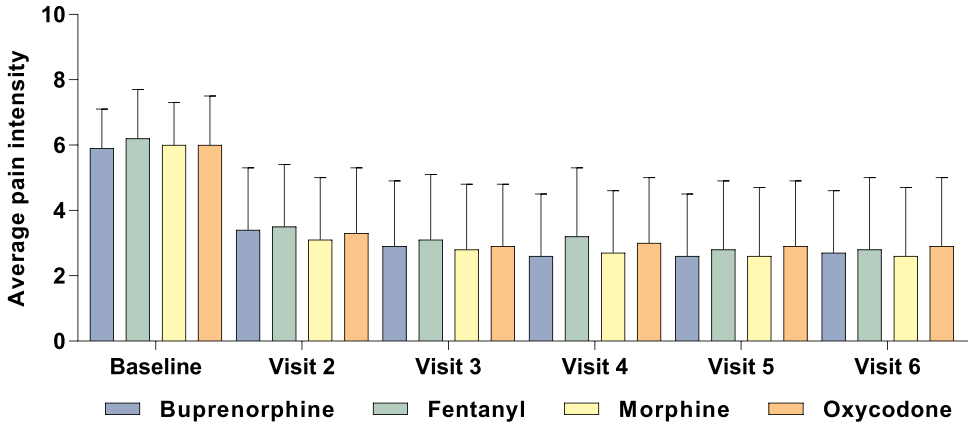

Figure 3 Efficacy of Transdermal Buprenorphine Compared With Conventional Opioids in Patients With Chronic Cancer Pain. Average pain intensity was measured on a numeric rating scale. Data are mean (SD). Data from Corli et al (2016).[45]

