Criteria for Use of Buprenorphine/Naloxone and Buprenorphine Sublingual Tablets

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These updated criteria are based on the best clinical evidence currently available. The recommendations in this document are dynamic, and will be revised as new clinical information becomes available. This guidance is intended to assist practitioners in providing consistent, high quality, cost effective drug therapy. These criteria are not intended to interfere with clinical judgment; the clinician must ultimately decide the course of therapy based on individual patient situations.

INTRODUCTION

Buprenorphine is a Schedule III partial opioid agonist that was approved by the FDA for the treatment of opioid dependence on October 8th, 2002. It is the first agent available in the U.S. for office-based treatment of opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA 2000), which allows qualified physicians to prescribe Schedule III to V drugs for treatment of opioid dependence in an office setting. The main objective of this law was to expand access to treatment for opioid dependence by incorporating the management of opioid dependence into mainstream medicine. These criteria were updated to reflect evidence that has become available since the original criteria were prepared. The ongoing implementation of buprenorphine in the VA continues to require careful consideration and planning.

VA CRITERIA FOR USE

Provider criteria

The provider must

- □ be a *qualifying physician* as defined by DATA 2000 (page 3). Individual physicians are limited to treating 30 patients under original waivers and 100 patients under second waivers.
- □ meet all SAMHSA and DEA notification and registration requirements for the Opioid Treatment Waiver Program (available at: http://www.dpt.samhsa.gov),

AND either

- □ have experience in addiction medicine or addiction psychiatry;

OR

- □ if inexperienced in addiction medicine, treat patients in consultation with a provider in the Physician Clinical Support System (PCSS) mentoring program (http://www.pcssmentor.org/). (The inexperienced clinician should consult the PCSS mentor early in therapy; e.g., during the induction phase of therapy, and the PCSS provider should preferably be familiar with the VA criteria for use of sublingual buprenorphine.)

Notes

Although physicians are not required to write a valid waiver identification number on each prescription in the VA, facilities must set up a process to verify that providers are authorized to prescribe buprenorphine for treatment of opioid dependence or to restrict buprenorphine prescribing to only authorized physicians.

Physicians should refer patients to appropriate ancillary services in a timely fashion.

Nonphysicians are prohibited from prescribing buprenorphine.

It is the physician's responsibility to make sure the necessary resources (such as referrals for ancillary treatment, cross-coverage by a qualified physician, urine drug screening, and secure medication storage) are in place before prescribing buprenorphine. The physician may delegate these responsibilities to other staff members but remains responsible for assuring that appropriate clinical care is delivered.

Similarly, *before* converting a stable patient from methadone to buprenorphine in accordance with Patient Criterion #2, the physician should make sure a qualified physician is available to accept the patient upon the patient's transition from an OAT center to primary care or outpatient psychiatry.

Patient criteria

Sublingual buprenorphine is indicated for opioid agonist treatment of opioid dependence (DSM-IV diagnosis), including medically supervised withdrawal, in

1) New patients not currently receiving OAT

   AND who meet at least one of the following 3 criteria:

   - □ Do not have timely access to a VA-supported OAT center.
   - □ Do not meet regulatory criteria for treatment in an OAT program.
   - □ Will have difficulty adhering to scheduled visits at a VA-supported OAT program (e.g., because of restrictive clinic hours).

2) Appropriately selected patients on stable methadone maintenance who have difficulty adhering to scheduled visits at a VA-supported OAT center or may not need close supervision. Opioid treatment programs should determine the criteria for appropriate selection of these patients, and the criteria should take into consideration such factors as the patient's psychosocial adjustment, lifestyle stability, job stability, level of physiologic opioid dependence, and need for higher doses of methadone (e.g., ≥ 80 mg daily) (see discussion on conversion doses under *Patients physically dependent on methadone or other long-acting opioids*, page 5).

3) Patients who have a documented severe, uncontrollable adverse effect or true hypersensitivity to methadone.

