

GMC Guidelines for Buprenorphine-Naloxone (Suboxone®) Prescribing

Basic Principles

- Buprenorphine-naloxone is a partial opioid agonist that is approved for treatment of opioid dependence or severe opioid use disorders (**ICD-10 code: F11.10 or F11.20**).
- **YOU MUST HAVE A SPECIAL X-license** in order to prescribe buprenorphine-naloxone. In accordance with federal statute, the Drug Addiction Treatment Act of 2000 (DATA 2000), physicians must have completed 8 hours of approved training to qualify for a waiver. You must also have filed a Notification of Intent to prescribe to SAMHSA. This form can be found on the SAMHSA web site (www.buprenorphine.samhsa.gov). Providers are limited to a total of **30 patients** in the first year; after that they may increase to 100 patients after informing CSAT (www.buprenorphine.samhsa.gov/howto.html).
- Buprenorphine-naloxone is a **schedule 3** medication meaning it can be called it, manually faxed (with an ink signature), or written on a secure prescription pad (recommended). *Please write your x-license number at the top of the prescription if it is not printed on the prescription.* Refills CAN be given for schedule 3 medications but this is discouraged until patient has been stable for ≥ 6 months. You must also enter the buprenorphine-naloxone prescription information into ECW even though it cannot be faxed.

Prescribing Buprenorphine-Naloxone in 1M

- It is generally advised that patients start on buprenorphine-naloxone at the **OBIC** (Outpatient Buprenorphine Induction Clinic; Intakes #415-552-6242, Provider Line #415-503-4785). Once on a stable dose, the patient can transfer the buprenorphine-naloxone prescribing to GMC.
- The 1M-Fine People's Clinic buprenorphine-naloxone clinic days will be on **Tuesday and Thursday**. *Priority should be given to schedule patients for Thursday afternoon appointments.* Dr. xx will supervise Thursday afternoon prescriptions (Dr. yy as back-up), and Dr. zz will supervise Tuesday afternoon prescriptions (Dr. xx as back-up).
- Experienced providers deciding to begin buprenorphine are recommended to do the following lab work prior to starting: *basic metabolic panel, CBC, LFTs, pregnancy test, urine drug screen, HIV, and hepatitis screening.*
- For patients receiving buprenorphine-naloxone from GMC, the following must be done:
 - Confirm that patient has a **diagnosis of opioid dependence or a severe opioid use disorder**. See DSM-5 check-list below.
 - *Patients with active alcohol, benzodiazepine, and/or barbiturate use disorders and psychiatric instability are generally NOT considered good candidates for treatment.*
 - Sign and review **informed consent** document (see below)
 - Ensure the patient can do **safe storage** of the medication.
 - Enter all patients prescriptions in a **provider log** (see below). This should be saved to the prescriber's personal drive on 1M clinic computers and be easily accessible if inspected (the DEA may request *3 months* of prescribing records)
 - **Monitoring patients**
 - urine drug screen and urine buprenorphine q month
 - LFTs q 6 months
 - Counseling with behavioral health

Informed Consent for Buprenorphine-Naloxone

As a participant in the buprenorphine protocol for treatment of opioid abuse and dependence, I freely and voluntarily agree to accept this treatment agreement/contract, as follows:

1. I agree to keep, and be on time to, all my scheduled appointments with the doctor and his/her assistant.
2. I agree to conduct myself in a courteous manner in the physician's office.
3. I agree not to arrive at the office intoxicated or under the influence of drugs. If I do, the doctor will not see me, and I will not be given any medication until my next scheduled appointment.
4. I agree not to sell, share, or give any of my medication to another individual. I understand that such mishandling of my medication is a serious violation of this agreement and would result in my treatment being terminated without recourse for appeal.
5. I agree not to deal, steal, or conduct any other illegal or disruptive activities in the doctor's office.
6. I agree that my medication (or prescriptions) can be given to me only at my regular office visits. Any missed office visits will result in my not being able to get medication until the next scheduled visit.
7. I agree that the medication I receive is my responsibility and that I will keep it in a safe, secure place.
8. I agree that lost medication will not be replaced regardless of the reasons for such loss.
9. I agree not to obtain medications from any physicians, pharmacies, or other sources without informing my treating physician.
10. I understand that mixing buprenorphine with other medications, especially benzodiazepines such as Valium® and other drugs of abuse, can be dangerous. I also understand that a number of deaths have been reported among individuals mixing buprenorphine with benzodiazepines.
11. I agree to take my medication as the doctor has instructed and not to alter the way I take my medication without first consulting the doctor.
12. I understand that medication alone is not sufficient treatment for my disease, and I agree to participate in the patient education and relapse prevention programs, as provided, to assist me in my treatment.

Name

Signature

Date

Provider Name: _____

Patient's Name:	Date of Birth:	MRN:	
Worksheet for DSM-5 criteria for diagnosis of opiate use disorder			
Diagnostic Criteria* (Opioid Use Disorder requires at least 2 within 12 month period)	Meets criteria		Notes/supporting information
	Yes	No	
1. Opioids are often taken in larger amounts or over a longer period of time than intended.			
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.			
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.			
4. Craving, or a strong desire to use opioids.			
5. Recurrent opioid use resulting in failure to fulfill major role obligations at work, school or home.			
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.			
7. Important social, occupational or recreational activities are given up or reduced because of opioid use.			
8. Recurrent opioid use in situations in which it is physically hazardous			
9. 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.			
10. *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			
11. *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			

• This criterion is not considered to be met for those individuals taking opioids solely under appropriate medical supervision.

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

Signed _____ Date _____

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

BUPRENORPHINE/NALOXONE TREATMENT AGREEMENT

Patient Name:

MR#:

I am requesting that my doctor provide buprenorphine/naloxone treatment for opioid
_____ addiction. I freely and voluntarily agree to accept this treatment
list drug(s)
agreement, as follows:

- (1) I agree to keep, and be on time to, all my scheduled appointments with the doctor and his/her assistant.
- (2) I agree to conduct myself in a courteous manner in the physician's or clinic's office.
- (3) I agree to pay all office fees for this treatment at the time of my visits. I will be given a receipt that I can use to get reimbursement from my insurance company if this treatment is a covered service. I understand that this medication will cost between \$5-\$10 a day just for medication and that the office visits are a separate charge.
- (4) I agree not to arrive at the office intoxicated or under the influence of drugs. If I do, the staff will not see me and I will not be given any medication until my next scheduled appointment.
- (5) I agree not to sell, share, or give any of my medication to another person. I understand that such mishandling of my medication is a serious violation of this agreement and would result in my treatment being terminated without recourse for appeal.
- (6) I understand that the use of buprenorphine/naloxone by someone who is addicted to opioids could cause them to experience severe withdrawal.
- (7) I agree not to deal, steal, or conduct any other illegal or disruptive activities in the vicinity of the doctor's office or anywhere else.
- (8) I agree that my medication (or prescriptions) can only be given to me at my regular office visits. Any missed office visits will result in my not being able to get medication until the next scheduled visit.
- (9) I agree that the medication I receive is my responsibility and that I will keep it in a safe, secure place. I agree that lost medication will not be replaced regardless of the reasons for such loss.
- (10) I agree not to obtain medications from any physicians, pharmacists, or other sources without informing my treating physician. I understand that mixing buprenorphine/naloxone with other medications, especially benzodiazepines (sedatives or tranquilizers), such as Valium (diazepam), Xanax (alprazolam), Librium (chlordiazepoxide), Ativan (lorazepam), and/or other drugs of abuse including alcohol, can be dangerous. I also understand that a number of deaths have been reported in persons mixing buprenorphine with benzodiazepines. I also understand that I should not drink alcohol while taking this medication as the combination could

produce excessive sedation or impaired thinking or other medically dangerous events.

- (11) I agree to take my medication as the doctor has instructed, and not to alter the way I take my medication without first consulting the doctor.
- (12) I understand that medication alone is not sufficient treatment for my disease and I agree to participate in the recommended patient education and relapse prevention program, to assist me in my recovery.
- (13) I understand that my buprenorphine/naloxone treatment may be discontinued and I may be discharged from the clinic if I violate this agreement.
- (14) I understand that there are alternatives to buprenorphine/naloxone treatment for opioid addiction including:
 - a. medical withdrawal and drug-free treatment
 - b. naltrexone treatment
 - c. methadone treatment

My doctor will discuss these with me and provide a referral if I request this.

Patient's Signature

Date

Witness Signature

Date

BUPRENORPHINE/NALOXONE MAINTENANCE TREATMENT FOR OPIOID DEPENDENCE

INFORMATION for FAMILY MEMBERS

Family members of patients who have been prescribed buprenorphine/naloxone for treatment of opioid addiction often have questions about this treatment.

What is an opioid?

Opioids are narcotics (medicines that are used to treat pain, cough or opioid addiction and which produce drowsiness, fuzzy thinking, and euphoria in some). Opioids are in the same family as opium, morphine, and heroin. This includes many prescription pain medications, such as Codeine, Vicodin, Lortab or Lorcet, Demerol, Dilaudid, Morphine, MSContin, Oxycontin, and Percodan or Percocet. Methadone and buprenorphine are also opioids. Buprenorphine is the opioid medicine in Buprenorphine/naloxone that treats opioid addiction

Why are opioids used to treat addiction?

Many family members wonder why doctors use buprenorphine to treat opiate addiction, since it is in the same family as heroin. Some of them ask “Isn’t this substituting one addiction for another?” But the medications used to treat addiction to heroin and prescription pain medications – methadone and buprenorphine are longer-acting than other opioids like heroin and so are not “just substitution.” Many medical studies since 1965 show that maintenance treatment with these long-acting opioids helps keep patients healthier, keeps them from getting into legal troubles, and helps to prevent them from getting other diseases such as Hepatitis and/or HIV/AIDS.

What is Buprenorphine/naloxone?

Buprenorphine/naloxone is a tablet or strip that combines the opioid medication, buprenorphine, and naloxone, a medication called an opioid antagonist, for treatment of opioid dependence. Buprenorphine/naloxone is a medicine that is taken once daily by dissolving under the tongue. Naloxone is inactive (poorly absorbed) when taken this way. However, naloxone when injected by someone whose body is physically dependent on opioids will produce opiate withdrawal. In this way, the naloxone helps to prevent abuse of buprenorphine/naloxone by injection.

What is the right dose of Buprenorphine/naloxone?

Family members of patients who have been addicted to heroin or prescription opioids have watched as their loved ones use a drug that makes them intoxicated or ‘high’ or have watched the painful withdrawal that occurs when the drug is not available. Sometimes the family has not seen the ‘normal’ person for years. They may have seen the patient misuse doctors’ prescriptions for opiate

narcotics to get 'high'. They are rightly concerned that the patient might misuse or take too much of the buprenorphine/naloxone prescribed by the doctor. They may watch the patient and notice that the patient seems drowsy, or stimulated, or restless, and think that the buprenorphine/naloxone will be just as bad as heroin or other prescription opioids that the patient is abusing.

Every opioid can have stimulating or sedating effects, especially in the first weeks of treatment. Once a patient is stabilized on the correct dose of buprenorphine, the patient should not feel "high," and there should be no excessive sleepiness or intoxication. The 'right' dose of buprenorphine/naloxone is the one that allows the patient to feel and act normally. Most patients will need 12/3 mg (buprenorphine/naloxone) to 16/4 mg of buprenorphine/naloxone daily to achieve relief of opiate withdrawal symptoms and craving. Most patients can be inducted onto the buprenorphine/naloxone and stabilized within a few days. Occasionally it may take a little longer to find the right dose (up to a few weeks). During the period of dose adjustment, the buprenorphine level in the buprenorphine/naloxone may be too high, or too low, which can lead to withdrawal, daytime sleepiness, or trouble sleeping at night. The patient may ask that family members help keep track of the timing of these symptoms, and write them down. Then the doctor can use all these clues to adjust the amount and time of day for the buprenorphine/naloxone dose.

Once the right dose is found, it is important to take it on time in a regular way (once daily), so the patient's body and brain can work well.

How can the family support good treatment?

Even though maintenance treatment for opioid addiction works very well, it is NOT a cure. This means that the patient will continue to need the stable dose of buprenorphine/naloxone, with regular monitoring by the doctor. This is similar to other chronic diseases, such as diabetes or asthma. These illnesses can be treated, but there is no permanent cure, so patients often stay on the same medication for a long time. The best way to help and support the patient is to encourage regular medical care, and encourage the patient not to skip or forget to take the medication.

- Regular medical care

Patients will be required to see the physician for ongoing buprenorphine/naloxone treatment at least every two to four weeks, once they are stable. If they miss an appointment, they may not be able to refill the medication on time, and may even go into withdrawal, which could be uncomfortable. The patient will be asked to bring the medication container to each visit, and may be asked to give urine, blood or breath samples at the time of the visit. Sometimes the patient may be called in randomly to have their pills counted and/or to give a urine sample to test for the presence of other drugs or alcohol. This is a regular part of drug abuse treatment and is done for the patient's safety and to make sure that they are getting the treatment needed.

- Special medical care

Some patients may also need care for other needle-related problems, such as hepatitis or HIV disease. They may need to go for blood tests or see several physicians for these illnesses.

- Counseling

Patients who are recovering from addiction need counseling and other psychosocial treatments. The patient may have regular appointments with an individual counselor or be involved in group therapy. These appointments are key parts of treatment, and work together with the buprenorphine/naloxone to improve success in treatment for addiction. Sometimes family members may be asked to join in family therapy sessions which also are geared to improve addiction care.

- Meetings

Most patients use some kind of recovery group to maintain their sobriety. It sometimes takes several visits to different groups to find the right 'home' meeting. In the first year of recovery some patients go to meetings every day, or several times per week. These meetings work to improve success in treatment, in addition to taking buprenorphine/naloxone. Family members may have their own meetings, such as Al-Anon, or ACA, to support them in adjusting to life with a patient who has addiction.

- Taking the medication

Buprenorphine/naloxone medication is unusual because it must be dissolved under the tongue, rather than swallowed. Please be aware that **this can take up to a few minutes**. While the medication is dissolving, the patient will not be able to answer the phone, or the doorbell, or speak very easily. This means that the family will need to get used to the patient being 'out of commission' for a few minutes whenever the regular dose is scheduled.

- Storing the medication

If buprenorphine/naloxone is lost or misplaced, the patient may skip doses or go into withdrawal, so it is very important to find a good place to keep the medication safely at home preferably in a locked cabinet or lock box – away from children or pets who can become seriously ill or even die if they accidentally take this medication. Always keep the medicine in the same location, so it can be easily found. The doctor may give the patient a few 'backup' pills, in a separate bottle, in case an appointment has to be rescheduled, or there is an emergency of some kind. **DO NOT** put the buprenorphine/naloxone next to the vitamins, or the aspirin, or other over-the-counter medications, to avoid confusion. If a family member or visitor takes buprenorphine/naloxone by mistake, he or she should be checked by a physician or taken to an emergency department immediately as serious adverse reactions can occur if someone who does not usually take this medicine were to take it by mistake.

What does buprenorphine/naloxone treatment mean to the family?

It is hard for any family when a member finds out he or she has a disease that is not curable. This is true for addiction as well. When chronic diseases go untreated, they have severe complications which can lead to disability and death. Fortunately, buprenorphine/naloxone maintenance can be a successful treatment, especially if it is integrated with counseling and support for life changes that the patient has to make to remain sober.