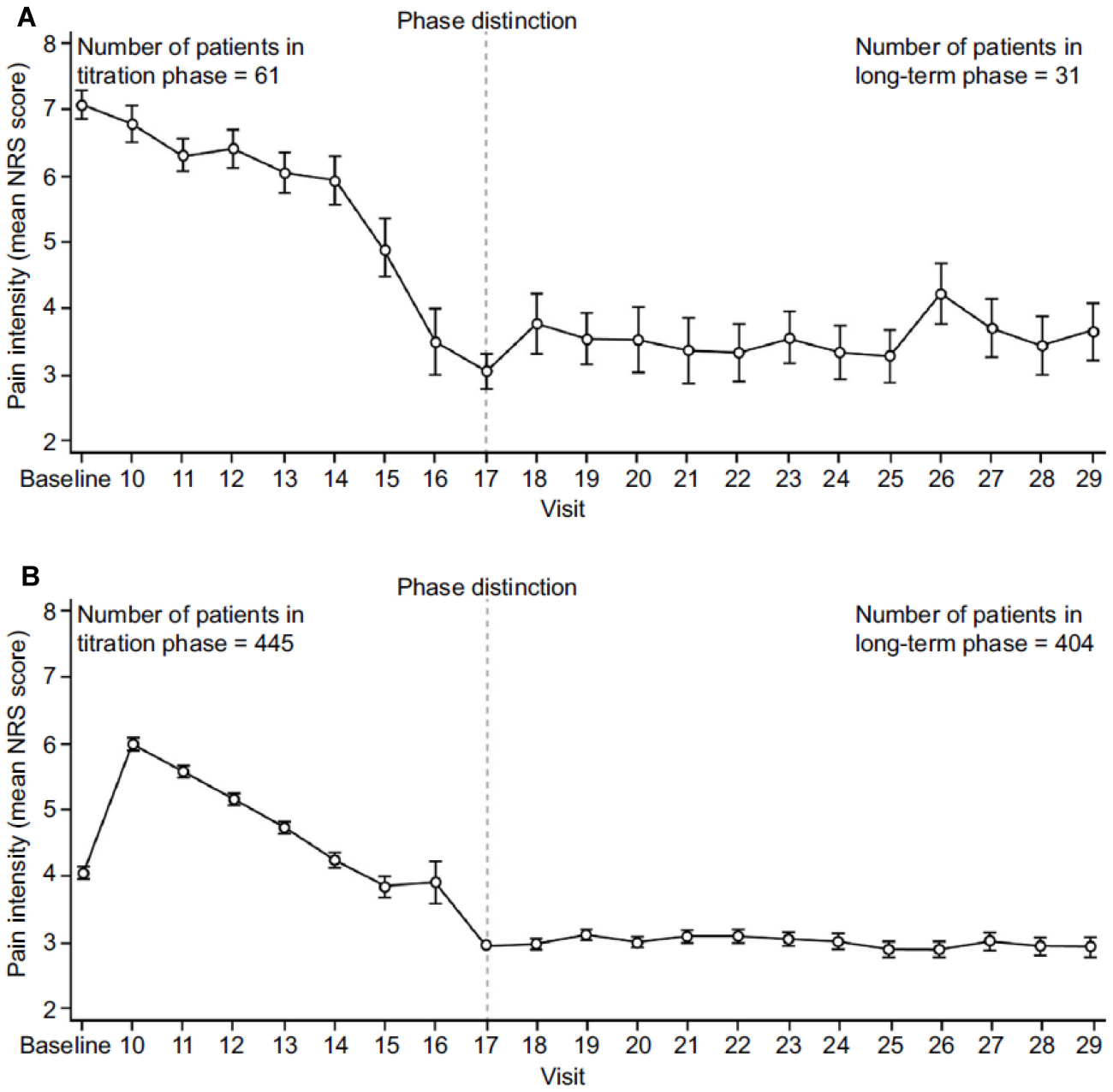

Figure 4 Efficacy of Buprenorphine Buccal Film in Patients With Chronic Low Back Pain. Mean NRS scores during the titration and long-term treatment phases with buprenorphine buccal film in (**A**) de novo patients and (**B**) rollover patients.

Notes: Copyright ©2017. Dove Medical Press. Reproduced from Hale M, Urdaneta V, Kirby MT, Xiang Q, Rauck R. Long-term safety and analgesic efficacy of buprenorphine buccal film in patients with moderate-to-severe chronic pain requiring around-the-clock opioids. *J Pain Res*. 2017;10:233–240.[50]

Abbreviation: NRS, numerical rating scale.

adequate analgesia in patients receiving high-dose opioid treatment (>80 mg MME factor/d).[20] The dose range of buprenorphine buccal film (75–900 µg) provides more flexibility to titrate to an optimal dose, making it a preferable option for patients whose needs exceed the doses available with the transdermal system. The highest dosage of transdermal buprenorphine available in the US is 20 µg/h (to be worn for 7 days), with the median equivalent dose of the buccal formulation being 300 µg/12 h.[53] Transdermal buprenorphine has the advantage of medication adherence with the ease of applying the product once a week, but it may also cause application site pruritus, erythema, and site rash,[44] which are treatment-emergent adverse events not reported in clinical studies of buprenorphine buccal film.[49–51] In

clinical studies, 14% of patients with chronic pain discontinued transdermal buprenorphine owing to lack of perceived efficacy compared with 5% who discontinued buprenorphine buccal film for the same reason.[7] In similar clinical trials, responder analysis of ≥30% or ≥50% reduction in pain intensity in opioid-experienced patients showed that the efficacy of buprenorphine buccal film was greater than transdermal buprenorphine (Figure 5).[7] The buccal film also has the advantage of additional safety data, where comparison with a conventional opioid (immediate-release oxycodone) in a clinical study assessing respiratory drive showed that, unlike oxycodone, buprenorphine buccal film had no significant impact on respiration.[54]

Benefit-Risk Assessment of Buprenorphine vs Conventional Opioids

Efficacy

Buprenorphine has a long-standing history of efficacy in postsurgical acute pain (IV formulation) and chronic pain (SL and transdermal formulations), and its clinical efficacy has been shown to be greater than that of morphine in some studies.[29,39,44] Buprenorphine has been suggested to be 25 to 115 times more potent as an analgesic than morphine (depending on the study), with no ceiling effect on analgesia.[9] Buprenorphine products no longer have an MME factor in the Centers for Disease Control opioid conversion guide, as they are not expected to be associated with overdose risk in the same dose-dependent manner as full μ-opioid receptor agonists.[55] In addition to morphine, the analgesic efficacy of buprenorphine has also been demonstrated to be equal to or greater than oxycodone (MME factor [mg]: 1.5) or fentanyl (MME factor for patch [μg]: 7.2) in chronic pain studies.[45,55–58] When compared across clinical studies, the efficacy of buprenorphine buccal film was similar to that of the conventional ER opioids hydromorphone, hydrocodone, and oxymorphone.[49,51,59–61] In a meta-analysis examining the effects of buprenorphine (SL, transdermal, and buccal) on chronic pain outcomes in patients with or without opioid use disorder (OUD), the authors found that efficacy was more pronounced in patients without OUD, and high doses may be needed for patients with OUD.[62] Overall, the data from these studies suggest that buprenorphine has equivalent or greater clinical analgesic efficacy than conventional opioids.