Uses Not Supported by Current Evidence

1) Off-label use solely for pain management
2) Use of sublingual buprenorphine primarily for analgesia in patients for whom buprenorphine was originally started for treatment of opioid dependence (DSM-IV)

See also *Uses Not Supported by Current Evidence* **on page 4.**

Discontinuation Criteria

1) *Discontinuation as a goal of therapy*. While many patients may require long-term maintenance therapy, after a period of social, medical, psychiatric, and substance abstinence stability, clinicians and patients may consider a monitored taper of buprenorphine. Individual response to therapy should determine when to attempt stopping opioid substitution therapy.
2) *Discontinuation for other reasons*. Buprenorphine therapy should be stopped if the patient:
   - □ Misuses, abuses, or diverts buprenorphine or other controlled prescription medications OR
   - □ Is noncompliant with required supportive care or other ancillary services related to therapy for opioid dependence (DSM-IV) OR
   - □ Does not experience suppression of physiologic signs and symptoms of withdrawal with buprenorphine 32 mg daily *after the induction phase*. In this situation, buprenorphine should be stopped, the treatment plan re-evaluated, and a more intensive level of care considered. Inadequate response during the *induction* phase and failure to obtain negative urine drug screens or abstinence should not be used as criteria for discontinuation of buprenorphine.

Notes

In general, in the VA, methadone should remain the substitution treatment of choice for patients needing opioid agonist maintenance therapy.

The use of buprenorphine and buprenorphine/naloxone for discontinuation of methadone maintenance therapy may be considered on a case-by-case basis

DATA 2000 definition of qualifying physician

Physicians who satisfy conditions 1 through 3 below.

1. Meet one or more of the following training requirements:
   - Hold a subspecialty board certification in addiction psychiatry from the American Board of Medical Specialties.
   - Hold an addiction certification from the American Society of Addiction Medicine.
   - Hold a subspecialty board certification in Addiction Medicine from the American Osteopathic Association.
   - Have completed not less than 8 hours of authorized training on the treatment or management of opioid-dependent patients. This training may include classroom situations, seminars at professional society meetings, electronic communications, or other media. The American Society of Addiction Medicine, American Academy of Addiction Psychiatry, American Medical Association, American Osteopathic Association, and the American Psychiatric Association are all authorized to provide this training.
   - Have participated as an investigator in one or more clinical trials leading to the approval of a narcotic drug in schedule III, IV, or V for maintenance or detoxification treatment, as demonstrated by a statement submitted to the Secretary of Health and Human Services by the sponsor of such approved drug.
   - Have such other training or experience as the State medical licensing board (of the State in which the physician will provide maintenance or detoxification treatment) considers to demonstrate the ability of the physician to treat and manage opioid-dependent patients.
   - Have such other training or experience as the Secretary considers to demonstrate the ability of the physician to treat and manage opioid-dependent patients. Any criteria of the Secretary under this subclause shall be established by regulation. Any such criteria are effective only for 3 years after the date on which the criteria are promulgated, but may be extended for such additional discrete 3-year periods as the Secretary considers appropriate for purposes of this subclause. Such an extension of criteria may only be effectuated through a statement published in the Federal Register by the Secretary during the 30-day period preceding the end of the 3-year period involved.
2. Have the capacity to provide or to refer patients for necessary ancillary services, such as psychosocial therapy.
3. Agree to treat no more than 30 patients at any one time during the first year after receiving the original waiver and agree to treat no more than 100 patients at any one time thereafter if a second waiver to treat up to 100 patients has been applied for through SAMHSA/CSAT. Under an amendment to DATA 2000 in December 2006, physicians may request an increase in their patient limit to 100 no sooner than 1 year after the original waiver was approved, if demand for buprenorphine in their practice warrants an increase in the patient limit.

Further information on DATA 2000 and physician qualifying requirements can be obtained at http://buprenorphine.samhsa.gov. The VA's Centers of Excellence in Substance Abuse Treatment and Education (CESATEs) are also available for advice and consultation on buprenorphine.