Chronic disease means the disease is there every day, and must be treated every day. This takes time and attention away from other things, and family members may resent the effort and time and money that it takes for buprenorphine/naloxone treatment and counseling. It might help to compare addiction to other chronic diseases, like diabetes or high blood pressure. After all, it takes time to make appointments to go to the doctor for blood pressure checks, and it may annoy the family if the food has to be low in cholesterol, or unsalted. Most families can adjust to these changes when they consider that it may prevent a heart attack or a stroke for their loved one.

Another very important issue for family members to know about is that addiction can be partly inherited. Research is showing that some persons have more risk for becoming addicted than others and that some of this risk is genetic. So when one member develops opioid addiction, it means that other blood relatives should consider themselves 'at risk' of developing addiction. It is especially important for young people to know that alcohol or drugs at parties might be dangerous for them, even more than for most of their friends.

It is common for people to think of addiction as a weakness in character, instead of as a disease. Perhaps the first few times the person used drugs it was poor judgment. However, by the time the patient is addicted, using every day, and needing medical treatment, it should be considered to be a 'brain disease' rather than a problem with willpower.

Sometimes when the patient improves and starts feeling normal, the family has to get used to the new "normal" person. The family interactions might have been all about trying to help this person in trouble, and now he or she is no longer in so much trouble. Some families can use some help themselves during this change and might ask for family therapy for a while.

In summary:

Family support can be very helpful to patients on buprenorphine/naloxone treatment. It helps if the family members understand how addiction is a chronic disease that requires ongoing care. It also helps if the family gets to know about how the medication works and how it should be stored at home to keep it safe.

Family life might have to change to allow time and effort for 'recovery work' in addiction treatment. Sometimes family members themselves can benefit from therapy.

Buprenorphine - Beginning Treatment

Day One: Before taking a buprenorphine tablet you want to feel lousy from your withdrawal symptoms. Very lousy. It should be at least 12 hours since you used heroin or pain pills (oxycontin, vicodin, etc.) and at least 24 hours since you used methadone.

Wait it out as long as you can. The worse you feel when you begin the medication, the better it will make you feel and the more satisfied you will be with the whole experience.

You should have a least 3 of the following feelings:

- twitching, tremors or shaking
- joint and bone aches
- bad chills or sweating
- anxious or irritable
- goose pimples



• very restless, can't sit still



• heavy yawning



• enlarged pupils



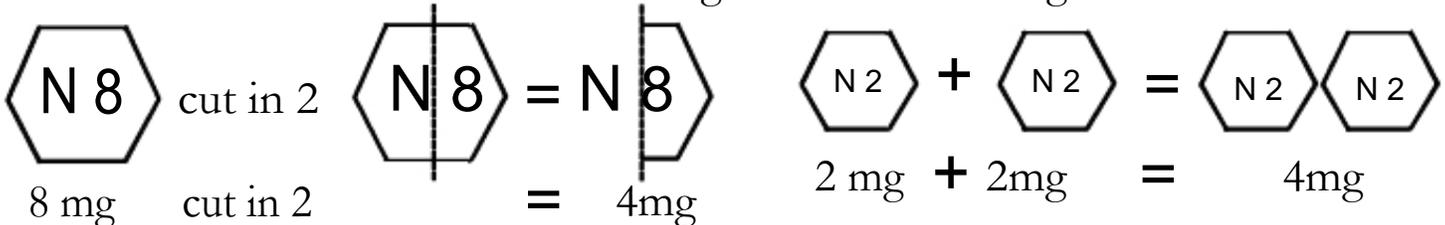
• runny nose, tears in eyes



• stomach cramps, nausea, vomiting, or diarrhea

First Dose: 4 mg of Buprenorphine (Bup) under the tongue.

This is one half of an 8 mg tablet or two 2 mg tablets:



Put the tablet (one half tablet of 8mg tabs, or two tablets if 2mg tabs) under your tongue. Keep it there. If you swallow Bup tablets they will not work, the medicine is best absorbed through the thin skin on the bottom of your tongue.

It takes 20-45 minutes for the medication to be absorbed and have an effect. Feel better? Good, the medicine is working. Still feel lousy after 45 minutes? Don't worry, you just need more medication.

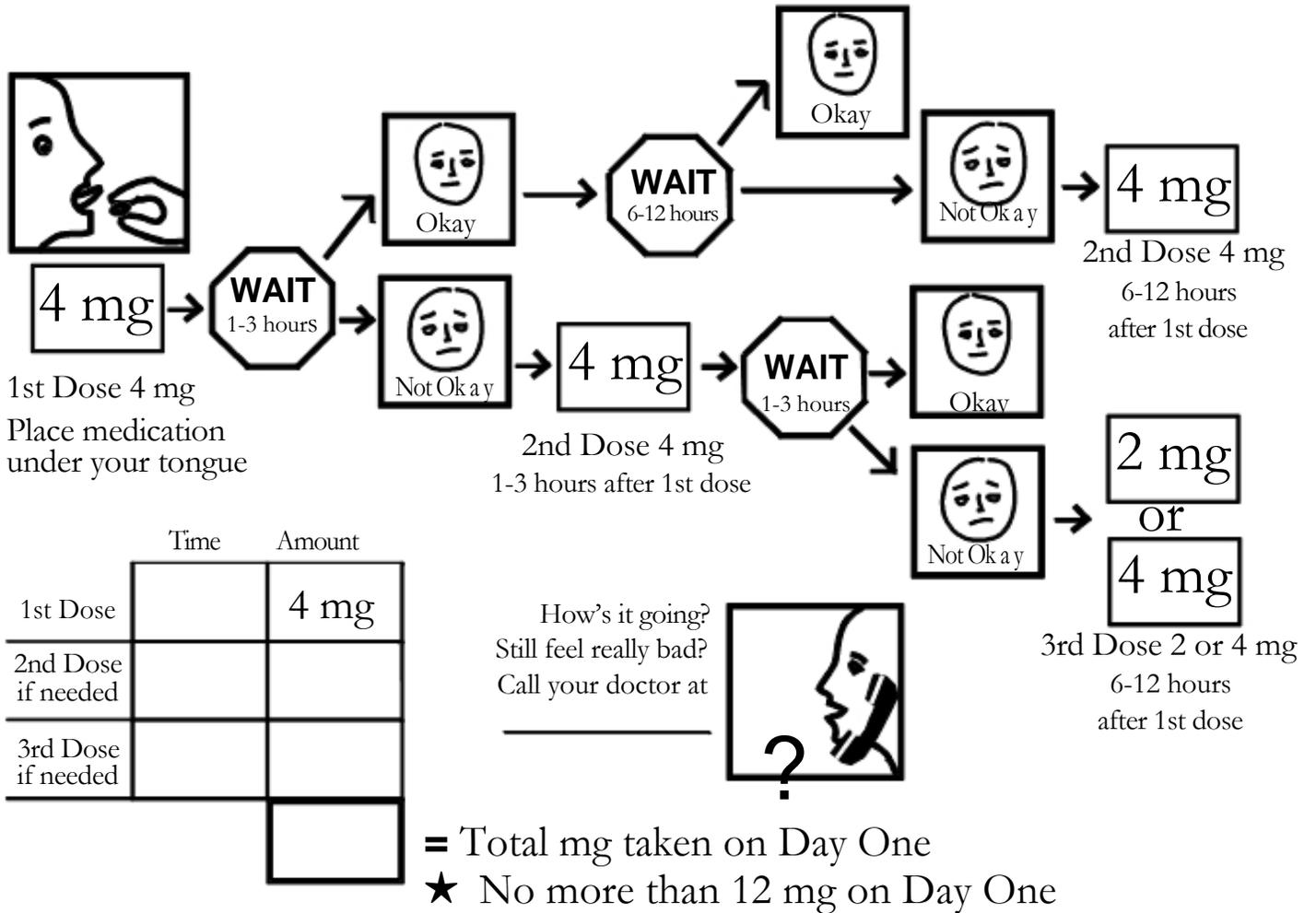
At 1-3 hours (60-180 minutes) after your first dose, see how you feel. If you feel fine after the first 4 mg, don't take any more, this may be all you need. If you have withdrawal feelings, take another 4 mg dose under your tongue.

Later in the day (6-12 hours after the first dose), see how you feel again. If you feel fine, don't take any more. If you have withdrawal feelings, take another 2 or 4 mg dose under your tongue.

Do not take more than 12 mg of Bup on the first day.

Most people feel better after the 4-12 mg on the first day. Still feel really bad, like a bad withdrawal? Call your doctor right away. You can call or page any time during the day if you are having difficulty.

Day One Summary: 4 mg under your tongue, wait 1-3 hours. If still feel sick, take 4 mg again. Wait 1-3 hours. If still sick, take 2-4 mg again. Do not take more than 12 mg on Day 1.



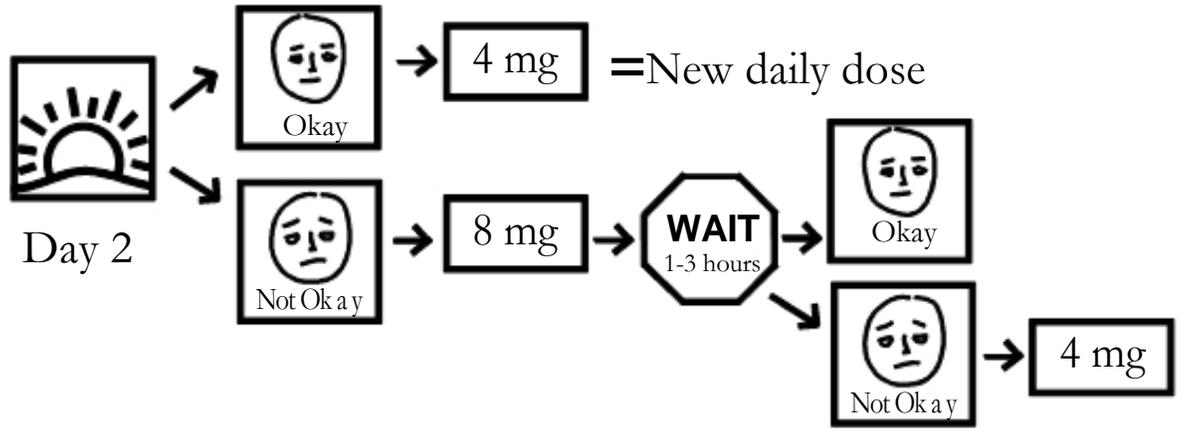
Day Two: The right dose depends on how you felt on Day One

<p>If the total on Day One was</p> <p>4 mg</p>	<p>If you took <u>4 mg total on Day 1 and feel fine the next morning</u>, then take 4 mg again on Day 2. This will be your new daily dose.</p> <p>If you took <u>4 mg total on Day 1 and feel some withdrawal the next morning</u>, then try starting with 8 mg on the morning of Day 2.</p> <p>Later in the day on Day 2, see how you feel. If you feel fine, there is no need to take more. If you still feel withdrawal, you can try taking another 4 mg dose.</p>
<p>If the total on Day One was</p> <p>8 mg</p>	<p>If you took <u>8 mg total on Day 1 and feel fine the next morning</u>, then take 8 mg again on Day 2. This will be your new daily dose.</p> <p>If you took <u>8 mg total on Day 1 and feel some withdrawal the next morning</u>, then try starting with 12 mg on the morning of Day 2.</p> <p>Later in the day on Day 2, see how you feel. If you feel fine, there is no need to take more. If you still feel withdrawal, you can try taking another 4mg dose.</p>
<p>If the total on Day One was</p> <p>12 mg</p>	<p>If you took <u>12 mg total on Day 1 and feel fine the next morning</u>, then take 12 mg again on Day 2. This will be your new daily dose.</p> <p>If you took <u>12 mg total on Day 1 and feel some withdrawal the next morning</u>, then try starting with 16mg on the morning of Day 2.</p>

Day Two Summary: 4-16 mg total, depending on how much you took on Day 1.

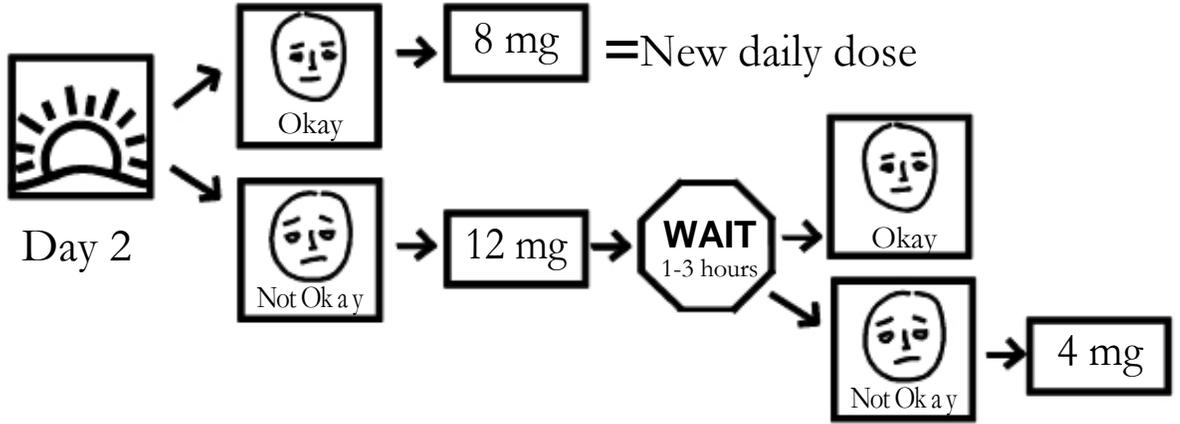
If the total on Day One was

4 mg



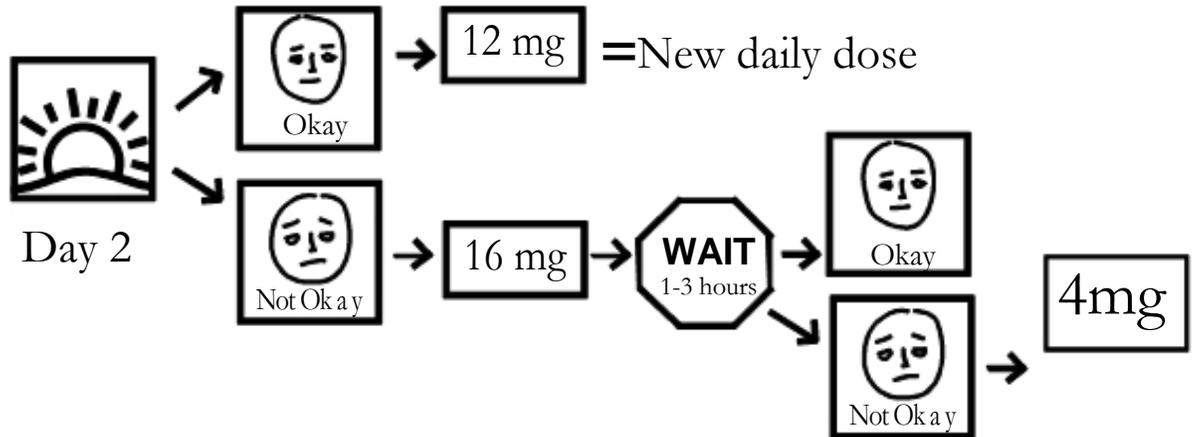
If the total on Day One was

8 mg



If the total on Day One was

12 mg



	Time	Amount	
1st Dose			= Total mg taken on Day One
2nd Dose if needed			
			= Total mg taken on Day Two