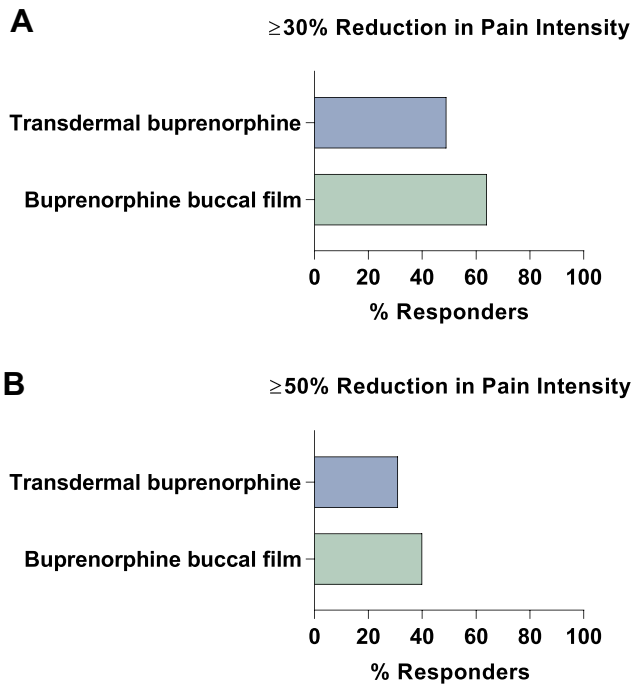

Figure 5 Efficacy of the Transdermal and Buccal Film Formulations of Buprenorphine. Responder analysis of similar opioid-experienced chronic pain clinical trials. Comparisons are of efficacy data for transdermal buprenorphine (20 μg/h) and buprenorphine buccal film (150–900 μg/12h) with response defined as (**A**) ≥30% or (**B**) ≥50% reduction in pain intensity.

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Safety

Buprenorphine is a Schedule III drug with a unique mechanism of action that has less potential for abuse than Schedule II drugs (eg, morphine, oxycodone, fentanyl).[63] The lower abuse potential of buprenorphine may mitigate the number of overdose deaths observed with conventional opioids.[64] Opioids are commonly used recreationally and carry a high risk of diversion; therefore, choosing an opioid medication with slower absorption and less drug liking and abuse potential is imperative during the current opioid crisis. The risks of drug dependence and analgesic tolerance are also lower for buprenorphine than for conventional opioids.[15,65,66]

Buprenorphine also reduces the potential for respiratory depression and death compared with conventional opioids.[1,10,11] No cases of respiratory depression were reported in any clinical trials of buprenorphine buccal film.[49–51] In a phase 1 study, buprenorphine buccal film 300, 600, or 900 μg did not negatively impact respiratory drive, whereas oxycodone 30 mg and 60 mg significantly reduced respiratory drive (Figure 6).[54] The clinical trials of buprenorphine buccal film included fewer than 1000