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USES NOT SUPPORTED BY CURRENT EVIDENCE

Pain management. The off-label use of sublingual buprenorphine solely for pain management cannot be supported at the doses available in the U.S. The doses used for opioid maintenance therapy (minimum 2 mg) are generally higher than those used for pain and given in a single daily dose while analgesic doses have usually been given in divided daily doses (analgesic duration: 6 to 9 hours). In the U.S., buprenorphine sublingual tablets in strengths lower than 2 mg are not available and the tablets are not scored. There is a risk of intoxication if a patient not currently tolerant to opioids were to receive a 2-mg dose. The optimal dose, the adequacy of analgesia with once daily dosing, and the superiority of buprenorphine over full opioid agonists have not been established. Patients who require therapy for acute or chronic pain and who are not being treated for addiction should be managed using standard analgesic treatments.

Buprenorphine-maintained patients with pain may experience pain relief due to buprenorphine, but the sublingual formulation of the drug should generally not be used primarily for analgesia. These patients should be treated with a trial of non-opioid analgesics while continuing buprenorphine maintenance. If additional opioid analgesia is required for either acute or chronic pain, then buprenorphine should be discontinued. It should be noted that buprenorphine may block or displace other opioid agonists from receptor sites and can precipitate withdrawal. When buprenorphine is to be restarted, recommended induction doses should be initiated at least 12 hours after the final dose of the opioid analgesic to avoid precipitating withdrawal.

There are no studies that have examined the analgesic effects of buprenorphine in patients on opioid substitution therapy for a DSM diagnosis of opioid dependence. It should be noted that the combined use of buprenorphine and a full agonist could result in precipitated abstinence from the full agonist. The once daily administration of sublingual buprenorphine as recommended for opioid maintenance therapy may provide insufficient pain relief. The optimal dose of sublingual buprenorphine in the simultaneous management of both opioid dependence and pain is not known.

DOSAGE AND ADMINISTRATION

Buprenorphine is available as a single drug in 2- and 8-mg tablets and as a combination of buprenorphine and naloxone in 2 mg/0.5 mg and 8 mg/2 mg tablets. Naloxone was added to discourage the intravenous misuse of buprenorphine. When taken orally or sublingually, naloxone has poor bioavailability, although blood concentrations of the drug are detectable. If given sublingually to opioid-dependent individuals after the opioid agonist effects have abated, naloxone is unlikely to produce clinically relevant effects. However, if sublingual naloxone is given to these individuals before the agonist effects of the opioid have diminished, precipitated withdrawal may occur. Buprenorphine/naloxone, when misused intravenously, is highly likely to precipitate intense withdrawal symptoms in individuals dependent on other opioid agonists.

> In every clinical situation, except when the patient is pregnant or has a documented intolerance or hypersensitivity to naloxone, the preferred formulation of buprenorphine is the buprenorphine/naloxone combination. Patients who are pregnant should be advised to be in an OAT program and use methadone as their treatment. Patients who are pregnant and cannot attend to an OAT program should use buprenorphine and not the buprenorphine/naloxone combination.
>
> *Hereinafter, buprenorphine refers to the buprenorphine/naloxone combination or the monodrug product (in the case of pregnancy or naloxone intolerance/hypersensitivity), unless specifically indicated as either formulation.*

If unsupervised administration of buprenorphine monotherapy is to be given for an extended period, precautions should be taken to minimize the possibility of diversion by experienced opioid addicts and the justification for its use should be documented.

Buprenorphine is generally administered once daily. More frequent administration of divided daily doses may also be used, and less than daily dosing (e.g., three times weekly) is possible for maintenance therapy. The tablets must be taken sublingually, allowing 5 to 10 minutes for the tablets to completely dissolve. Oral administration of the tablets reduces the bioavailability of the drug.

Dosing for opioid agonist substitution (maintenance) therapy

A brief summary of dosing recommendations are provided here. For more detailed instructions on dosage and administration of buprenorphine, consult appropriate references such as the *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction* Treatment Improvement Protocol (TIP) 40 available from the Center for Substance Abuse Treatment (CSAT) (see http://buprenorphine.samhsa.gov/publications.html).

The use of buprenorphine should be part of a comprehensive treatment plan that includes psychosocial treatment

modalities. As with other controlled drugs used in the treatment of opioid dependence, providers should take appropriate precautions to prevent the diversion and abuse of buprenorphine.