Still feel really bad?
Call your doctor at



Day Three

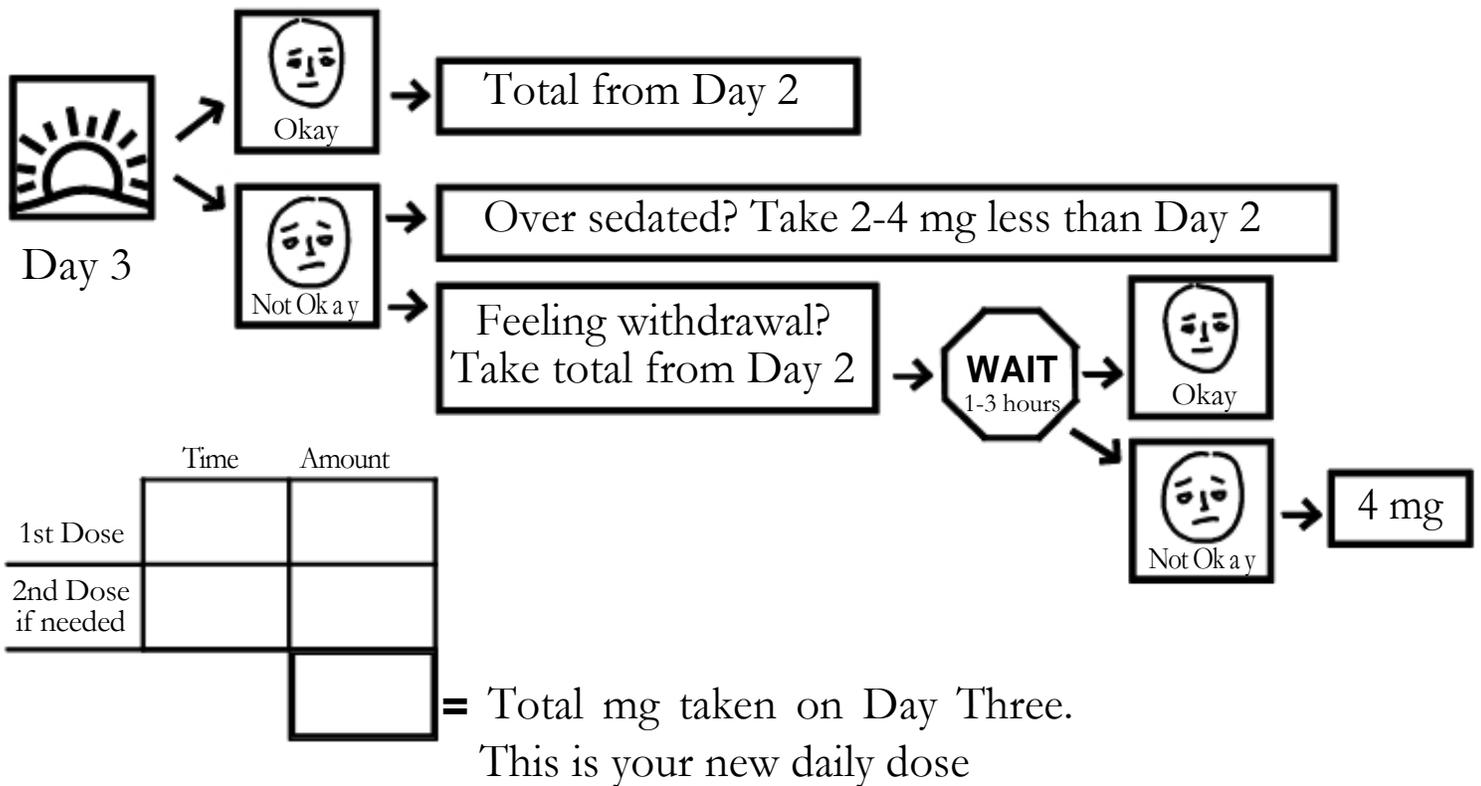
The right dose for you on Day 3 depends on how you felt on Day 2. Did you still feel unwell, like you were in some withdrawal by the evening or night of Day 2? Or did you feel like the medication was too strong, leaving you too groggy or sedated? Different people need different doses of Bup: some feel fine on just 4 mg per day, and others can need up to 32 mg per day to feel comfortable.

If you felt good at the end of Day 2, repeat the dose you took on Day 2. This is your new daily dose.

If you felt too tired, groggy, or over sedated on Day 2, try taking a lower dose on Day 3. Take 2-4 mg less on Day 3 than you took on Day 2.

If you still felt some withdrawal at the end of Day 2, start Day 3 by taking the same total dose you took on Day 2. If you still have withdrawal symptoms later on Day 3, take another 4 mg later in the day.

Day Three Summary: Take the total Day 2 dose under your tongue in the morning. You can try a little less if the Day 2 dose felt too strong and you can take an extra 4 mg dose if you still feel withdrawal.



Day Four and Beyond

On Day 4 and beyond, take the dose you used on Day 3. This is now your daily dose. You can take more or less depending on how you feel overall, whether or not you still have cravings or are still using, etc. You should discuss any dose adjustments after this point with your doctor. If you do need to increase your dose, you should not change it by more than 4 mg per day.

- ★ Never take more than 32 mg of Buprenorphine in one day.
- ★ Come back to your next clinic appointment.

Clinical Opiate Withdrawal Scale

Introduction

The Clinical Opiate Withdrawal Scale (COWS) is an 11-item scale designed to be administered by a clinician. This tool can be used in both inpatient and outpatient settings to reproducibly rate common signs and symptoms of opiate withdrawal and monitor these symptoms over time. The summed score for the complete scale can be used to help clinicians determine the stage or severity of opiate withdrawal and assess the level of physical dependence on opioids. Practitioners sometimes express concern about the objectivity of the items in the COWS; however, the symptoms of opioid withdrawal have been likened to a severe influenza infection (e.g., nausea, vomiting, sweating, joint aches, agitation, tremor), and patients should not exceed the lowest score in most categories without exhibiting some observable sign or symptom of withdrawal.

APPENDIX 1 Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name: _____ Date and Time ____/____/____:_____	
Reason for this assessment: _____	
Resting Pulse Rate: _____ beats/minute <i>Measured after patient is sitting or lying for one minute</i> 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 sitting 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 or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches <i>If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored</i> 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 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection
Runny nose or tearing <i>Not accounted for by cold symptoms or allergies</i> 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	<p style="text-align: right;">Total Score _____</p> <p style="text-align: center;">The total score is the sum of all 11 items</p> Initials of person completing assessment: _____

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

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9/25/10

BUPRENORPHINE/NALOXONE MAINTENANCE TREATMENT

PHYSICIAN/OFFICE INFORMATION

Progress Note Structure

Date/Time

Subjective: Patient statement of status in treatment

Objective: Current pertinent history, drug/alcohol use, adherence to buprenorphine/naloxone, craving, medical/psychiatric issues, psychosocial issues, participation in other therapies

Physical Examination (as indicated)

Laboratory/Urine Drug Screen Results

Assessment: Current problems

Plan: Medication prescribed, any new medical/psychiatric interventions, next visit

9/25/10

Progress Notes – Sample #2

Patient 2

9/3/10

1. *Denies heroin or other illicit drug use. Last urine (date) was positive for cocaine, which patient adamantly denies using.*
2. *Indicates increasing marital discord related to his drug use.*
3. *Although he agrees that going to a support group is a good idea, he has actually attended only once in the past month.*
4. *Liver enzymes slightly elevated on lab of (date), otherwise wnl. Patient seems more irritable, although when this is pointed out to patient, his response was “now don’t you start on me too.”*

5. *Patient refused permission for me to talk with his wife.*

Impression

1. *Patient has likely relapsed to cocaine use*
2. *Appears to be in denial about the severity of drug use and its adverse effects on his relationship.*
3. *Liver enzyme elevation probably secondary to HCV, which was previously diagnosed.*

Rx plan

1. *Increase office visits and urine testing to weekly*
2. *Get patient to accept referral to intensive outpatient treatment program as a condition of continuing buprenorphine treatment.*
3. *Referral to gastroenterologist for evaluation of HCV*

##



PCSS Guidance

Topic: Buprenorphine Induction

Original Author: Paul P. Casadonte, MD

Last Updated: 11/27/13 (Maria A. Sullivan M.D., Ph.D.)

Guideline Coverage:

This topic is fully addressed in: **TIP 40. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction:** Laura McNicholas, Consensus Panel Chair M.D. Ph.D. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment
<http://www.kap.samhsa.gov/products/manuals/index.htm>

Clinical Questions:

1. What can I do to insure a successful buprenorphine induction?
2. How can I determine if the patient is ready?
3. Do I have to do the induction in my office?
4. What do I do if the patient experiences a precipitated withdrawal?

Background:

Buprenorphine induction, performed at the right time, remains one of the most satisfying procedures a patient and his/her physician can experience. While there may be initial fears or concerns about precipitating withdrawal, if the patient presents with objective signs of withdrawal and doses are slowly titrated upwards, the patient will leave the office much happier than he/she has been in a long time. The physician will see immediate positive results -- a rare occurrence in clinical practice.

The goal of the induction phase is to transfer the patient from an abused opioid to a dose of buprenorphine which will provide relief from withdrawal and make induction the first step to assist the patient in discontinuing or markedly diminishing use of other opioids. Even during induction phase, the physician must emphasize the need for counseling to manage the behavioral issues related to opioid use and to address the social, medical and psychiatric problems associated with opioid dependence.

The Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment, Treatment Improvement Protocol Number 40 provides clear guidelines and protocols for buprenorphine induction. Trainings in the use of buprenorphine emphasize the need to observe and document mild-to-moderate withdrawal from the opioid of choice prior to giving the first dose of buprenorphine.

General Principles:

To help the patient prepare for buprenorphine induction, it is important to work closely with him/her during the screening process to determine how long it will take to attain mild to moderate opiate withdrawal symptoms. It is also important to learn how fearful the individual is of withdrawal, as this fear may complicate the induction process. It is helpful to ask the patient to recall what his or her first withdrawal symptoms are and advise that it is while experiencing these that he/she should be walking into the office. If the patient is not sure, it may be useful to ask the patient to experiment and hold off as long as possible from opiate use to determine and record the length of time it takes from last use until he/she absolutely needs relief from withdrawal. Many patients are surprised that they can go without their opioid for much longer than anticipated. This period will vary by patient based on a number of factors. These include the patient's level of tolerance and the dose of substance that they ingest. In general, this should take 12-16 hours for short-acting opioids (heroin, hydrocodone, oxycodone-immediate release), 17-24 for intermediate-acting opioids (oxycodone-sustained release), and 30-48 hours, or longer, for long-acting opioids such as methadone. The longer one can hold off on giving the first dose of buprenorphine, the easier the induction

will be, so waiting beyond these above time ranges is advisable. The Clinical Opiate Withdrawal Scale (COWS) is easy to use and can be inserted into the medical record to document withdrawal. The COWS is available at:

<http://pcssmat.org/wp-site/wp-content/uploads/2013/10/2.15.12-CLINICAL-OPIATE-WITHDRAWAL-SCALE.pdf>.

Some physicians may choose to use buprenorphine mono product for the first few days, especially in patients being transferred from methadone. This is generally not necessary, and can cause patient objections and complaints when buprenorphine/naloxone is started. In some cases buprenorphine induction and stabilization may last a week or more. The COWS can be used at each office visit during the first week to assess for continued withdrawal. To help assure that the patient comes in for their next visit, medication should be prescribed only until the next visit. During the first weeks the patient should be seen regularly (once to twice per week) and not given a month's supply after the first visit.

1. Observed inductions

Recommendations:

Level of Evidence: **High - Clinical trials**

1. Evaluate the level of withdrawal with the COWS.
2. Wait until a COWS score of 6-10 is observed (see Nielsen et al. 2013).
3. Instruct the patient how to take the medication, under the tongue, no talking and swallow when fully dissolved.
4. Administer the first dose of 2-4 mg under observation in the office or inpatient setting.
5. Keep the patient in the office for at least an hour to determine the effect of the first dose, and then document the effect of the first doses in the medical record.
6. Depending on the amount and type of opioid use, the first day's dose may range from 2 to 16 mgs. Lower doses are required in patients with a lower level of physical dependence.
7. If withdrawal occurs after the patient leaves the office, request that the patient return for withdrawal assessment. This will be time-consuming, discouraging and not likely to happen. Avoid this complication by taking the time to assure moderate withdrawal discomfort prior to the first dose.
8. If the individual in the office is pressing for relief and the doctor is still not certain that he is in sufficient withdrawal then a low dose of 2 mg can be given and doses provided for later in the day.
9. Remain in contact with the patient by telephone during the first day or two. even in the case of a successful induction, as doses may need to be adjusted prior to the next office visit.
10. Give sufficient medication only until the next visit, within 3-4 days

2. Inductions not directly observed by physician: Home Inductions

Background:

Since the approval of buprenorphine for office practice, increasing numbers of patients have been treated with buprenorphine and physicians have become more comfortable using the medication. Although data are not currently available, we can safely speculate that a large number of individuals have started and stopped buprenorphine with and without physician input. One observational study reported on the successful unobserved induction in a cohort of 41 individuals. A larger observational study in 101 individuals has reported outcomes for home induction (Lee. et al. 2009). In this study, researchers provided significant patient education, including a detailed handout, that covered how and when to start buprenorphine/ naloxone. In this trial, home-based buprenorphine induction was feasible and appeared safe. If the physician has previously treated a returning patient, has conducted an observed induction with this patient, and trusts that he/she has a history of responsible use of his medication, the patient and physician may decide to re-start buprenorphine without direct physician observation. It is, however, possible that a physician may see a new patient in an office consultation, and decides, due to problematic office logistics, to prescribe buprenorphine for home induction. It is expected that the physician will provide explicit instructions on how and when to start buprenorphine/naloxone, along with clear requirements for maintaining telephone contact. While home induction may be growing, we must emphasize that there is limited safety data on not maintaining the patient under direct observation during induction. One recent observational cohort study found that participants with patient-centered home-based inductions had similar reductions in opioid use and greater reductions in any drug use than those with standard-of-care office-based inductions (Cunningham et al. 2011).

Recommendations:

Level of Evidence: **Low/Moderate - Further controlled studies needed uncontrolled case series, expert opinion**

Unobserved induction remains outside the TIP Guidelines, remains under investigation, and there is no evidence to support its use by inexperienced clinicians or with unstable patients.

1. If a physician decides to pursue this strategy, it is advisable to use after patient education, in previously treated patients who are known to be reliable, or for patients who demonstrate clear documented knowledge of the risks of unobserved induction and are willing to come to the office in the event of problems. If a patient has expressed significant fear of withdrawal, he/she may not be a good candidate for home induction due to the potential for starting buprenorphine too early and causing a precipitated withdrawal.
2. Patients should be provided with explicit written instructions regarding the subjective and objective assessment of opioid withdrawal, the timing and dose of buprenorphine, and phone numbers for assistance.
3. The physician should maintain close telephone contact with the patient during the course of the unobserved induction and document these interactions.
4. The patient should be seen within 2 days of starting buprenorphine.
5. All telephone calls and contacts should be documented in the physician's medical record. Many unobserved home inductions are likely performed without adverse consequences. However it is important to note that the majority of the research and clinical care guidelines on the use of buprenorphine are based upon observed induction.