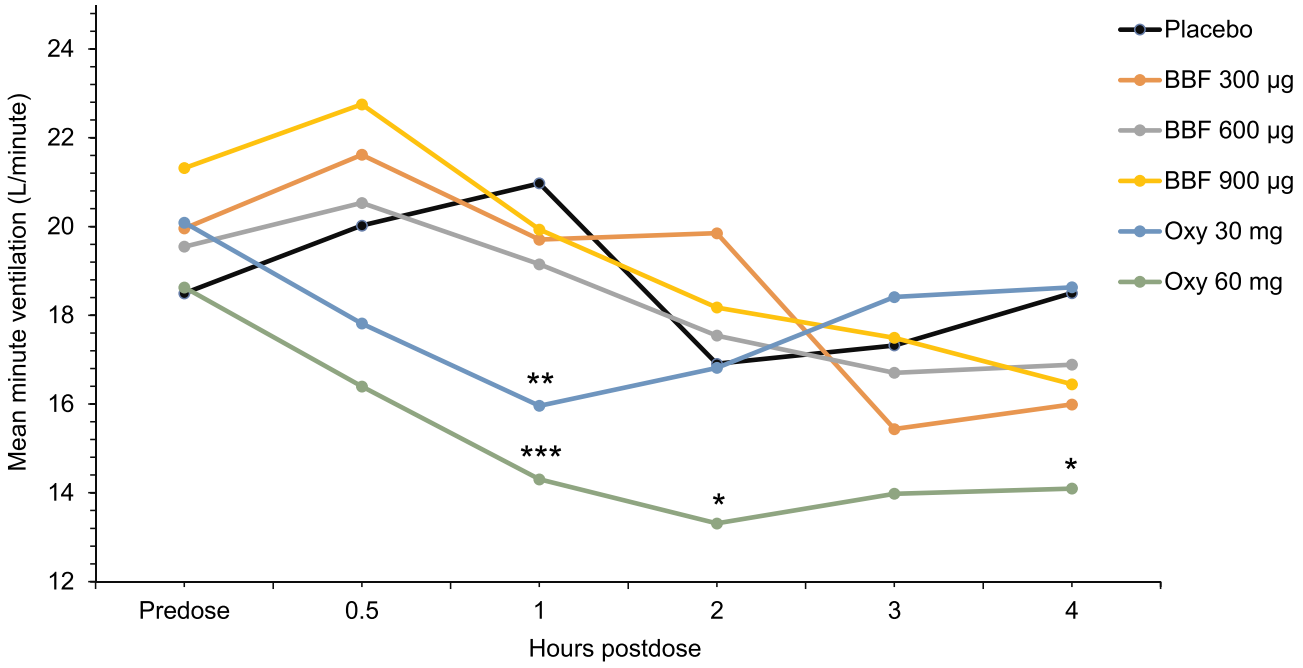

Figure 6 Effect of Buprenorphine Buccal Film and Oxycodone Hydrochloride on Minute Ventilation. Effect of each drug treatment on respiratory drive: mean minute ventilation over time. In the partial completer population (n=16), mean minute ventilation for BBF was not significantly different from placebo at any time point. *p<0.05, **p<0.01, ***p<0.001.

Notes: Reprinted by permission from Springer Nature, *Adv Ther*, Webster LR, Hansen E, Cater J, Smith T, Phase A. I placebo-controlled trial comparing the effects of buprenorphine buccal film and oral oxycodone hydrochloride administration on respiratory drive. Copyright 2020;37(11):4685–4696.[54]

Abbreviations: BBF, buprenorphine buccal film; Oxy, oxycodone.

patients each, but in a postmarketing survey of 13,179 patients receiving transdermal buprenorphine, only 1 (0.01%) patient experienced respiratory depression.[67] This is approximately 80 times less than what was observed in a separate study of transdermal fentanyl.[68] While IV buprenorphine may cause some respiratory depression, studies have demonstrated that it plateaus with a ceiling effect, whereas conventional opioids such as fentanyl do not.[11,12] Sedatives such as benzodiazepines and alcohol increase the risk of respiratory depression, and benzodiazepines are not recommended to be prescribed in combination with any opioids.[1] Because the risk of respiratory depression appears to be lower with buprenorphine than with conventional opioids, an overdose may be less likely to result in a fatality.

In addition to a decreased risk of respiratory depression, other tolerability factors like constipation are more favorable with buprenorphine. Constipation rates for ER full µ-opioid receptor agonists range from 8% to 23%,[69–72] while constipation was reported in only 4% of patients receiving buprenorphine buccal film and in 13% of patients receiving transdermal buprenorphine.[20,21] In a postmarketing surveillance study, 128 (1%) of 13,179 patients receiving transdermal buprenorphine experienced constipation.[67] Opioid-induced constipation is associated with increased economic burden and reduced quality of life, so buprenorphine may be preferable to conventional opioids when considering this adverse event.[73] In addition, a comparison of adverse events reported in clinical trials for buprenorphine buccal film and ER formulations of oxycodone, hydromorphone, and oxymorphone showed that the proportion of patients who experienced nausea, vomiting, constipation, headache, dizziness, somnolence, anxiety, and dry mouth was lower with buprenorphine buccal film than with conventional opioids (Figure 7).

Unlike with conventional opioids, additional benefits of buprenorphine due to its unique metabolism include suitability for use in patients requiring concomitant medications, those with renal or hepatic impairment, and the elderly.[14] Most patients with OUD have been found to also have chronic pain, and among them, the majority had chronic pain before their first OUD diagnosis, making appropriate treatment in this subset of patients essential.[74] Patients with comorbid chronic pain and OUD have reported satisfaction with buprenorphine treatment.[75] Also, buprenorphine is not immunosuppressive,[76,77] does not negatively impact the