Induction

For induction, the use of buprenorphine/naloxone combination is recommended except, if the patient is pregnant or has intolerance or hypersensitivity to naloxone, then the buprenorphine monodrug formulation is recommended. It is important to start induction with buprenorphine when signs of early opioid withdrawal have appeared, taking into consideration the type of opioid dependence (i.e., short- or long-acting opioid).

Day 1

Patients physically dependent on heroin or other short-acting opioids

Initiate buprenorphine at least 4 hours, preferably at least 12 to 24 hours, after the patient last used opioids or **preferably when the patient exhibits definite signs of withdrawal**. The maximal recommended induction dose of buprenorphine is 8 mg on day 1 (given at once or in divided doses as clinically indicated).

Patients physically dependent on methadone or other long-acting opioids

The criteria for use of sublingual buprenorphine require that a patient either (1) be an appropriate selected patient on stable methadone who has difficult adhering to scheduled visits at a VA-supported OAT center or may not need close supervision; or (2) have a documented severe, uncontrollable adverse effect or true hypersensitivity to methadone before the physician considers switching to buprenorphine. Patients who are stable on methadone maintenance and who do not have a compelling reason to switch therapy should continue maintenance on methadone.

Limited controlled experience with the conversion of methadone-maintained patients to buprenorphine suggests that precipitated withdrawal symptoms are possible, particularly in patients maintained on methadone doses greater than 30 to 40 mg daily or when buprenorphine is started shortly after the last methadone dose. Therefore, to avoid precipitating withdrawal symptoms when conversion from methadone or other long-acting opioid to buprenorphine, it is recommended that the dose of the long-acting opioid be tapered to the equivalent of methadone 30 to 40 mg daily or less and the last dose of methadone be taken at least 24 hours before starting buprenorphine. (This *conversion* dose of methadone should not be considered as the dose *equivalent* to a starting dose of buprenorphine.) The induction dose of buprenorphine should start at a minimum of 2 mg, repeating doses as needed up to 8 mg in 24 hours.

Day 2 and onward

If no serious adverse effects or evidence of withdrawal emerge within two hours of the administration of a dose, the patient is ready to move on to the next step in induction. On day 2, the dose should be advanced by 2 to 4 mg. Adjust the buprenorphine dose in increments or decrements of 2 or 4 mg per day to a level that holds the patient in treatment and suppresses opioid withdrawal effects. The recommended target dose of buprenorphine is 12 to 16 mg per day to be achieved within the first week, unless adverse effects occur. Should adverse effects occur, the dose of buprenorphine should be maintained or decreased until these adverse effects abate. If the patient continue to have problems adjusting to buprenorphine (experiencing withdrawal symptoms or feeling compelled to use illicit drugs), the dosage may need to be increased more rapidly.

Physicians should attempt to achieve an adequate maintenance dose, titrated to clinical effectiveness, as quickly as possible to prevent the patient from developing undue opioid withdrawal symptoms. In some studies, gradual induction over several days led to a high rate of dropouts during the induction period. In one study, buprenorphine 8 mg was given on day 1 and 16 mg on day 2. Induction was accomplished over 3 to 4 days depending on the target dose.[1]

Stabilization (approximately one to two months)

The induction phase is completed and the stabilization phase has begun when the patient has discontinued or markedly reduced the use of illicit drugs, is experiencing no withdrawal symptoms, is experiencing minimal or no side effects, and no longer has cravings for the drug of abuse. Dosage adjustments may still be necessary during this period. Doses may be increased in 2- to 4-mg increments per week until stabilization is achieved. The majority of patients should stabilize on doses between 12 to 16 mg, but doses can be increased up to 32 mg.

Maintenance

For induction and stabilization, once daily dosing of buprenorphine is preferable. For maintenance, once daily dosing has also usually been used; however, less frequent dosing of buprenorphine is possible due to the drug's long duration of action.

Alternate-day dosing,[2-6] thrice weekly,[7-9,10] twice weekly,[10] every-third-day,[6,9] and every-fourth-day[9] dosing of buprenorphine have been shown to be as effective as daily dosing.. In general, the same total equivalent weekly dose is given in divided doses over extended dosing intervals.