3. Management of precipitated withdrawal

Recommendations:

Level of Evidence: **Low-clinical experience**

If an unexpected precipitated withdrawal occurs during the early phases of the induction period, supportive treatment with or without medication will be necessary.

Types of supportive **treatment:**

1. Repeated 2 mg doses of buprenorphine every 1-2 hours
2. Clonidine 0.1 mg every 8 hours (caution regarding hypotension)
3. Antiemetics for nausea
4. Non-steroidals for arthralgias and myalgias

Some patients may resist supportive treatment and return to full agonist opioid use as a method to self-medicate their precipitated withdrawal.

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TIP 40. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction: Laura McNicholas. Consensus Panel Chair M.D. Ph.D. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment <http://www.kap.samhsa.gov/products/manuals/index.htm>

Wesson D, Ling W The Clinical Opiate Withdrawal Scale (COWS) *Journal of Psychoactive Drugs* V 35 (2) April-June 2003 p 253-61

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High = Further research is very unlikely to change our confidence in the estimate of effect

Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low = Any estimate of effect is very uncertain.

Type of evidence:

Randomised trial = **high**

Observational study = **low**

Any other evidence = **very low**

* Grading quality of evidence and strength of recommendations

British Medical Journal. 2004;328:1490-



PCSS Guidance

Topic: Transfer from Methadone to Buprenorphine

Original Author: Paul P. Casadonte, M.D.

Last Updated: 12/5/13 (Maria A. Sullivan, M.D., Ph.D.)

Guideline Coverage:

TIP #40, Treatment Protocols: Patients dependent on long-acting opioids (pgs. 52-54)

Clinical Questions:

1. Which patients receiving methadone should be considered good candidates for transfer to buprenorphine?
2. How should I transition a patient from methadone to buprenorphine?

Background:

Patients receiving methadone may seek transfer to buprenorphine treatment. There are a large number of clinical scenarios that would cause a patient receiving methadone to seek induction onto buprenorphine. It is incumbent upon the physician to weigh the clinical issues carefully prior to agreeing to assist in the transfer. If a patient is stable on methadone, it is generally not advisable to agree to transfer to buprenorphine without a careful evaluation of the factors motivating the desire to transfer. However, if in the physician's medical judgment, buprenorphine treatment is appropriate and the patient is well-informed of the risks and benefits, transfer may be a reasonable option.

Among the potential benefits of transfer to buprenorphine include lower risk of overdose or sedation, lower risk of QT prolongation and ventricular arrhythmias, less severe withdrawal if a dose is missed, the capacity to obtain medication at a local pharmacy and the option of treatment in a doctor's office.

A number of factors might motivate a patient's request to transfer from methadone. These include; a desire to no longer receive his or her treatment from an opioid treatment program, perceived stigma associated with receiving methadone, concern about having methadone in the house, a desire to travel frequently for work, concern about having a large numbers of methadone bottles in one's possession when traveling, concern about losing methadone bottles without the possibility of replacement, less need for the required counseling/medication dispensing/urine collection in regulated opioid treatment programs, and/or living a long distance from a treatment program. In some cases, the development of QT prolongation or a ventricular tachycardia has necessitated that methadone-maintained patients be transferred to buprenorphine to resolve these adverse cardiac effects (Hanon et al. 2010). In addition, some methadone-maintained patients seek induction onto buprenorphine as a transition to antagonist treatment.

Alternatively, the patient may not be doing well on methadone, continuing to use opiates, stimulants (cocaine or methamphetamines) or benzodiazepines and wish to leave the structure of an opioid treatment program. Finally, it is possible that a patient may be buying methadone on the street and is now seeking legitimate treatment.

Patient Education:

When a patient is seeking transfer from methadone to buprenorphine, it is advisable to determine if the request is based on realistic expectations. It is important for the prospective patient to know that, in an effort to lower the patient's level of opioid physical dependence, it is advised that most patients taper their

dose of methadone prior to transferring to buprenorphine. Unfortunately, for some patients, the transfer process may be associated with a period of discomfort, both from tapering methadone and from starting buprenorphine. Individuals on moderate to high-doses of methadone, over 60-100 mg, may not be able to taper without discomfort and a risk of relapse. As the methadone dose is tapered, if the patient begins to experience withdrawal that interferes with their functioning or leads to relapse, he/she can be advised that transfer at a later time may be advisable.

Coordination:

If the buprenorphine practitioner is not associated with the patient's methadone clinic, it will be important to work with the methadone physician and treatment team to coordinate the taper and the timing of the transfer. One should work with the methadone clinic staff to insure continuity of care and a smooth transition, and know that if the transfer fails, that the patient may return to methadone treatment. In some cases, the methadone clinic staff may oppose the patient's transfer. The buprenorphine prescriber should be cautious about being perceived as forcing the transfer, yet encourage the patient to advocate on their own behalf if needed and appropriate.

Recommendations:

Level of evidence: **Low - observational studies and a limited number of randomized studies**

Transfer Process:

Studies of transfer from methadone to buprenorphine are limited (Levin, Fishman, et al 1997; Breen, Harris et al 2003; Law, FD et al. 1997; Clark, Lintzeris et al, CPDD 2006; Salsitz et al. 2010) but offer helpful insights into the transfer process on both inpatient and outpatient settings. It is advisable for the patient to arrange a few days off from work, to go through the transfer.

As with any induction, the patient must be essentially free of opioid full agonists before taking the first dose of buprenorphine. It is not necessary to start with buprenorphine mono then transfer to buprenorphine/naloxone a few days later. The minimal absorption of naloxone is not likely to cause a precipitated withdrawal if the patient is in adequate withdrawal when he or she receives the first dose of buprenorphine.

With the long-acting agonist methadone, the timing of the first dose of buprenorphine may be more difficult to determine than when starting someone who is using a short acting-opioid. Methadone undergoes significant storage in body tissue, especially the liver, so the length of time until withdrawal is experienced is dependent upon factors such as hepatic function, dose of methadone, duration of methadone, etc. While a patient may know how long it takes to go into withdrawal while using heroin, he or she may not have ever missed a methadone dose and so be unaware of the timing of withdrawal symptoms.

Higher methadone doses and a shorter timeframe between last methadone dose are clinical concerns in the methadone to buprenorphine transfer process. Generally it is advisable to taper a patient to 20-30 mg methadone, and to maintain that dose for a week or more prior to initiating buprenorphine induction. Buprenorphine may be started 36-72 hours after the last methadone dose, but it is advisable to observe for objective signs of withdrawal (Clinical Opiate Withdrawal Scale of 13-15) and not rely only on time lapsed since the last methadone dose. The key to a smooth transition is not the length of time since the last methadone dose, but rather how much objective withdrawal the patient is in when he or she presents for the first buprenorphine dose. Both the doctor and the patient may be surprised to learn that it may take much longer than 36 hours to begin methadone withdrawal. Clonidine, anxiolytics, including benzodiazepines, non-steroidal anti-inflammatory agents may be used judiciously to assist the withdrawal process, and continued during the induction as well. Withdrawal anxiety will be one of the more common concerns.

Alternatively a patient may taper to the dose at which he or she reports discomfort, and if withdrawal signs are observed by the practitioner, the patient can then be started on buprenorphine with results similar to a taper to 30 mg methadone. (Breen, Harris, Lintzeris 2003)

One study from Australia, conducted on an inpatient unit with doses of buprenorphine that are not available in the U.S., presented at the College on the Problems of Drug Dependence (2006 Clark, Lintzeris) evaluated 3 induction schedules-low (0.8 mg qid on day 1 increasing to 32 mg by day 5; standard (4 mg day 1, increasing to 32 mg at day 5) or high (32 mg day 1 and maintain through day 5). The authors conclude that the high- and low-dose induction proved more tolerable than the standard induction. In addition, it was advised to wait as long as possible after the last dose of methadone to perform the

buprenorphine induction.

It may not be possible to admit a patient on high-dose methadone (over 40 mg) to an inpatient service, nor to taper methadone to 30 mg. After obtaining a COWS score of 15, it appears advisable to start at 2 mg, and continue to dose until the patient is comfortable, dosing up to 32 mg on day 1. If withdrawal is precipitated, management with ancillary medications is advisable. Discomfort may persist for up to 96 hours.

Post-transfer Management*

It may be helpful to maintain contact with the patient and provide reassurance and telephone consultation up to 3 times daily for the first few days. This can be an intensive process for the physician as well as the patient, so it may be inadvisable to start the transfer late in the week. After 3-5 days, the patient will be stable and comfortable, but it may be necessary to add medications to assist with some of the discomforts associated with the withdrawal/transfer process. The patient may lose patience with the discomfort and want to return to methadone. The clinician will need to work with the patient either to accomplish this, or to encourage him or her to wait a bit longer, by provide additional therapeutic support and/or increasing ancillary medications.

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Type of evidence:

Randomized trial = **high**

Observational study = **low**

Any other evidence = **very low**

* Grading quality of evidence and strength of recommendations

British Medical Journal. 2004;328:1490-



PCSS Guidance

Topic: Management of Psychiatric Medications in Patients Receiving Buprenorphine/Naloxone

Original Author: John A. Renner, Jr., M.D.

Last Updated: 11/28/13 (Maria A, Sullivan, M.D., Ph.D.)

Guideline Coverage:

This topic is also addressed in Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction (TIP 40), pages 18-22 and 75-76. http://buprenorphine.samhsa.gov/Bup_Guidelines.pdf and in Methadone-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs (TIP 43), page 36-42.

Clinical Question:

How do I manage medications for co-occurring psychiatric disorders in a patient receiving buprenorphine/naloxone (bup/nx) for the treatment of opioid dependence?

Background:

Among opiate-dependent patients the lifetime prevalence of affective disorders has been reported to be 85.4% in women and 70.0% in men (Rounsaville, 1982), with a current prevalence of major depression of 15.8% (Brunner, 1997). The lifetime prevalence of anxiety disorders was reported to be 13.2% in women and 24.5% in men (Rounsaville, 1982). Post-traumatic stress disorder (PTSD) is also common, though patients may deny a PTSD history until they feel confident in their treating clinician. Villagomez (1995) reported a lifetime prevalence of PTSD of 20% in women and 11% in men.

There are few data on the prevalence of co-occurring psychiatric conditions among patients entering office-based treatment with buprenorphine, and unfortunately there is little research literature available to guide the treatment of patients with these co-occurring psychiatric conditions. Savant et al. (2013) found that major depression was the most prevalent mood disorder (19% current, 24% past) among patients seeking primary care office-based buprenorphine/naloxone. A minority of patients met criteria for current dysthymia (6%), past mania (1%), or past hypomania (2%). The literature on the treatment of these conditions in methadone maintenance patients is sparse, but it offers the most likely relevant clinical guidance. In a placebo-controlled trial, Nunes (1998) showed an improvement in depression in methadone maintenance patients treated with imipramine. Kosten reported a poor outcome in a study that treated depressed opioid-dependent patients with the combination of desipramine and buprenorphine and recommended against using this combination (2004). There have been mixed, but generally negative results with the use of selective serotonin reuptake inhibitors (SSRI's) in this population (Petrakis, 1998). Some success has been reported with sertraline in depressed methadone patients (Hamilton, 2000; Carpenter, 2004). A recent meta-analysis (Pani et al. 2010) found low evidence supporting the clinical use of antidepressants for the treatment of depression among patients treated with opioid agonists. This finding was recently replicated in a second meta-analysis. Among patients with major depression or dysthymia in methadone maintenance treatment, no difference in depressive outcomes was found, regardless of whether patients were on medication or placebo (Pedrelli et al. 2011).

In the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC waves 1,2), lifetime non-medical prescription opioid use was found to be associated with any anxiety disorder and generalized anxiety disorder (GAD in wave 2; Martins et al. 2012) While it is common clinical practice to prescribe

SSRIs and other antidepressants to treat anxiety disorders in patients maintained on methadone and buprenorphine, there is even less research available to guide the management of anxiety disorders in this population. Yet buprenorphine-maintained patients are frequently diagnosed with anxiety (23-42%), and benzodiazepine prescriptions are filled at high rates (47-56%) in this population (Mark et al, 2013). Buspirone, a partial 5HT1A receptor agonist which has low abuse liability and does not induce tolerance, has not been demonstrated to be effective in treating anxiety disorders in methadone patients (McRae, 2004). Short-acting benzodiazepines are generally avoided because of both abuse and toxicity problems (Borron, 2002). However, there is one study that described the successful use of the long-acting benzodiazepine, clonazepam, for maintenance treatment of anxiety disorders in methadone patients with a history of benzodiazepine abuse (Bleich, 2002). Current guidelines recommend against prescribing buprenorphine in patients with uncontrolled use of benzodiazepines due to overdoses noted with combined buprenorphine and benzodiazepines in Europe (Kintz, 2001; Obadia, 2001; Boyd, 2003).

Buprenorphine, like methadone and LAAM, is metabolized chiefly by the cytochrome P450 3A4 system. This presents the potential for clinically significant interactions with several classes of medications commonly prescribed in the treatment population. The following lists include those medications that may theoretically affect buprenorphine levels. (See also PCSS-MAT Clinical Guidance, "Clinically Relevant Drug Interactions: Buprenorphine or Methadone with Other Frequently Prescribed Drugs.")

3A4 Inhibitors: These drugs may raise buprenorphine levels: e.g. fluoxetine (Prozac), fluvoxamine (Luvox), nefazodone (Serzone), cimetidine (Tagamet). antiretrovirals (e.g. delavirdine)

3A4 Substrates: These drugs may raise buprenorphine levels: e.g. trazodone (Desyrel), alprazolam (Xanax), diazepam (Valium), buspirone (Buspar), Zolpidem (Ambien), caffeine, haloperidol (Haldol), pimozide (Orap), erythromycin, nifedipine, oral contraceptives

3A4 Inducers: These drugs may lower buprenorphine levels e.g. carbamazepine. phenobarbital, phenytoin, barbiturates, primidone. St. John's Wort, rifampin, efavirenz, nevirapine

A more complete list of inhibitors, inducers and substrates is available at www.drug-interactions.com and TIP 40, page 21. There is minimal specific information available about the actual clinical impact of combinations of buprenorphine and many of these medications, though some studies are underway. Pharmacokinetic interactions identified between buprenorphine and antiretroviral medications have not been correlated with serious adverse events to date. Because of the high affinity of buprenorphine for the mu-opioid receptor and the long duration of binding at the receptor, it seems relatively unlikely that any specific interaction would occur during the course of buprenorphine treatment. Unlike the experience with both methadone and LAAM, where dose adjustments or medication changes are frequently required because of drug-drug interactions, most clinicians have not encountered clinically significant problems using bup/nx in combination with other drugs metabolized by the P450 3A4 system.

General Principles:

Inform patient of your knowledge of the pharmacotherapy options for treating various psychiatric disorders and of the drug-drug interactions involving buprenorphine, and provide reassurance that his or her addiction will not be an obstacle to the treatment of any co-occurring psychiatric disorders. Include the patient in the decision-making process to allay anxiety about relapse. Offer addiction counseling as needed.