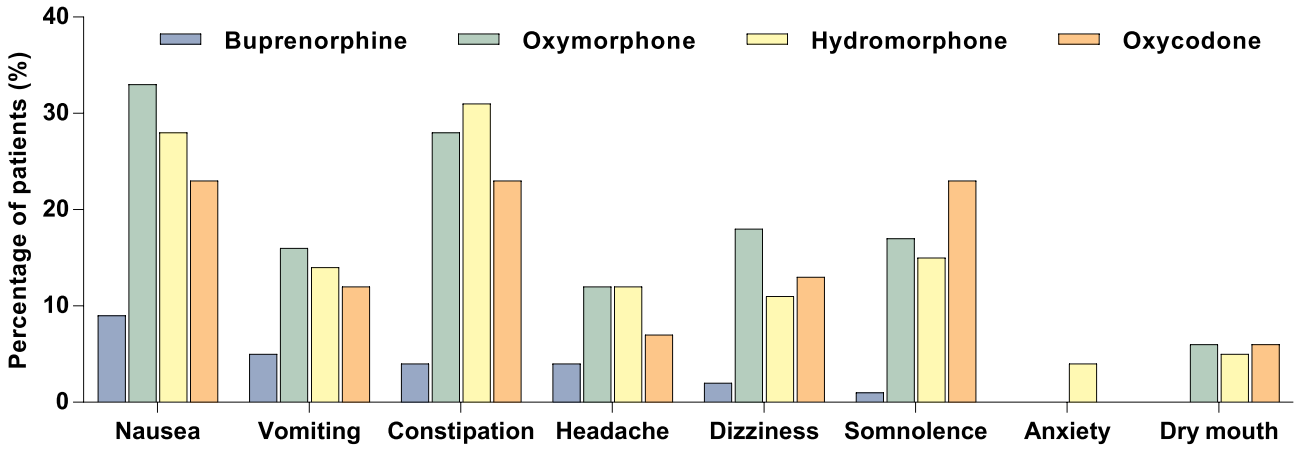

Figure 7 Adverse Events Reported in Clinical Trials of Buprenorphine Buccal Film Compared With Conventional Opioids for Chronic Pain. The percentage of patients who reported adverse events in clinical trials for buprenorphine buccal film[21] compared with those reported for extended-release formulations of oxymorphone,[87] hydromorphone,[88] and oxycodone.[69]

Notes: Copyright ©2019. Dove Medical Press. Adapted from Pergolizzi JV, Jr., Raffa RB. Safety and efficacy of the unique opioid buprenorphine for the treatment of chronic pain. *J Pain Res*. 2019;12:3299–3317.[7]

hypothalamic-pituitary-adrenal pathway,[78–80] and may reduce anxiety and depression.[81–84]

Overall, the safety data and additional benefits of buprenorphine suggest that it has a lower risk of adverse events compared with conventional opioids, most notably with respiratory depression. However, all opioids, including buprenorphine, carry the risk of adverse events and addiction potential, depending on the dose. Therefore, careful consideration should be given to the risks and benefits of each opioid before prescribing. Health care providers should consider using one or more opioid risk screening tools before the initiation of any opioid therapy.[85,86]

Conclusions

Clinical safety and efficacy data in this narrative review suggest that buprenorphine may be a more tolerable alternative with equivalent or superior analgesia to conventional opioids for patients with pain. IV buprenorphine has been the most extensively studied formulation and is FDA-approved for acute pain, while the transdermal patch and buccal film are FDA-approved for chronic pain. The transdermal patch has demonstrated efficacy for chronic pain with once-weekly dosing. Health care providers may find that the buprenorphine buccal film formulation has favorable bioavailability, available doses, efficacy, adverse event profile, and benefit-risk assessments for the treatment of chronic pain. Clinicians should always consider the benefits and risks of various therapeutic options for pain management and are encouraged to explore their unique aspects, long-term clinical impact, and individual patient needs.

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Author Contributions

All authors contributed to the conception and design of the manuscript, analysis and interpretation of data, and critical evaluation of the manuscript for scientific accuracy and intellectual content; approved the final manuscript for publication; and agreed to be accountable for all aspects of the work.

Disclosure

MH has served on advisory boards for BioDelivery Sciences International, Inc. and was principal investigator for multiple buprenorphine trials. MG has served on advisory boards for Daiichi Sankyo, Inc. RBR is the CSO of Neumentum Inc.; cofounder of CaRafe Drug Innovation, LLC; and cofounder of Enalare Therapeutics Inc. The authors report no other conflicts of interest in this work.

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SAMHSA
Substance Abuse and Mental Health Services Administration

BUPRENORPHINE
QUICK START GUIDE

Important Points to Review With the Patient

Specifically discuss safety concerns:

- **Understand that discontinuing buprenorphine increases risk of overdose death upon return to illicit opioid use.**
- **Know that use of alcohol or benzodiazepines with buprenorphine increases the risk of overdose and death.**
- **Understand the importance of informing providers if they become pregnant.**
- **Tell providers if they are having a procedure that may require pain medication.**

Facts About Buprenorphine

- FDA approved for Opioid Use Disorder treatment in an office-based setting.
- For those with tolerance to opioids as a result of OUD, buprenorphine is often a safe choice.
- Buprenorphine acts as a partial mixed opioid agonist at the μ-receptor and as an antagonist at the κ-receptor. It has a higher affinity for the μ-receptor than other opioids, and it can precipitate withdrawal symptoms in those actively using other opioids.
- It is dosed daily, has a long half-life, and prevents withdrawal in opioid dependent patients.
- Can be in tablet, sublingual film, or injectable formulations.
- Many formulations contain naloxone to prevent injection diversion. This formulation is the preferred treatment medication. The buprenorphine only version is often used with pregnant women to decrease potential fetal exposure to naloxone.
- There is a "ceiling effect" in which further increases above 24mg in dosage does not increase the effects on respiratory or cardiovascular function.
- Buprenorphine should be part of a comprehensive management program that includes psychosocial support. Treatment should not be withheld in the absence of psychosocial support.
- Overdose with buprenorphine in adults is less common, and most likely occurs in individuals without tolerance, or who are using co-occurring substances like alcohol or benzodiazepines.