Most of the published trials evaluating extended dosing intervals have used buprenorphine alone.[2-9,10] A single trial has investigated the buprenorphine/naloxone combination.[3] Physicians are advised to consult a specialist in opioid dependence treatment before deciding to use extended dosing intervals with buprenorphine/naloxone.

Dosage reduction and treatment discontinuation

The decision to discontinue treatment with buprenorphine or buprenorphine/naloxone should be made as part of a comprehensive treatment plan in partnership with the patient. The best method of discontinuing treatment has not been determined. Patients may be more likely to complete withdrawal using a gradual rather than rapid dosage reduction.[11] Withdrawal symptoms upon abrupt discontinuation or rapid taper of buprenorphine tend to be delayed and milder than with full opioid agonists.

Dosing for medically supervised withdrawal (detoxification)

The optimal sublingual buprenorphine (tablet) dose for detoxification is unclear. For short-term medically supervised withdrawal, the only available comparative evaluation of optimal buprenorphine dosing suggests that a 5-day course of a high-dose (8 mg/8 mg/8 mg/4 mg/2 mg) regimen may have a slight advantage over a low-dose (2 mg/4 mg/8 mg/4 mg/2 mg) regimen (Grade I)[12] Combination buprenorphine / naloxone has also been used for medically supervised withdrawal in a 13-day treatment course.[13] Buprenorphine/naloxone was started at 4/1 to 8/2 mg on day 1, 12/3 mg on day 2, 16/4 mg on day 3, and followed by a stepwise reduction to 2/0.5 mg on day 13.

Other dosing considerations in medically supervised withdrawal are available in the ***Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction*** **TIP 40** (page 58 of hard copy; page 85/198 in PDF), available at **http://buprenorphine.samhsa.gov/publications.html** .

Dosing in special populations

Hepatic disease: Plasma concentrations of buprenorphine and naloxone, which are both extensively metabolized, are expected to be higher in patients with moderate and severe hepatic impairment. Dosage should be adjusted and the patient monitored for symptoms of precipitated withdrawal.

Renal disease: No specific recommendations for dosage adjustment are given. There have been no differences in buprenorphine pharmacokinetics in dialysis and normal individuals. The pharmacokinetics of naloxone in renal failure are unknown.

Pregnancy: The buprenorphine monotherapy formulation, rather than the buprenorphine / naloxone combination, is recommended in pregnant women. There are no adequately designed studies of either buprenorphine (pregnancy category C) or naloxone (category B) in pregnant women.

Elderly: Data are lacking on the use of buprenorphine in individuals 60 years or older. Use caution when dosing buprenorphine in the elderly, particularly during induction.

Patients admitted to hospital: If a patient has been admitted to hospital for reasons other than treatment of opioid dependence, physicians without a waiver may maintain or detoxify the patient with buprenorphine (or methadone) during the hospital stay (21 U.S.C. Section 823 (g)(2) and 21 CFR 1306.07). In this situation, consultation with a qualified physician or addiction specialist should be obtained. If a patient is admitted to hospital primarily for treatment of opioid dependence, then only a DATA-waivered physician can order buprenorphine treatment.

Quantity Prescribed

Prescriptions for buprenorphine should have no refills and should be limited to a 7-day supply during the induction period and a 30-day supply at any time. Exceeding the 30-day supply limit may be considered only under extraordinary circumstances.

MONITORING

Patients must be closely supervised and monitored at the clinic for several hours after administration of each induction dose. Therefore, appropriate space and trained nursing support are needed to manage patients during the induction phase. Supervised administration of the initial maintenance doses is also recommended.

As patients improve, unsupervised administration and take-home supplies of buprenorphine may be considered. Consult appropriate references for more detailed recommendations on monitoring frequency.

Hepatic events ranging from cytolytic hepatitis to hepatic failure have been observed in addicts during treatment with buprenorphine. A causal relationship to buprenorphine is unclear. Pre-existing liver enzyme abnormalities, viral hepatitis, hepatotoxic drugs, and illicit intravenous drug use may be causal or contributing factors in the development of hepatic events. Liver enzyme tests should be checked at baseline and periodically thereafter.