Recommendations:

Level of evidence: **Low - expert opinion/clinical experience**

For patients receiving bup/nx who require pharmacotherapy of a co-occurring psychiatric disorder, the following steps are recommended:

1. Patients should be screened for co-occurring psychiatric disorders during the initial evaluation for buprenorphine treatment. Patients who present any immediate risks to themselves or others should be referred for specialty care and /or inpatient treatment

2. After two to three week stabilization on buprenorphine, any psychiatric symptomatology should be reassessed. Depressive syndromes are common at the time of admission to buprenorphine treatment and anxiety symptoms may be caused by opiate withdrawal. Substance-induced psychiatric disorders will clear within 1 to 2 weeks, once the patient is stabilized on buprenorphine.
3. Any psychiatric symptoms that continue for more than 30 days after the termination of illicit drug use suggest the presence of an independent psychiatric disorder. If the diagnosis is confirmed, treatment should be initiated. In situations where a pre-existing psychiatric disorder is well documented, treatment can begin immediately after buprenorphine treatment is initiated.
4. Because of the lack of evidence-based studies on the efficacy of pharmacotherapy of co-occurring psychiatric disorders in buprenorphine patients, clinicians should rely on the general recommendations for opioid-dependent patients. Evidence suggests efficacy for doxepin, imipramine, and desipramine in depressed methadone patients, although the use of desipramine in patients receiving buprenorphine has not been successful; there is less consistent evidence to support the use of the SSRI's though general clinical experience supports the use of all of the newer antidepressants in this population. Benzodiazepines should be used with caution in buprenorphine-treated patients.

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Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low = Any estimate of effect is very uncertain.

Type of evidence:

Randomised trial = **high**

Observational study = **low**

Any other evidence = **very low**

* Grading quality of evidence and strength of recommendations

British Medical Journal. 2004;328:1490-

PCSS-B Guidance

Topic: Clinically Relevant Drug Interactions: Buprenorphine or Methadone with Other Frequently Prescribed Drugs

Original Author: Elinore F. McCance-Katz, M.D., Ph.D.

Last Updated: 9/24/10

Clinical questions:

1. What drug interactions of clinical significance occur between buprenorphine or methadone and other medications?
2. In thinking about opioid therapy for an opioid dependent patient, how can I determine whether to select methadone or buprenorphine as the treatment medication?

Background:

Drug interactions are a leading cause of morbidity and mortality. Methadone and buprenorphine are frequently prescribed for the treatment of opioid addiction. Patients needing treatment with these medications often have co-occurring medical and mental illnesses that require medication treatment. The abuse of illicit substances is also common in opioid-addicted individuals. These clinical realities place patients being treated with methadone and buprenorphine at risk for potentially toxic drug interactions. A substantial literature has accumulated on drug interactions between either methadone or buprenorphine with other medications when ingested concomitantly by humans. This guidance will summarize that literature in tabular form below (Adapted from Reference 1 below).

HIV Medications	Methadone	Buprenorphine
AZT	Increase in AZT concentrations; possible AZT toxicity	No clinically significant interaction
Didanosine (in tablet form)	Significant decrease in didanosine concentrations	Not studied in human pharmacokinetics studies
Stavudine	Significant decrease in stavudine concentrations	Not studied in human pharmacokinetics studies
Delavirdine	Increased methadone (and LAAM) concentrations; no cognitive impairment	Increased buprenorphine concentrations; no cognitive impairment
Atazanavir	Not associated with increased levels of methadone	Significant increases in buprenorphine and report of cognitive dysfunction
Darunavir	Opiate withdrawal may occur	Under study
Efavirenz	Opiate withdrawal may occur	No clinically significant interaction
Fosamprenavir	Data suggest that the PK interaction is not clinically relevant; however, patients should be monitored for opiate withdrawal symptoms	Under study
Nelfinavir	Methadone levels are decreased. Opiate withdrawal may occur	No clinically significant interaction
Nevirapine	Opiate withdrawal may occur	No clinically significant interaction
Lopinavir/ritonavir	Opiate withdrawal may occur	No clinically significant interaction

Tuberculosis Medications		
Rifampin	Opiate withdrawal may occur	Opiate withdrawal may occur
Rifabutin	No clinically significant interaction	Reduction in buprenorphine and rifabutin levels not likely to be clinically significant
Hepatitis C		
Interferon	No clinically significant interaction	Not studied in human pharmacokinetics studies
Ribavirin	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Other Infections		
Fluconazole	Increased methadone plasma concentrations	Not studied in human pharmacokinetics studies
Voriconazole	Increased methadone plasma concentrations	Not studied in human pharmacokinetics studies
Ciprofloxacin	Increased methadone plasma concentrations	Not studied in human pharmacokinetics studies
Clarithromycin	Increased methadone plasma concentrations	Not studied in human pharmacokinetics studies
Antidepressants		
Fluoxetine	Reported association with increased levels of methadone	Not studied in human pharmacokinetics studies
Fluvoxamine	May cause increased methadone plasma levels and discontinuation has been associated with onset of opioid withdrawal	Not studied in human pharmacokinetics studies
Sertraline	No reported adverse drug interaction	No clinically significant interaction
Citalopram	No reported significant interaction	No clinically significant interaction
Mirtazepine	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Duloxetine	May potentially lead to increased duloxetine exposure, but not studied in humans	Not studied in human pharmacokinetics studies
Amitriptylene	Could be associated with increases in plasma methadone concentrations	Not studied in human pharmacokinetics studies

St. John's Wort	Increased metabolism and elimination of methadone	Increased metabolism and elimination of buprenorphine
Desipramine	Associated with increased desipramine levels	Not studied in human pharmacokinetics studies
Dextromethorphan	Associated with delirium	Not studied in human pharmacokinetics studies
Antipsychotics		
Quetiapine	Increased plasma methadone concentrations	Not studied in human pharmacokinetics studies
Risperidone	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Clozapine	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Aripiprazole	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Olanzapine	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Ziprasodone	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Anxiolytics		
Diazepam	Associated with increased sedation and impaired performance on psychological tests	Associated with increased sedation and impaired performance on psychological tests
Alprazolam	Fatalities have been associated with combined use	Fatalities have been associated with combined use
Anticonvulsants		
Carbamazepine	Associated with opiate withdrawal	Not studied in human pharmacokinetics studies
Phenytoin	Associated with opiate withdrawal	Not studied in human pharmacokinetics studies
Phenobarbital	Associated with opiate withdrawal	Not studied in human pharmacokinetics studies
Oxcarbazepine	No clinically significant interaction reported	Not studied in human pharmacokinetics studies
Lamotrigene	No clinically significant interaction reported	Not studied in human pharmacokinetics studies

Topiramate	No clinically significant interaction reported	Not studied in human pharmacokinetics studies
Psychostimulant Medications		
Methylphenidate	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Pemoline	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Modafinil	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Antihistamines		
Promethazine	May have synergistic depressant effect	Not studied in human pharmacokinetics studies
Diphenhydramine	May have synergistic depressant effect	Not studied in human pharmacokinetics studies
Cardiac and Pulmonary Disease Medications		
Digoxin	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Quinidine	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Verapamil	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Heparin	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Theophylline	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Aspirin	No clinically significant interaction reported; but potential for aspirin accumulation	Not studied in human pharmacokinetics studies
Psychostimulants		
Cocaine	Decrease in trough methadone concentrations	Increased buprenorphine metabolism and diminished plasma concentrations
Methamphetamine	Not studied in human pharmacokinetics studies	Not studied in human pharmacokinetics studies
Alcohol	Severe adverse events including death, eliminated more rapidly in methadone maintained	Not studied in human pharmacokinetics studies

Patient education: When a patient is seeking pharmacotherapy for opioid dependence, they should be informed of the risks and benefits of methadone or buprenorphine therapy including the possibility of adverse drug interactions that might be associated with either symptoms of opiate withdrawal (to date this has been observed with certain antiretroviral medications and methadone, some anticonvulsants and methadone, and tuberculosis medications (i.e.: rifampin) and either methadone or buprenorphine) or opiate excess (this has been observed in two clinical situations: 1. when a medication that inhibits opioid metabolism or has a synergistic pharmacodynamic interaction with the opioid is given with either methadone (potential exists for such interactions with several antidepressant and anxiolytic medications (see above) or buprenorphine (potential for adverse drug interactions with benzodiazepines) or 2. when methadone has been given with a medication that induces its metabolism resulting in higher doses of methadone needed, then the inducing medication is discontinued without a concomitant reduction in methadone dose leading to methadone toxicity).

Recommendations: Level of evidence: **High – Clinical observation and controlled pharmacokinetics/pharmacodynamics studies**

- 1. For the patient who is methadone-maintained and requires initiation of a medication(s) that may alter methadone metabolism or have a pharmacodynamic interaction with methadone:** Patients should continue on their current methadone dose and should be informed of the potential for drug interactions that may cause them to experience either symptoms of opiate withdrawal or opiate excess (sleepiness, impaired thinking). Patients should be encouraged to immediately report any adverse symptoms to their prescribing provider and to clinical staff at the methadone maintenance program (should the patient be methadone-maintained). It should be recognized that patients receiving medications that alter methadone exposure may require methadone dose adjustments. For those in methadone maintenance therapy, a trough methadone level prior to initiation of a medication that might alter plasma methadone concentrations, as well as a trough methadone level when a patient experiences symptoms thought to be opiate withdrawal/excess may be helpful. A significant decrease or increase in trough methadone concentration would indicate a need for increasing/decreasing the methadone dose. In patients experiencing acute, severe opiate withdrawal symptoms; the methadone dose should be addressed immediately. In a patient showing evidence of acute onset of opiate withdrawal, the methadone dose can be increased immediately to prevent non-adherence to prescribed medications and/or abuse of illicit/nonprescribed drugs. The methadone dose can be increased by up to 5-10 mg every 2-3 days until the patient is restabilized (if the patient requires an increase of 20-25% of the starting methadone dose; follow the response for 5-7 days before continuing methadone dose increases unless moderate to severe opiate withdrawal remains). It is suggested that an objective opiate withdrawal scale (either the Objective Opiate Withdrawal Scale (OOWS) or the Clinical Opiate Withdrawal Scale (COWS) be used to determine the severity of opiate withdrawal when a patient is receiving a medication that may induce methadone metabolism. Dose increases should not be based only on subjective report. Another challenge for patients who are receiving methadone therapy can occur when the patient requires a change in a medication necessitating discontinuation of a medication with properties that result in the induction of methadone metabolism. This can result in increased methadone plasma concentrations that

can place the patient at risk for opioid toxicity unless the methadone dose is also reduced. Another potential toxicity associated with methadone excess is cardiac arrhythmia due to either increased methadone exposure resulting from concomitant treatment with a medication that inhibits methadone metabolism or when a medication that can induce methadone metabolism is discontinued resulting in increased methadone exposure (2). Once a medication that is inducing CYP 450 enzymes associated with methadone metabolism (CYP 450 3A4, 2B6, 2D6) is stopped, the methadone dose should be tapered over 1-2 weeks to return the patient to their previous therapeutic dose of methadone (i.e. that dose on which the patient was stable before starting the HAART regimen) (McCance-Katz et al. 2000).

- 2. For the patient who is buprenorphine-maintained and requires initiation of a medication that may alter its metabolism or be associated with a pharmacodynamic interaction:** Patients should continue on their current buprenorphine/naloxone dose. Patients should be informed of the potential for drug interactions with some medications that may cause them to experience symptoms of opiate excess (sleepiness, impaired thinking) (this has been observed only with atazanavir/ritonavir and some case reports of toxicities with buprenorphine and benzodiazepines in combination to date) or potentially, opiate abstinence (this has been observed with rifampin). Patients should be encouraged to report any adverse events experienced which should be clinically evaluated and if necessary, buprenorphine dose adjustment should be made. If opiate withdrawal is experienced in a buprenorphine-maintained patient taking a medication that induces buprenorphine metabolism (such as the CYP 450 3A4 inducer, rifampin), a 25-50% increase in buprenorphine dose can be given for 1 week followed by reduction to the former, lower buprenorphine dose on which the patient was stable.
- 3. For the opiate-addicted patient considering opioid therapy:** The choice of opioid therapy should be based on the assessment of patient clinical needs. Thus far, buprenorphine has fewer clinically significant drug interactions with other medications than does methadone. However, patients who are not good candidates for buprenorphine/naloxone therapy or with high amounts of daily opiate use, those who have a history of high-dose methadone maintenance treatment (> 100 mg daily), those with chronic pain conditions which may require opioid therapy with a full mu opioid agonist medication, pregnant women (at this time methadone maintenance remains the standard of care for pregnant, opiate-addicted patients), and those who may benefit from the increased structure of the methadone maintenance program may be better suited to methadone treatment. Those with opioid addiction who have physicians that can provide buprenorphine treatment may be best treated by that physician for both opioid dependence and other medical disorders. Patients requiring methadone for analgesia and their clinicians should be aware of potential drug interactions as described above and appropriate adjustments in methadone dose made when clinically indicated.

References:

1. McCance-Katz EF, Sullivan LS, Nallani S: Drug interactions of clinical importance between the opioids, methadone and buprenorphine, and frequently prescribed medications: A review. *Am J Addictions*, 19: 4–16, 2009.

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Type of evidence:

Randomized trial = **high**

Observational study = **low**

Any other evidence = **very low**

* Grading quality of evidence and strength of recommendations
British Medical Journal, 2004;328;1490-



PCSS Guidance

Topic: Adherence, Diversion and Misuse of Sublingual Buprenorphine

Original Author: Judith Martin, MD

Last Updated: 1/10/14 (Maria A, Sullivan, M.D., Ph.D.)

Guidelines Coverage:

Tip 43, Medication-Assisted Treatment of Opioid Addiction in Opioid Treatment Programs, pages 81-85 (<http://www.kap.samhsa.gov/products/manuals/index.htm>)

Tip 40, Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction (<http://www.kap.samhsa.gov/products/manuals/index.htm>)

Draft, Physician's Guide to Opioid Agonist Medical Maintenance Treatment, Center for Substance Abuse Treatment, chapter 4 and 5.

Clinical Question:

What procedures and interventions might be used in the office-based setting to minimize misuse and diversion of sublingual buprenorphine?

Background:

Buprenorphine is an effective treatment for opioid dependence but can be misused and diverted, causing potential danger to patients and the public. The guidance reviews the types of buprenorphine diversion reported, and some of the monitoring and diversion-control methods available in office practice.

In 2006, participants in the National Survey on Drug Use and Health were asked about sources of misused pain relievers. 70% said they had obtained the pain reliever from a friend or relative. 21% directly from a doctor, 4% from a drug dealer, and 0.1% via the internet.[1] Detailed information is lacking about the sources of misused buprenorphine, but considering the possibility that prescribed buprenorphine prescribed may become diverted to other individuals, it is important to be alert to these potential behaviors in the population of opioid-dependent patients.

Estimates of the frequency of diversion and misuse and diversion of buprenorphine preparations vary. There are several reports of misuse of buprenorphine. In a survey of needle exchange participants in Sweden, 89% of heroin injection drug users reported using buprenorphine, most of these were self-treating withdrawal, with only 11% seeking euphoria with injected buprenorphine.[2] A survey of 316 injection drug users in Melbourne, Australia, showed that 32% had injected buprenorphine in the preceding three months, and for 10% it was their most commonly injected drug. Injecting buprenorphine in this group was associated with having been prescribed sublingual buprenorphine for the treatment of opioid dependence.[3] A U.S. survey of 1000 patients seeking treatment for prescription opioid abuse at 100 drug treatment programs around the country showed that 20 to 35% had misused buprenorphine "to get high" in the past 30 days, but fewer than 3% were primarily addicted to buprenorphine. [4] Some patients in Suboxone (buprenorphine/naloxone) treatment employ a "harm reduction" strategy of sequentially using Suboxone then heroin to avoid withdrawal and to continue their misuse of opioids.