Checklist for Prescribing Medication for the Treatment of Opioid Use Disorder

1

Assess the need for treatment

For persons diagnosed with an opioid use disorder,* first determine the severity of patient's substance use disorder. Then identify any underlying or co-occurring diseases or conditions, the effect of opioid use on the patient's physical and psychological functioning, and the outcomes of past treatment episodes.

Your assessment should include:

- A patient history
- Ensure that the assessment includes a medical and psychiatric history, a substance use history, and an evaluation of family and psychosocial supports.
- Access the patient's prescription drug use history through the state's Prescription Drug Monitoring Program (PDMP), where available,

to detect unreported use of other medications, such as sedative-hypnotics or alcohol, that may interact adversely with the treatment medications.
- A physical examination that focuses on physical findings related to addiction and its complications.
- Laboratory testing to assess recent opioid use and to screen for use of other drugs. Useful tests include a urine drug screen or other toxicology screen, urine test for alcohol (ethyl glucuronide), liver enzymes, serum bilirubin, serum creatinine, as well as tests for hepatitis B and C and HIV. Providers should not delay treatment initiation while awaiting lab results.

2

Educate the patient about how the medication works and the associated risks and benefits; obtain informed consent; and educate on overdose prevention.

There is potential for relapse & overdose on discontinuation of the medication. Patients should be educated about the effects of using opioids and other drugs while taking the prescribed medication and the potential for overdose if opioid use is resumed after tolerance is lost.

3

Evaluate the need for medically managed withdrawal from opioids

Those starting buprenorphine must be in a state of withdrawal.

4

Address co-occurring disorders

Have an integrated treatment approach to meet the substance use, medical and mental health, and social needs of a patient.

5

Integrate pharmacologic and nonpharmacologic therapies

All medications for the treatment of the opioid use disorder may be prescribed as part of a comprehensive individualized treatment plan that includes counseling and other psychosocial therapies, as well as social support through participation in mutual-help programs.

6

Refer patients for higher levels of care, if necessary

Refer the patient for more intensive or specialized services if office-based treatment with buprenorphine or naltrexone is not effective, or the clinician does not have the resources to meet a particular patient's needs. Providers can find programs in their areas or throughout the United States by using SAMHSA's Behavioral Health Treatment Services Locator at www.findtreatment.samhsa.gov.

*See The Criteria from American Psychiatric Association (2013). Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,. Washington, DC, American Psychiatric Association, page 541.

Induction Considerations

The dose of buprenorphine depends on the severity of withdrawal symptoms, and the history of last opioid use (see flowchart in appendix for dosing advice).

- **Long acting opioids, such as methadone, require at least 48-72 hours since last use before initiating buprenorphine.**
- **Short acting opioids (for example, heroin) require approximately 12 hours since last use for sufficient withdrawal to occur in order to safely initiate treatment. Some opioid such as fentanyl may require greater than 12 hours.**
- **Clinical presentation should guide this decision as individual presentations will vary.**

Determine Withdrawal

Objective withdrawal signs help establish physical dependence

The risk with initiating buprenorphine too soon is that buprenorphine has a very high affinity for the mu receptor and will displace any other opioid on the receptor, thereby causing precipitated opioid withdrawal.

COWS Clinical Opiate Withdrawal Scale

Wesson & Ling, J Psychoactive Drugs. 2003 Apr-Jun;35(2):253-9.

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 Pulse rate 80 or below 1 Pulse rate 81-100 2 Pulse rate 101-120 4 Pulse rate greater than 120	GI Upset: *over last 1/2 hour* 0 No GI symptoms 1 Stomach cramps 2 Nausea or loose stool 3 Vomiting or diarrhea *5* Multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 No report of chills or flushing 1 Subjective report of chills or flushing 2 Flushed or observable moistness on face 3 Beads of sweat *on* brow or face 4 Sweat streaming off face	Tremor *observation of outstretched hands* 0 No tremor 1 Tremor can be felt, but not observed 2 Slight tremor observable 4 Gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 Able to sit still 1 Reports difficulty sifting still, but is able to do so 3 Frequent shifting or extraneous movements of legs/arms 5 Unable to sit still for more than a few seconds	Yawning *Observation during assessment* 0 No yawning 1 Yawning once or twice during assessment 2 Yawning three or more times during assessment 4 Yawning several times/minute
Pupil size 0 Pupils pinned or normal size for room light 1 Pupils possibly larger than normal for room light 2 Pupils moderately dilated *5* Pupils so dilated that only the rim of the iris is visible	Anxiety or irritability 0 None 1 Patient reports increasing irritability or anxiousness 2 Patient obviously irritable anxious 4 Patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 Not present 1 Mild diffuse discomfort 2 Patient reports severe diffuse aching of joints/ muscles 4 Patient is rubbing joints or muscles and is unable to sit still because of discomfort	Gooseflesh skin 0 Skin is smooth 3 Piloerrection of skin can be felt or hairs standing up on arms *5* Prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 Not present 1 Nasal stuffiness or unusually moist eyes 2 Nose running or tearing 4 Nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing Assessment:_____