The potential of buprenorphine to prolong the QT interval has been demonstrated in vitro[14] but there have been no published clinical reports of buprenorphine-related cardiac arrhythmias or QT prolongation. Electrocardiographic monitoring is not recommended at this time.

DRUG INTERACTIONS

CYP 3A4 inhibitors or inducers: If CYP 3A4 inhibitors or inducers are co-administered with buprenorphine, patients should be closely monitored and dosage adjusted if necessary. Increased plasma concentrations of buprenorphine have been observed when it was co-administered with the potent CYP 3A4 inhibitor, ketoconazole. Dose reduction may be indicated if buprenorphine is given with CYP 3A4 inhibitors such as azole antifungal agents (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), HIV protease inhibitors (e.g., ritonavir, indinavir, and saquinavir), the antidepressant, nefazodone, or grapefruit juice. The interaction between buprenorphine and CYP 3A4 inducers (e.g., phenobarbital, carbamazepine, phenytoin, and rifampicin) has not been studied.

CNS depressants: Patients who receive buprenorphine with other central nervous system (CNS) depressants (e.g., other opioid analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative-hypnotics, or alcohol) may experience increased CNS depression. Consider reducing the dose of one or both agents if the two agents are co-administered. Buprenorphine tablets, taken orally or sublingually or by injection, has been implicated in fatal drug abuse-related overdoses, particularly when used with benzodiazepines.[15-17]

COST

The VA acquisition cost for combination buprenorphine/naloxone is less than that of the buprenorphine monodrug product (Table 1). The manufacturer priced the combination product at an advantage to encourage its use over the monodrug product for reducing potential buprenorphine abuse. FSS prices for buprenorphine are available only through direct purchase from the manufacturer.

Table 1 Drug acquisition costs for opioid agonist treatments

	Buprenorphine			Buprenorphine/Naloxone			Methadone			
	2 mg/d tab	8 mg/d tab	16 mg/d tab	2/0.5 mg/d tab	8/2 mg/d tab	16/4 mg/d tab	20 mg/d disp tab	80 mg/d disp tab	20 mg/d conc	80 mg/d conc
Cost/Dose	$1.82	$3.42	$6.84	$1.62	$2.81	$5.62	$0.12	$0.48	$0.08	$0.32
Cost/Mo	$54.60	$102.60	$205.20	$49.60	$84.30	$168.60	$3.60	$14.40	$2.40	$9.60

These are lowest available VA prices **(effective** 28 November 2005). FSS prices for buprenorphine (shown) are available only by **direct purchase**.

Further information on buprenorphine can be found in the *National PBM Drug Monograph: Buprenorphine and Buprenorphine/Naloxone* available at: www.pbm.va.gov or vaww.pbm.va.gov.

Evidence Table

Strength of Recommendation and Evidence Rating	References	Quality of Evidence	Overall Quality
Grade A (always indicated and acceptable):			
Sublingual buprenorphine for opioid agonist treatment of opioid dependence (DSM-IV diagnosis), including medically supervised withdrawal	Gowing (2005)[18] Mattlick (2005)[19]	Good Good	Good
Grade B (may be useful/ effective):			
No recommendations			
Grade C (may be considered):			
Sublingual buprenorphine for discontinuation of methadone maintenance therapy	Breen (2003)[20] Janiri (1994)[21] Levin (1997)[22]	Fair Fair Poor	Fair
Sublingual buprenorphine for selected patients on stable methadone maintenance	Greenwald (2003)[23] Glasper (2005)[24]	Poor Poor	Poor
Grade D (may not be useful/ effective; possibly harmful):			
No recommendations			
Grade I (insufficient evidence to recommend for or against):			
Sublingual buprenorphine (high-dose, tablets) for pain management in patients with or without opioid dependence (DSM-IV)	Ray (2004)[25] Malinoff (2005)[26]	Poor Poor	Poor

Evidence rating scheme based on the methods used by the third U.S. Preventive Services Task Force[27]

Updated November 2005. Contact person: F. Goodman

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