A recent large survey (N=503) of prescription opioid users found that factors which predicted increased risk of use of diverted buprenorphine included an inability to access buprenorphine treatment, meeting

criteria for generalized anxiety disorder and past 30-day use of Oxycontin, methamphetamine, and/or alcohol. These results suggest that improving, rather than limiting, access to buprenorphine treatment may be an effective public health strategy to mitigate buprenorphine abuse (20). Another strategy for decreasing buprenorphine diversion and misuse is that of continuing medical education (CME). Since many physicians have limited addictions training, provision of CME courses focused on buprenorphine clinical pharmacology and best practices has been shown to significantly enhance knowledge and practice behaviors, and to decrease the risks of buprenorphine misuse, diversion, and other adverse events (21).

General Principles:

Buprenorphine is available as a buprenorphine only (mono) preparation and a more common (in the U.S. market) buprenorphine/naloxone combination preparation. Generic preparations of mono and combination products are also available. Buprenorphine diversion can result in use by individuals who take the medication for one of two primary reasons: (1) to prevent opioid withdrawal or (2) to experience euphoria.

The effect that the person experiences from buprenorphine-only and buprenorphine/naloxone will depend on his or her clinical state and the route of administration as outlined below:

Patient	Effect Buprenorphine-only	Effect Buprenorphine/naloxone
Opioid naïve	Opioid agonist effect, euphoria	Opioid agonist effect, euphoria: effect attenuated with injected route
Opioid tolerant with full agonist opioid on receptors	Buprenorphine -nduced withdrawal, aversive (for both oral and injected route)	Buprenorphine-induced withdrawal, aversive (for both oral and injected route)
Opioid tolerant with no opioid agonist on receptors (opioid withdrawal)	Opioid agonist effect, withdrawal relief	Opioid agonist effect, withdrawal relief (possible precipitated withdrawal if injected)
Opioid tolerant with buprenorphine/naloxone on receptors	Primary buprenorphine effect, (possible euphoria if injected)	Primary buprenorphine effect, (low probability of euphoria if injected)

Types of aberrant use of buprenorphine:

- Sharing or selling prescribed medication
- stockpiling medication for use later or in a higher dose.
- Insufflating (snorting), injecting, or rectal use (plugging) of medication intended for sublingual use.
- Poor storage (open medicine cabinet, carried in purse, left in glove compartment, on desk, etc.), loss of pills, or failure to ensure safekeeping of pills from children/others.
- Doctor shopping, with multiple prescribers, or forged prescriptions
- Supplementing legitimate prescriptions with street drugs.

Buprenorphine/naloxone to minimize misuse:

Current evidence from post-marketing surveillance indicates that the majority of buprenorphine that is diverted to use by others is used to prevent opioid withdrawal, not for euphoria. Reports of injected abuse of the buprenorphine (mono product) in Europe and New Zealand prompted the development of a buprenorphine/naloxone combination product in the U.S. (Suboxone®, Zubsolv). The naloxone component is not significantly bio-available when orally or sublingually consumed, but may diminish the agonist effect or precipitate withdrawal if injected. [5, 6] Blinded opioid-dependent research subjects rated the injected buprenorphine/naloxone combination as not desirable compared to the buprenorphine-only preparation or to injected morphine.[5] The buprenorphine/naloxone could not be differentiated from naloxone alone in a blinded setting.[7] In an attempt to evaluate the 'street value' of the buprenorphine/naloxone, participants were asked what they would pay for each of a series of injected substances to which they were blinded, and the estimated street value was significantly less for the combination product than all other preparations except naloxone.[5]

The combination pill was introduced in Finland in the context of widespread abuse of the buprenorphine-only pill by injection. A survey at needle exchange sites showed that 80% of those who had tried the injected buprenorphine/naloxone combination had a bad experience, and the reported street value was half of that of the buprenorphine-only pill.[8] Theoretically the naloxone would not be a disincentive to the opioid-naive injector, and one study showed that in recently detoxified heroin-dependent volunteers, positive subjective ratings were higher after intravenous administration of buprenorphine compared with buprenorphine/naloxone. [9] In addition, research demonstrates that the injection of the buprenorphine/naloxone combination in patients maintained on buprenorphine does not precipitate withdrawal [10]

Other studies have demonstrated that the abuse liability of buprenorphine among heroin-dependent individuals is low; in a comparison with other commonly abused opioids, buprenorphine (at doses up to 8 mg/70 kg) was the only drug not self-administered (17). And among buprenorphine-maintained intravenous heroin abusers, intravenous buprenorphine/naloxone was self-administered less frequently than buprenorphine or heroin ($P < .0005$). In addition, participants reported that they would pay significantly less money for buprenorphine/naloxone than for buprenorphine or heroin (18). In sum, the combination product reduces, but does not eliminate, intravenous misuse. Clinicians thus need to monitor patients in opioid agonist therapy and to take measures to lower the likelihood of diversion.

Types of monitoring:

Four types of adherence/diversion monitoring are available easily in office-based settings: toxicology tests, pill counts, unannounced monitoring [11] and observed ingestion.

Urine tests for buprenorphine and drugs of abuse: Dipsticks or laboratory-based tests for buprenorphine in the urine are inexpensive and can be part of routine office-based monitoring. The presence of buprenorphine in the urine indicates that the patient has taken some portion of the prescribed dose. Absence of buprenorphine in the urine supports non-adherence. Testing for buprenorphine metabolites (only present if buprenorphine is metabolized) may be included to minimize the possibility that buprenorphine is added directly to the urine sample.

Of course, urine tests can be subverted or replaced unless the collection is also observed. Common strategies to minimize falsified urine collections are to: disallow carry-in items (purses, backpacks) into the bathroom, turning-off running water and coloring toilet water to eliminate possibility of dilution, monitoring the bathroom door so that only one person can go in, and testing the temperature of the urine immediately after voiding. The presence of drugs of abuse in a tested sample has implications for treatment, and supports increased structure or a higher level of care. In the case of CNS depressants (e.g. benzodiazepines, alcohol) there is concern about synergistic sedation with the prescribed buprenorphine.

Pill counts: Having the patient bring in the bottle for a pill count at every visit and maintain a medication-taking log helps to ensure that the medication is being taken as prescribed.

Unannounced monitoring: Both urine testing and pill counts can be done 'randomly.' The patient is contacted and must appear to give a urine test and have a pill count within a specified time, for example 24 hours after a phone call. Of course, pill counting can also be subverted, and anecdotal reports of "pill renting" are common.

Observed ingestion: In this type of monitoring the medication is taken in front of a physician or a trained monitor and is observed to gradually shrink under the patient's tongue until it completely absorbed. Some physicians use this type of observation during induction to assure that the patient knows how to take the sublingual medication properly. In addition, if the patient's symptoms of craving or withdrawal do not come under control at usual doses of buprenorphine it might be useful to observe how the patient takes the sublingual medication, whether it is completely absorbing, or whether medication's bioavailability is decreased by swallowing or spitting. Patients who are having difficulty adhering to their buprenorphine can have their medication provided under directly observed therapy thrice weekly from the office, if staffing allows.

Limiting medication supply. When directly observed doses are not practical, short prescription time-spans can be used: for example, weekly or three days at a time.

Use of buprenorphine-only products:

Increased prescribing of buprenorphine-only tablets in the U.S. could result in diversion problems, as have been seen in countries where buprenorphine without naloxone has been used (see above). Diversion and potential increase in overdose deaths from injected use becomes a public health consideration. Based on observed patterns of diversion, a risk-benefit evaluation suggests that use of the buprenorphine-only tablet prescriptions should be limited to patients with low diversion risk and a history of stability who have trouble tolerating or affording the buprenorphine-naloxone combination. In patients who do not meet stability criteria, observed dosing with the buprenorphine-only tablet may be a useful strategy, allowing patients who otherwise might not have access to participate in treatment. Observed dosing is not customary in US pharmacies, but could be done in the office, including less-than daily frequency. For example, Monday thru Friday observed dosing, with Saturday and Sunday doses given at the same time as the Friday dose. Alternate day, twice and three times a week (M,W,F) dosing from the office has also been shown to be effective in several clinical trials.[11-14]

Criteria for unobserved dosing:

The federal regulations governing methadone treatment (42CFR Part 8.12) specify eight clinical considerations that the physician must take into account when allowing unobserved dosing (take-home medication). Although not formulated for office-based practice with buprenorphine, the listed criteria are consistent with markers of improvement in treatment of addictive disorders:

.. "(i) Absence of recent abuse of drugs (opioid or nonnarcotic), including alcohol; (ii) Regularity of clinic attendance; (iii) Absence of serious behavioral problems at the clinic; (iv) Absence of known recent criminal activity, e.g., drug dealing; (v) Stability of the patient's home environment and social relationships; (vi) Length of time in comprehensive maintenance treatment; (vii) Assurance that take-home medication can be safely stored within the patient's home, (viii) Whether the rehabilitative benefit the patient derived from decreasing the frequency of clinic attendance outweighs the potential risks of diversion." [15]

Increased adherence to buprenorphine medication is associated with increased retention and decreased illicit drug use.[16] Observation of every single dose is usually beyond the need or scope of office-based practice, but weekly visits are not unusual, and could be combined with observation on the visit day if necessary. Pharmacies, visiting nurses, or trained significant others (parents, spouses) can observe consumption of doses in some communities. When sublingual buprenorphine/naloxone is dispensed at treatment programs and in some office-based and primary care settings, nurses or other ancillary medical staff observe the dose. Some practices have the patient sit within view of the dispensing nurse or pharmacist until the pill is dissolved, others only check the placement of the pill under the tongue.

"Red Flag" behavior:

Inappropriate use of medication can be associated with changes in behavior suggesting relapse such as: positive toxicology screens, erratic ability to keep appointments or provide payment, requests for early

refills, sudden request for dose increases in a previously stabilized patient, purported intolerance or allergy to naloxone, lost prescriptions, multiple prescribers, prescription forgery, ongoing close ties to those who are selling opioids, close acquaintances (e.g. significant others, spouse, friends) with opioid dependence who are not in treatment

Response to misuse or red flag behavior:

How to respond to misuse of buprenorphine varies by context and patient. Someone with a good track record of adherence to appointments and counseling visits would be treated differently from someone who never stabilized in treatment. Egregious behaviors, such as selling pills, may result in immediate expulsion from the practice. Relapse, which is part of the disease we are treating, is usually addressed by intensifying treatment (higher dose, increased visit frequency, supervised administration) until the patient begins to improve. Other patients may need intensive outpatient or residential care.

Recommendations:

Level of evidence: **Low to Moderate**

1. Use buprenorphine/naloxone instead of the buprenorphine-only product when cost is not a major barrier.
2. Reserve buprenorphine-only product in patients who have trouble affording the combination tablet, and who have a history of stability in treatment and low diversion risk, or with arrangements for observed dosing. Buprenorphine-only is the product of choice for pregnant women.
3. Select appropriate patients for unobserved and take-home dosing.
4. Monitor for "red flag" behaviors that might indicate non-adherence and diversion.
5. Consider checking for the presence of buprenorphine in the urine of patients who are suspected of diversion or non-adherence.
6. Consider pill counts, unannounced monitoring, observed ingestion in patients who are suspected of diversion or non-adherence.
7. Advise patients regarding appropriate medication storage.
8. Patients who are illegally selling or distributing buprenorphine products should be removed from office-based care. If this behavior is related to addiction, for example selling to buy stimulants, referral to a higher level of care in addiction treatment may be indicated.

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PCSS Guidances use the following levels of evidence*:

High = Further research is very unlikely to change our confidence in the estimate of effect.

Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low = Any estimate of effect is very uncertain.

Type of evidence:

Randomized trial = **high**

Observational study = **low**

Any other evidence = **very low**

* Grading quality of evidence and strength of recommendations

British Medical Journal, 2004;328:1490-



How to Prepare for a Visit from the Drug Enforcement Agency (DEA) Regarding Buprenorphine Prescribing

The following document was prepared by the partner organizations of the Physicians' Clinical Support System-Buprenorphine. It provides background information regarding DEA inspection procedures and suggestions on how buprenorphine waived physicians can prepare for a DEA inspection of their office-based practice.

1. Regulations

Congress passed the Drug Addiction Treatment Act (DATA) on October 17, 2000. This act permits qualified physicians to administer or dispense Schedule III, IV, or V narcotic medications, that have been approved for the maintenance and detoxification treatment of a narcotic dependent person. Thus far, the Food and Drug Administration has only approved the use of buprenorphine (mono formulation) and buprenorphine/naloxone for this purpose. The DEA is authorized by the Controlled Substances Act (21 U.S.C. 822 (f) 880 and 21 CFR 1316.03 to enter controlled premises (registered locations) and conduct periodic inspections to ensure compliance with recordkeeping, security and other requirements of the Controlled Substances Act.

2. DEA Inspections of DATA-Waived Physicians

The Drug Enforcement Administration (DEA) is responsible for ensuring that physicians who are registered with DEA pursuant to the Drug Addiction Treatment Act of 2000 (DATA 2000) comply with recordkeeping, security, and other requirements for administering, dispensing or prescribing controlled substances under the CSA. As a result, they conduct on-site, unannounced inspections under the authority of the Controlled Substances Act (CSA). All physicians who administer, dispense, or prescribe Schedule III substances, including buprenorphine, are subject to these routine, random inspections.

3. Inspections vs. Audits

It is important to understand the difference between a DEA audit and a DEA inspection. An "audit" determines the accountability of the controlled substances received and dispensed. The audit is one component of the "inspection" process. With an "inspection," DEA will look only at the records required to be kept for patients receiving buprenorphine products. In most cases, the practitioner will be inspected, not audited. When they arrive, DEA inspectors will

issue a notice of inspection. If the practitioner dispenses buprenorphine products, then an audit will also be conducted of the controlled substances received and dispensed.

4. Required Records

Physicians prescribing buprenorphine and buprenorphine/naloxone should maintain the records required to be kept on every patient in treatment with documentation consistent with the recommendations of the DEA and Federation of State Medical Boards (TIP 40 Appendix F). Assessment Forms such as those available in TIP 40 Appendix B may also be included in patient records. All records must be kept for at least 2 years, and be available for inspection by the DEA and copying by officers and employees of the U.S. authorized by the Attorney General.

- Patients: Waivered physicians may treat up to 30 patients at any one time during the first year after the waiver has been granted to that physician, and thereafter the physician must submit a second notification to CSAT to increase their patient limit to 100 if they wish to increase the number of patients that they treat above 30. Notification forms are available at:
www.buprenorphine.samhsa.gov/howto.html
- Physicians' DEA certificates of registration indicate the patient limit to which they must adhere. The physicians should have a method to keep track of the number of patients for whom they are actively prescribing buprenorphine and/or buprenorphine/naloxone.
- Prescriptions: Prescriptions for buprenorphine and/or buprenorphine/naloxone must include full identification of the patient's name, address, and drug name, strength, dosage, form, quantity, and directions for use. Prescriptions for buprenorphine and/or buprenorphine/naloxone must be dated as of, and signed on, the day when issued [See 21 CFR 1306.05(a)]. Both the physician's regular DEA registration number and the physician's DATA 2000 identification number (which begins with the prefix X) must be included on the prescription [See 21 CFR 1301.28 (d)(3)].
- Records or Copies of the following records must be maintained at the location listed on the practitioner's DEA registration (office):
 - Copy of current DEA registration
 - Copy of state narcotics license (if applicable)
 - Copy of state medical license
- We also recommend the physician maintain:
 - Log of active buprenorphine patients
 - Prescription log

5. The Inspection Process - What to expect

- The investigation should be conducted by a DEA Diversion Investigator who will appear in professional attire (e.g. suit and tie) and will not carry a weapon. DEA policy is to have

at least 2 investigators visit any office. At least one investigator will be a Diversion Investigator, and the second may be a DEA Special Agent or Task Force Officer depending on their staffing for that day. While there is always a chance that the accompanying field personnel will be authorized to have a weapon, DEA has informed the DATA organizations that agents are instructed to be as discreet and professional as possible when arriving at a physician's office.