Score: 5-12 mild; 13-24 moderate; 25-36 moderately severe; more than 36 = severe withdrawal

Information on Precipitated Withdrawal

- Precipitated withdrawal can occur due to replacement of full opioid receptor agonist (heroin, fentanyl, or morphine) with a partial agonist that binds with a higher affinity (Buprenorphine).
- Symptoms are similar to opiate withdrawal.
- Avoid by ensuring adequate withdrawal before induction (COWS > 12; Fentanyl may require higher COWS score and lower initial dosing), starting Buprenorphine at a lower dose (2.0mg/0.5 mg), and reassessing more frequently.
- Should precipitated withdrawal occur, treatment includes:
  - Providing support and information to the patient
  - Management of acute symptoms
  - Avoid the use of benzodiazepines
  - Encourage the patient to try induction again soon

Buprenorphine Side Effects

- **Buprenorphine's side effects may be less intense than those of full agonists. Otherwise, they resemble those of other mu-opioid agonists.**
- **Possible side effects include: Oral numbness, constipation, tongue pain, oral mucosal erythema, vomiting, intoxication, disturbance in attention, palpitations, insomnia, opioid withdrawal syndrome, sweating, and blurred vision**
- **Buprenorphine FDA labels list all potential side effects**

Co-prescribing of overdose reversal agents such as Naloxone is also recommended

Maintenance Therapy

Goal = once-daily dosing, no withdrawal between doses. Ideally, average dosing does not exceed 16 mg/4 mg (See flowchart in appendix)

- **Check PDMP regularly to ensure prescriptions are filled, and to check other prescriptions.**
- **Order urine drug testing (UDT) and consider confirmatory testing for unexpected results. UDT can facilitate open communication to change behavior.**
- **Assess for readiness for extended take-home dosing**

Psychosocial Therapies

- **Although people often focus on the role of medications in MAT, counseling and behavioral therapies that address psychological and social needs may also be included in treatment. To find treatment, please consult www.findtreatment.gov.**

Diversion

Diversion is defined as the unauthorized rerouting or misappropriation of prescription medication to someone other than for whom it was intended (including sharing or selling a prescribed medication); misuse includes taking medication in a manner, by route or by dose, other than prescribed.

How can providers minimize diversion risk?

1. Early in treatment patients should be seen often, and less frequently only when the provider determines they are doing well.
2. Providers should inquire about safe and locked storage of medications to avoid theft or inadvertent use, especially by children. Patients must agree to safe storage of their medication. Counsel patients about acquiring locked devices and avoiding storage in parts of the home frequented by visitors.
3. Limit medication supply. Prescribe an appropriate amount of medications until the next visit. Do not routinely provide an additional supply "just in case."
4. Use buprenorphine/naloxone combination products when medically indicated. Reserve daily buprenorphine monoproducts for pregnant patients and/or patients who could not afford treatment if the combination product were required.
5. Counsel patients on taking their medication as instructed and not sharing medication.
6. Ensure that the patient understands the practice's treatment agreement and prescription policies. Providers can utilize the sample treatment agreement in SAMHSA's TIP 63, Page 3-78. A treatment agreement and other documentation are clear about policies regarding number of doses in each prescription, refills, and rules on "lost" prescriptions.
7. Directly observe ingestion randomly when diversion is suspected.
8. Providers should order random urine drug testing to check for other drugs and for metabolites of buprenorphine. Providers should also consider periodic point of care testing.
9. Doctors should schedule unannounced pill/film counts. Periodically ask patients to bring in their medication containers for a pill/film count.
10. Providers should make inquiries with the Prescription Drug Monitoring program in their state to ensure that prescriptions are filled appropriately and to detect prescriptions from other providers.
11. Early in treatment, providers can ask the patient to sign a release of information for a trusted community support individual, such as a family member or spouse, for the purpose of communicating treatment concerns including diversion.

What should I do if a patient diverts or misuses the medication?

- Misuse or diversion doesn't mean automatic discharge from the practice.
- Document and describe the misuse and diversion incident. Also document the clinical thinking that supports the clinical response, which should be aimed at minimizing future risk of diversion while still supporting the use of MAT.
- Strongly consider smaller supplies of medication and supervised dosing.
- Treatment structure may need to be altered, including more frequent appointments, supervised administration, and increased psychosocial support.
- When directly observed doses in the office are not practical, short prescription time spans can be considered.
- In situations where diversion is detected, open communication with the patient is critical. Providers may consider injectable and implantable buprenorphine to reduce diversion, once verified.