- The inspector(s) should present his/her DEA credentials and a "Notice of Inspection" which explains the process of the inspection and your rights. You have the right to refuse to consent to the inspection and insist that DEA obtain an administrative warrant. If you believe you require legal advice, you should contact a local attorney.
- The primary purpose of the inspection is to ensure compliance with the recordkeeping and security requirements under CSA and DATA 2000. They will likely verify your credentials including DEA registrations and state licensure and will ask to see three (3) months of records.
- The inspectors will verify the number of patients you are treating to ensure that they are in line with the limits in DATA 2000. **You must keep any log of patients who are treated with buprenorphine, as well as copies of prescriptions for each patient, in the location listed on your DEA registration** (i.e.: if you are treating patients at more than one practice location, you must bring copies of prescriptions/patient logs from each location and store those at the location listed on your DEA registration. This means that not only will you have information in an individual patient record for your buprenorphine-treated patients, but you will also need to keep a separate record of all patients/prescription copies at the location listed on your DEA registration. Failure to do this will result in problems during the inspection as DEA will not be able to easily determine your adherence to patient limits.
 - *NOTE: It is important to note that DEA does not stipulate the way the prescriptions records have to be maintained. A log or file would be an efficient way to maintain the record, but DEA cannot mandate this format. If you have kept a complete log of all of your patients receiving buprenorphine treatment, they should not need to look at individual patient records.*
 - If you have all of this information easily accessible, the inspection should be fairly rapid. You do not have to be with them as they check your logs. You can have a staff person/office manager, etc. do this. Typically inspection visits last between 1 and 2 hours.
- If you are dispensing or administering buprenorphine in addition to prescribing, they will probably take an inventory of the product on hand and reconcile that with the records of what was received/dispensed/administered. The investigator will also be checking to see that the drugs are properly secured within the facility.

- **Storage and Dispensing:** For those physicians dispensing medication directly from their office, 21 CFR 1301.75 stipulates that buprenorphine/naloxone and buprenorphine should be stored in a securely locked, substantially constructed cabinet. The physician must keep a record of the amount received and dispensed (21 CFR 1304.22) and a physical inventory of all stocks on hand pursuant to 21 CFR 1304.11. The individual practitioner must also include the identification number on all records when dispensing and on all prescriptions when prescribing these narcotic drugs. See 21 CFR 1301.28 (d)(3). The physician must notify the local DEA office, in writing, of the theft or significant loss of any buprenorphine or buprenorphine/naloxone, within one business day.

6. If there is a violation

If the DEA investigator finds that there are administrative violations, s/he can issue a “Letter of Admonition” outlining the problems found in the audit. The physician then has 30 days to respond to DEA with information about how the problem was corrected. If you receive an onsite inspection and experience any problems, please contact the Providers’ Clinical Support System – for Medication Assisted Treatment at pcssmat@aaap.org

7. References

- **TIP 40: Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction**, Chapter 6, pp 79-85; Appendix F p 135; Appendix Band C p. 101-119. Laura McNicholas, Consensus Panel Chair M.D. Ph.D. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment
<http://www.kap.samhsa.gov/products/manuals/index.htm>
- DEA Requirements for DATA-Waived Physicians Who Treat Narcotic Addiction Using Buprenorphine:
http://www.deadiversion.usdoj.gov/pubs/docs/dwp_buprenorphine.htm
- SAMHSA/CSAT Information on Record Keeping:
<http://www.buprenorphine.samhsa.gov/faq.html#A9>
- For additional information about the recordkeeping and security requirements for controlled substances, please see:
<http://www.deadiversion.usdoj.gov/faq/general.htm#rr-1>



PCSS Guidance

Topic: Physician Billing for Office-based Treatment of Opioid Dependence

Last updated: 11/27/13 (Maria A, Sullivan, M.D., Ph.D.)

Office-based treatment is regular medical care provided in customary settings by regular physicians. Therefore, billing procedures are standard ones.

The ICD-9 Code for opioid dependence is 304.0x. The fifth (x) digit sub-classifications are: 0=unspecified, 1=continuous, 2=episodic, 3=in remission

Physicians code for professional services using billing codes developed by the AMA. Current Procedural Terminology (CPT) codes are developed by consensus panels and updated regularly. All payers accept CPT billing codes.

There are no Addiction Medicine-specific CPT codes. Addiction medicine physician services for inpatient detoxification, outpatient detoxification, and office-based maintenance, are the same as codes for other ambulatory care services.

Non-psychiatric Physicians use CPT codes they are accustomed to using for outpatient evaluation and management:

- Outpatient New Patient (99201-05)
- Outpatient Consultation (99241-45)
- Outpatient Established Patient Revisit (99211-15)

Psychiatrists usually choose to use regular psychiatric CPT codes

- Outpatient New Patient (90872): Psychiatric diagnostic evaluation with medical services; includes prescribing of medications
- Outpatient Consultation (99241-45)
- Outpatient Medication Management (99213): Individual outpatient treatment with medical evaluation
- Outpatient Psychotherapy*(90832-36)
- Outpatient Group Psychotherapy (90853)

Psychiatrists' CPT codes are time-based. Other physicians' CPT codes are complexity-of-service based. Services for office-based treatment of opioid dependence provided within the context of Intensive Outpatient Services can use Group Therapy codes, but most physicians will submit an MD/DO-specific charge instead of having charges wrapped into IOP charges.

Healthcare Common Procedure Coding System (HCPCS) are codes used by doctors and other healthcare professionals Injection, naltrexone, depot form (J2315)



PCSS Guidance

Topic: Pregnancy and Buprenorphine Treatment

Original Author: Judith Martin, M.D.

Updated: 2/4/2014 (Maria A. Sullivan, M.D., Ph.D.)

Guideline Coverage:

This topic is also addressed in:

1. TIP 43: Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs, SAMHSA 2008.
2. TIP 40: Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction, pp.68-70. <http://www.kap.samhsa.gov/products/manuals/tips/numerical.htm>

Clinical Questions:

1. If a female patient of child-bearing age is requesting buprenorphine treatment, what should I do? (i.e. informed consent, birth control, etc)
2. If a patient is already on buprenorphine. Should I keep her on it during a pregnancy?
3. Does it matter whether she is given the mono (buprenorphine) or combo (buprenorphine/naloxone) product?
4. If a new opioid-dependent patient is pregnant and requests buprenorphine treatment, what should I do?
5. Is buprenorphine treatment during pregnancy safe?
6. How can detoxification (medically supervised withdrawal) be carried out if a pregnant patient wants to stop all opioids, including buprenorphine?
7. How does buprenorphine treatment compare with methadone treatment for pregnant women?
8. Does treatment of pregnant women change, depending on whether the patient abuses heroin or prescription opioids?
9. Is breastfeeding safe while taking buprenorphine?
10. What neonatal withdrawal is expected when mothers take buprenorphine?

Background:

The prevalence of opioid use among pregnant women ranges from 1-2% to as high as 21% (Minozzi et al. 2013). Heroin or prescription opioid abuse during pregnancy is often closely associated with a multitude of environmental factors that can contribute to adverse consequences including fetal growth restriction, premature labor, miscarriage and low birth weight, an important risk factor for later developmental delay. Methadone maintenance has been the treatment of choice for opioid-dependent women since the 1970s, and given in the context of comprehensive care improves outcomes compared to heroin. Treatment of pregnant opioid-dependent women with methadone, in combination with prenatal care, has been found to reduce the incidence of

neonatal mortality due to low birth weight (Finnegan et al. 1977). However, prenatal methadone exposure may result in a neonatal withdrawal syndrome (sometimes called neonatal abstinence syndrome).

Although neonatal opioid withdrawal can be treated successfully with pharmacotherapy, the effects of intra-uterine narcotic exposure on the developing nervous system are not fully characterized. Methadone-exposed neonates have consistently been found to smaller lateral ventricles and smaller head circumferences during the first few months of life, but there do not appear to be any developmental sequelae related to prenatal opioid exposure (Kaltenbach and Finnegan 1989). However, in carefully selected patients, detoxification may be accomplished during the second or early third trimester (Stanhope et al. 2013).

The neonatal abstinence syndrome (NAS) is a generalized disorder, occurring in over half of opioid-dependent women, characterized by signs and symptoms indicating opioid withdrawal, including dysfunction of the autonomic nervous system, gastrointestinal tract and respiratory system.¹ With appropriate intervention, withdrawal signs can be alleviated without damaging consequences. If a withdrawal syndrome occurs, it typically peaks at three days after birth, and even in carefully managed patients on split dosing requires treatment in over 40 percent of cases.² There are case studies showing that buprenorphine is safe and effective for the treatment of neonatal abstinence syndrome (Kraft et al. 2008).^{3,4} A large non-randomized observational prospective study comparing methadone and buprenorphine showed similar neonatal outcomes with both medications.⁵ Yet certain differences in the profile of neonatal abstinence syndrome between methadone- and buprenorphine-exposed neonates have been identified. Total NAS score and several specific signs (tremors, hyperactive Moro reflex, excessive irritability, failure to thrive) have been observed to be significantly more frequent in methadone-exposed neonates, while sneezing was more frequent among buprenorphine-exposed neonates. Also, methadone-exposed infants require treatment significantly earlier in the postnatal period than do buprenorphine-exposed infants (Gaalema et al. 2012).

There are no specific studies examining maternal and neonatal outcomes following buprenorphine treatment during pregnancy using women who were dependent on prescription opioids. Overall, findings from comparative studies of methadone and buprenorphine, including randomized clinical trials, indicate that both medications are effective in preventing relapse to illicit opioids in opioid-dependent pregnant patients. Fetal monitoring has suggested that buprenorphine results in less fetal cardiac and movement suppression than does methadone. In addition, buprenorphine results in less severe neonatal abstinence syndrome than does methadone (Jones et al. 2012).

Buprenorphine is pregnancy category C; there are limited data in humans, but potential benefits may warrant use of the drug in women despite potential risks. Physicians should use buprenorphine in pregnancy using a risk/benefit analysis, informing the patient about the still unproven status of buprenorphine treatment. A recent secondary analysis failed to support failed to find a relationship between maternal dose at delivery and any of 10 neonatal clinical outcomes, including NAS severity (Jones et al. 2014). Methadone is also a pregnancy category C medication, although with longer clinical use, and methadone maintenance is the current standard of care in the US. Repeated episodes of fetal withdrawal are considered harmful, hence tapering or detoxification is relatively contraindicated. Breastfeeding while in treatment with buprenorphine is likely safe, due to its known poor oral bioavailability, in spite of the package insert statement that it is not recommended. A growing body of observational and controlled trials suggests that buprenorphine is emerging as a first-line treatment for pregnant opioid users.

Recommendations:

Level of evidence: Low/moderate, three trials of pregnant women comparing outcomes for buprenorphine and methadone (Minozzi et al. 2013). There is still a need for randomized controlled trials of adequate sample size comparing different opioid agonist maintenance treatments.

Although methadone maintenance is associated with better treatment retention than buprenorphine, buprenorphine maintenance during pregnancy was associated with improved maternal and fetal outcomes, compared with no medication-assisted treatment. Rates of neonatal abstinence syndrome are similar among infants born to methadone- vs. buprenorphine-maintained mothers, but symptoms were less severe for infants whose mothers were treated with buprenorphine maintenance (Thomas et al. 2014). Pregnant patients should be offered methadone maintenance when available, to prevent relapse in the mother and to avoid withdrawal in the fetus. Pregnant patients should be informed that buprenorphine is not a proven treatment during pregnancy, and the clinician should obtain the patient's signature documenting her refusal of methadone maintenance and her understanding of the unproven status of buprenorphine treatment during pregnancy. Pregnant opioid-dependent women should be co-managed with an obstetrician familiar with high-risk pregnancy and neonatal withdrawal treatment.

If a patient is taking buprenorphine during pregnancy, every effort should be made to prevent fetal withdrawal. The way to do this is to prevent maternal withdrawal by encouraging regular and adequate dosing, and by discouraging tapers. Surrogate markers for fetal withdrawal are maternal withdrawal, including craving, and increase in fetal motion. If a patient absolutely refuses maintenance and desires medically supervised withdrawal, this should be carried out in collaboration with obstetric care, if possible with fetal monitoring. It is thought that the second trimester is the safest time to carry out MSW in order to avoid miscarriage or premature labor.

If the patient is being maintained on buprenorphine during pregnancy, most experts recommend that she be given the mono product, as few studies have investigated the efficacy of buprenorphine with naloxone, and the combination product has been suggested to possibly have teratogenic effects in (Sokya 2013). For women who become pregnant while using the combination product, switching to the mono product is recommended.

In the case of unstable patients, smaller prescriptions, observed dosing, or more frequent visits are recommended, to avoid injection abuse of the mono product. But there is growing evidence that the combination product may also be safe in pregnancy. A small study of 10 opioid-dependent women treated with the buprenorphine + naloxone film product concluded that maternal findings were unremarkable and comparable to those seen with the mono product (Debelak et al. 2013). While four out of ten neonates were treated for neonatal abstinence syndrome (NAS), its severity was similar to outcomes observed with the mono product. And a recent meta-analysis comparing buprenorphine/naloxone to buprenorphine and methadone in the treatment of opioid dependence during pregnancy found no significant differences in maternal outcomes for buprenorphine + naloxone, compared to buprenorphine, methadone, or methadone-assisted withdrawal (Lund et al. 2013). Preliminary findings suggested no adverse maternal or neonatal outcomes associated with the use of the combination product during pregnancy. Neonatal head circumference was significantly higher in the group exposed in utero to buprenorphine + naloxone, compared to neonates exposed to methadone-assisted withdrawal. This finding is consistent with earlier studies suggesting that opioid maintenance is associated with better prenatal care and lower risk of relapse than is abstinence without pharmacologic support.

A retrospective study of the relationship between breastfeeding and neonatal abstinence syndrome in women maintained on buprenorphine during pregnancy found that more than three quarters of women chose to breastfeed their infants after birth (O'Connor et al. 2013). Although the findings did not reach statistical significance, infants who were breastfed has less severe NAS and were less likely to require pharmacologic treatment (23.1% vs. 30.0%) than infants who were not breastfed.

In summary, it is essential that clinicians take a collaborative, multidisciplinary care approach for pregnancies complicated by chronic narcotic use (Stanhope et al. 2013). A growing body of evidence suggests that management of opioid dependence with either methadone or buprenorphine is appropriate during pregnancy and breastfeeding. Prescription monitoring programs such as the Risk Evaluation and Management Strategy (REMS) may help to prevent inappropriate prescribing or diversion.

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High = Further research is very unlikely to change our confidence in the estimate of effect

Moderate= Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low = Any estimate of effect is very uncertain.