DSM-5 Criteria for Diagnosis of Opioid Use Disorder

Diagnostic Criteria*
These criteria not considered to be met for those individuals taking opioids solely under appropriate medical supervision.

Check all that apply

	Opioids are often taken in larger amounts or over a longer period of time than intended.
	There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
	A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
	Craving, or a strong desire to use opioids.
	Recurrent opioid use resulting in failure to fulfill major role obligations at work, school or home.
	Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
	Important social, occupational or recreational activities are given up or reduced because of opioid use.
	Recurrent opioid use in situations in which it is physically hazardous
	Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.
	*Tolerance, as defined by either of the following: (a) a need for markedly increased amounts of opioids to achieve intoxication or desired effect (b) markedly diminished effect with continued use of the same amount of an opioid
	*Withdrawal, as manifested by either of the following: (a) the characteristic opioid withdrawal syndrome (b) the same (or a closely related) substance are taken to relieve or avoid withdrawal symptoms

Total Number Boxes Checked: _____

Severity: **Mild**: 2-3 symptoms. **Moderate**: 4-5 symptoms. **Severe**: 6 or more symptoms

*Criteria from American Psychiatric Association (2013). Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,. Washington, DC, American Psychiatric Association page 541. For use outside of IT MATTTRs Colorado, please contact ITMATTTRsColorado@ucdenver.edu

Important Considerations: Buprenorphine/Naloxone Dosing

- Tablets/film may be split if necessary
- May take up to 10 min to dissolve completely (no talking, smoking, or swallowing at this time)
- Absorption better with moistened mouth

SUBOXONE sublingual tablets, including generic equivalents	Corresponding dosage strength of ZUBSOLV sublingual tablets
One 2 mg/0.5 mg buprenorphine/naloxone sublingual tablet	One 1.4 mg/0.36 mg ZUBSOLV sublingual tablet
One 8 mg/2 mg buprenorphine/naloxone sublingual tablet	One 5.7 mg/1.4 mg ZUBSOLV sublingual tablet
12 mg/3 mg buprenorphine/naloxone taken as: • One 8 mg/2 mg sublingual buprenorphine/naloxone tablet AND • Two 2 mg/0.5 mg sublingual buprenorphine/naloxone tablets	One 8.6 mg/2.1 mg ZUBSOLV sublingual tablet
16 mg/4 mg buprenorphine/naloxone taken as: • Two 8 mg/2 mg sublingual buprenorphine/naloxone tablets	One 11.4 mg/2.9 mg ZUBSOLV sublingual tablet

Algorithm for In-Office Induction (for home induction prescriptions may be given)

Initial Assessment

History and Physical
Concurrent medical issues and substance use
Medication history (with review of the PDMP)
Allergies
Mental health status and social history
Social history

Lab Workup
CBC, CMP, HIV, hepatitis A, B & C
Urine drug testing, and
consider pregnancy & STD screen

Referral
Refer to specialists as indicated
Refer to counseling
Refer to case management

Provide Patient Education
Treatment goals and medication education
Side-effects
How to store medication at home
Patient should update provider with new medications or other changes
Establish open communication

Discuss Safety Concerns
Altered tolerance to opioids on buprenorphine/suboxone
No co-administration of alcohol or benzodiazepines
Alert provider if planning pregnancy or pregnant
Planned procedures that may require opiate analgesia

Day One (Induction)

Last opioid use >6-12 hours ago → Moderate Withdrawal (COWS >12) → **Give First Dose of Buprenorphine/Naloxone (2 – 4mg)** → After 1 Hour: Monitor for precipitated withdrawal; If present, treat symptoms; Attempt induction 24 hours later

2 – 4 Hours Later: Withdrawal Symptoms Relieved?
- No → Give further 2 – 4mg dose
- Yes → Prescribe one dose; Return to clinic on day two for observation and review

2 – 4 Hours Later: Withdrawal Symptoms Relieved?
- No → Give further 2 – 4mg dose, up to 8mg total
- Yes → Prescribe one dose; Return to clinic on day two for observation and review

Day Two

Adequate symptom relief achieved After induction?
- No → Give day 1 dose and additional 2 – 4mg up to 16mg total
- Yes → Induction Complete - Give induction dose as ongoing dose, and review in 1 day

2 – 4 Hours Later: Withdrawal Symptoms Relieved?
- No → Give further 2 – 4mg dose, up to 16mg
- Yes → Induction Complete - Give induction dose as ongoing dose, and review in 1 day

Maintenance

Patient Stable On Current Dose?
- No → Consider further 2 – 4mg dose, up to 16mg
- Yes → Continue once daily dosing with regular review

Perform monthly urinary drug screens, and check PDMP regularly. Ensure on-going attendance at counseling and support groups. When patient stable on medication, assess readiness for take-home dosing