Type of evidence:

Randomised trial = **high**

Observational study = **low**

Any other evidence = **very low**

* Grading quality of evidence and strength of recommendations

British Medical Journal.2004:328:1490-



PCSS Guidance

Topic: The Off-Label Use of Sublingual Buprenorphine and Buprenorphine/Naloxone for Pain

Original Author: Adam J. Gordon, MD, MPH, FACP, FASAM

Last Updated: 11/29/13 (Maria A. Sullivan, M.D., Ph.D.)

Guideline Coverage:

This topic is briefly addressed in Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction (TIP 40), pages 75-76. http://buprenorphine.samhsa.gov/Bup_Guidelines.pdf

Clinical Questions:

1. Do buprenorphine and buprenorphine/naloxone effectively treat pain syndromes?
2. Should one use buprenorphine and buprenorphine/naloxone for pain syndromes?

Background:

Buprenorphine is a partial agonist at the mu opioid receptor. Buprenorphine is available as a sublingual analgesic tablet in low doses (e.g. 0.2 mg) internationally but not in the United States. Current commercially available formulations in the U.S. include a sublingual tablet and an intravenous formulation.

The sublingual formulations of buprenorphine (buprenorphine SL tablets and buprenorphine/naloxone SL film) are Schedule III medications that are approved by the Food and Drug Administration (FDA) for use in opioid dependence (addiction) treatment. This approval does not include explicit or implicit approval of buprenorphine SL and buprenorphine/naloxone SL for pain syndromes (either acute or chronic).

The parenteral formulation of buprenorphine is approved for the treatment of pain. Federal documents indicate that parenteral buprenorphine is not approved for the treatment of opioid dependence (addiction). <http://buprenorphine.samhsa.gov/faq.html#A3>

There is low quality evidence from clinicians who have used buprenorphine SL and buprenorphine/naloxone SL formulation for the primary treatment of pain syndromes in patients with and without a diagnosis of opioid dependence (addiction). Practitioners who are prescribing buprenorphine SL or buprenorphine/naloxone SL for the primary treatment of opioid dependence (addiction) in patients with co-existing pain syndromes would be prescribing under the auspices of DATA 2000.

Practitioners who are prescribing buprenorphine SL or buprenorphine/naloxone SL for pain in patients without opioid dependence (addiction) diagnosis would be prescribing a controlled, Scheduled III, medication in an off-label manner.

There are several challenges to off-label use of buprenorphine SL or buprenorphine/naloxone SL for the primary treatment of pain. [1] No peer-reviewed published data or clinical practice guidelines are available to advise as to the type of pain, the severity of pain, appropriate dose or appropriate dosing intervals of buprenorphine SL or buprenorphine/naloxone SL for the management of acute or chronic pain. Buprenorphine's relatively short duration of action as an analgesic (6-9 hours) contrasts with its protracted efficacy as a medication for the treatment of opioid dependence (addiction) which can be dosed on a daily or less-than-daily basis.[2] There is no evidence that buprenorphine or buprenorphine/naloxone SL provides better analgesia than short-acting oral opioids, although buprenorphine does have a favorable safety effect profile and a ceiling on its agonist effects. When used as a primary medication for the treatment of chronic pain, buprenorphine or buprenorphine/naloxone induces physiological dependence but would not be expected to lead to addiction if taken as prescribed. As a partial mu-agonist with high

affinity for that receptor, buprenorphine SL or buprenorphine/naloxone SL effectively blocks the analgesic properties of other opioids that could be used to treat acute pain. Therefore, buprenorphine SL or buprenorphine/naloxone SL generally precludes the use of other opioids as an adjunctive treatment for pain syndromes. Finally, there is concern that widespread use of buprenorphine SL or buprenorphine/naloxone SL for use in pain syndromes may raise the likelihood of diversion and misuse of buprenorphine products, potentially leading to a restriction in the expansion of treatment of opioid dependence which was the intent of DATA 2000.

There are few methodologically rigorous studies to support the use buprenorphine SL or buprenorphine/naloxone SL in treating pain. One case series using an unvalidated pain rating scale examined whether buprenorphine/naloxone SL provided pain relief in 95 patients with chronic pain transitioned from opioid full agonists (8% met criteria for opioid dependence/addiction).[3] Patients received 2 to 20 mg buprenorphine/naloxone SL in unspecified divided doses at unspecified intervals. Quantitative results on the outcome of pain were not provided. Eighty-six percent reported qualitative improvement in their pain ratings although the timing, duration or magnitude, statistical or clinical significance of the improvement was not provided by the authors. A second unblinded, non-randomized study reported on a case series of 23 patients receiving limited to no benefit from full agonist opioids for pain who underwent medically supervised withdrawal with buprenorphine or buprenorphine and ibuprofen. Treatment was provided in an inpatient setting for 21 of the 23 subjects over a maximum of 180 days. Pain scores decreased in both groups over time with no statistically significant difference between the two groups.[4]

More rigorous evidence for the effectiveness and wide safety margin of buprenorphine in pain management has slowly begun to accumulate. One recent trial of buprenorphine/naloxone for the treatment of opioid-abusing patients with chronic pain found that sublingual buprenorphine/naloxone (2, 8, and 16 mg per day dosed QID) significantly reduced pain in a 7-week inpatient study, compared to preadmission ratings. Buprenorphine/naloxone also reduced patients' preference for oxycodone in a drug vs. money human subjects laboratory paradigm (5). Since buprenorphine/naloxone has been noted to produce a dose-related reduction in some of the effects of acutely administered oxycodone (6), buprenorphine/naloxone may have potential to serve as an analgesic in patients with a history of opioid abuse. But further research is needed to replicate these findings regarding the efficacy of buprenorphine as an analgesic. One large (N=76) study has recently provided additional support for buprenorphine as an effective pain treatment and method of stabilizing opioid dosing. Following brief hospitalization (median stay 2 days), two thirds of patients previously treated with morphine-equivalent doses exceeding hundreds of milligrams per day were stabilized on buprenorphine (median daily discharge dose was 8 mg). Two thirds of patients reported moderate to dramatic improvements in pain and functional status, including a return to employment (7).

General Principles:

1. Sublingual tablet formulations of buprenorphine and buprenorphine/naloxone are only FDA-approved for the treatment of severe opioid use disorder (addiction).
2. Sublingual tablet formulations of buprenorphine and buprenorphine/naloxone are not FDA-approved for the treatment of pain. Use of the medications in this manner is not illegal but constitutes off-label prescribing.
3. Sublingual formulations of buprenorphine and buprenorphine/naloxone may provide mild analgesia in opioid-dependent (addicted) individuals with acute and chronic pain [low]
 - a) Dividing the dose of buprenorphine SL and buprenorphine/naloxone SL to twice, or three, times a day may impart more consistent analgesia effect than single daily doses [low]

Recommendations:

1. Sublingual tablet formulations of buprenorphine and buprenorphine/naloxone should be used for the treatment of opioid dependence (addiction).
2. Sublingual tablet formulations of buprenorphine and buprenorphine/naloxone may be used in patients with opioid use disorder (addiction) who have an acute or chronic pain condition (See PCSS guidance: Treatment of acute pain in patients receiving buprenorphine/naloxone).
3. Further studies that examine the efficacy and comparative effectiveness of sublingual tablet formulations of buprenorphine and buprenorphine/naloxone for pain should be conducted.

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Observational study = **low**

Any other evidence = **very low**

* Grading quality of evidence and strength of recommendations

British Medical Journal. 2004;328:1490-



PCSS Guidance

Topic: Treatment of Acute Pain in Patients Receiving Buprenorphine/Naloxone

Original Author: David Fiellin, M.D.

Last Updated: 03/09/14 (Maria A. Sullivan, M.D., Ph.D.)

Guideline Coverage:

This topic is also addressed in:

- (1) SAMHSA Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction (TIP 40), page 75-76. <http://www.ncbi.nlm.nih.gov/books/NBK64245/pdf/TOC.pdf>
- (2) Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Treatment Improvement Protocol (TIP) Series 43. HHS Publication No. (SMA) 12-4214. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2005. Available online at: <http://www.ncbi.nlm.nih.gov/books/NBK64164/pdf/TOC.pdf>

Clinical Question:

How do I manage acute pain in a patient receiving buprenorphine/naloxone (bup/nx; Suboxone, Zubsolv) for the treatment of opioid dependence?

Background:

Sublingual buprenorphine/naloxone (Bup/nx), a partial agonist at the mu opioid receptor, is approved for addiction treatment and may be a useful strategy for pain management, particularly for opioid-treated chronic pain patients with non-adherence behaviors. In Europe, transdermal buprenorphine is commonly used for the management of non-cancer, moderate-to-severe chronic pain (Gatti et al., 2010, Likar et al., 2006). For sublingual buprenorphine, the duration of analgesic effect is limited to 6-8 hours; thus, pain management with buprenorphine would require dosing on a TID or QID schedule. As a mu agonist, buprenorphine effectively blocks, or significantly attenuates, the analgesic properties of other opioids that could be used to treat acute pain. In addition, providing buprenorphine can result in precipitated withdrawal in a patient who has recently taken a full agonist opioid medication to treat acute pain.

Emerging Evidence for Management of Acute Pain in Buprenorphine-maintained Individuals:

As the use of buprenorphine or buprenorphine/naloxone agonist treatment for opioid dependence has increased in the past decade, managing acute and sub-acute post-operative pain in such patients has become a recognized clinical challenge. The high-affinity mu-receptor binding of buprenorphine renders other opioids ineffective or reduces their efficacy. Yet it is important to continue opioid substitution therapy for patients undergoing surgery. A recent study found that, among surgical patients who had been maintained on buprenorphine pre-operatively, withholding buprenorphine on the day after surgery significantly increased their requirement for patient-controlled analgesia opioid ($p=.02$), compared with those who had received their daily dose (Macintyre et al., 2013). And similarly, in patients taking buprenorphine (Suboxone, Subutex, Zubsolv) who require oral surgery, it is important to be certain that procedural sedation and analgesia is sufficient, and to be aware of the risk of significant interactions between buprenorphine and other opioids, in order to avoid perioperative complications (Wasson et al., 2013). If buprenorphine is discontinued, re-starting it while there is a full opioid agonist present can precipitate acute opioid withdrawal. Thus, resuming buprenorphine maintenance should be deferred until the opioid being administered for acute pain is withdrawn. The general principles of buprenorphine induction will then be applicable (see PCSS-MAT Clinical Guidance on this topic; Lee et al., 2009). In general, it is necessary to wait 12-18 hours after administration of a short opioid, and 24-36 hours after administration of a long-acting opioid. Buprenorphine should be resumed by starting with a small test dose

of 1-2 mg and observing for signs and symptoms of opioid withdrawal. If the patient tolerates the dose well (relief of withdrawal, either temporary or sustained), then a second dose of 2-4 mg can be given, and the dose quickly titrated up over the next 1-2 days to achieve the previous maintenance dose.

It is important to distinguish the management of acute pain in patients taking buprenorphine from the use of buprenorphine in patients with chronic pain. In treatment settings for opioid dependence such as methadone programs or residential treatment, rates of current pain are as high as 80% (Rosenblum et al. 2003). In the past few years, buprenorphine/naloxone has been increasingly prescribed off-label for chronic pain management (Rosen et al., 2014). Buprenorphine/naloxone has been found to provide analgesic relief in a few recent trials of patients at risk of opioid abuse (Roux et al., 2013, Neumann et al., 2013). In one study, transitioning patients with chronic pain and high tolerance to opioids to buprenorphine was found to be associated with significant reductions in pain (Daitch et al., 2012), and it has been suggested that buprenorphine may exert an anti-hyperalgesic effect. But another recent investigation found that non-adherent patients on either high (>300 mg) or low (\leq 20 mg) doses of baseline oral morphine were more likely to have early adverse events when switched to buprenorphine/naloxone (Rosenblum et al., 2012) and to discontinue treatment. These findings point to the importance of flexible dosing standards for practitioners treating patients with off-label buprenorphine/naloxone for concurrent pain and opioid addiction, and they also suggest that there is an optimal baseline opioid dosing range associated with successful transition to buprenorphine/naloxone.

General Principles:

Inform patient of your awareness of his or her addiction and provide reassurance that a history of opioid addiction will not be an obstacle to acute pain management. Include the patient in the decision-making process to allay anxiety about relapse. Offer addiction counseling as needed. Patients who are opioid dependent should not be denied pain treatment with opioids when medically indicated. Maintenance opioids should not be expected to adequately treat new onset acute pain, and discontinuation of buprenorphine/naloxone in patients experiencing acute pain will increase the patient's requirement for acute analgesic relief. Patient-controlled anesthesia (PCA) can be used in opioid-dependent patients with acute pain. To avoid precipitated withdrawal, resuming buprenorphine maintenance should be deferred until the opioid being administered for acute pain is withdrawn.

Recommendations:

Level of evidence: **Low – moderate: expert opinion/clinical experience, non-controlled trials, and small controlled trials**

For patients receiving bup/nx who develop or are anticipated to have acute and limited (e.g. 2 hours to 2 weeks) pain that will not be adequately treated with non-opioid analgesia, the following steps are recommended:

1. Anticipated pain (e.g. elective surgery, tooth extraction)
 - Temporarily discontinue bup/nx 24-36 hours prior to anticipated need for analgesia
 - Provide adequate opioid analgesia, titrate to effect. It is good practice to know the usual doses needed for patients undergoing the planned procedure. Discuss with your colleagues and remember that patients who are opioid dependent and who have recently received bup/nx will likely need higher-than-usual doses of opioid analgesics due to their physical tolerance and/or narcotic blockade from recent doses of bup/nx.
 - Do not provide bup/nx while patient is receiving opioid analgesia.
 - Discontinue opioid analgesia once pain has remitted or can be managed with non-opioid analgesia.
 - Allow patient to experience mild to moderate opioid withdrawal.
 - Re-induce patient onto bup/nx as per usual induction protocol.
 - Note: single doses of opioid analgesics (e.g. post dental extraction) may be effective even if bup/nx has not been discontinued. However, patients should be cautioned to avoid bup/nx dosing during period that opioid analgesic is likely to be occupying receptors.
2. Unanticipated pain (e.g. major trauma, renal colic, acute fracture)
 - Determine when the last dose of bup/nx was ingested and temporarily stop bup/nx.
 - Options to consider: regional anesthesia, increased dose of buprenorphine, high potency opioid such as fentanyl, providing alternate opioid agonist treatment such as methadone during period

- of pain management.
- Provide adequate opioid analgesia, titrate to effect. It is good practice to know the usual doses needed for patients who experience this event. Discuss with your colleagues and remember that patients who are opioid dependent and who have recently received bup/nx will likely need higher than usual doses of opioid analgesics due to their physical tolerance and/or narcotic blockade from recent doses of bup/nx.
- Monitor/caution patients regarding the potential for over-sedation during the first 72 hours after the last bup/nx dose. While the initial effect of a full agonist may be blocked by buprenorphine, as this blockade fades, the full agonist effect may become clinically evident.
- Do not provide bup/nx while patient is receiving opioid analgesia.
- Discontinue opioid analgesia once pain has remitted or can be managed with non-opioid analgesia.
- Allow patient to experience mild-to-moderate opioid withdrawal for safe re-initiation of bup/nx.
- Re-induce patient onto bup/nx as per usual induction procedure.

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Type of evidence:

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Observational study = **low**

Any other evidence = **very low**

* Grading quality of evidence and strength of recommendations

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Buprenorphine Online Certification Links:

<http://buprenorphine.samhsa.gov/pls/bwns/training> (repository with several sources)

AAAP

<http://www.aaap.org/education-training/buprenorphine/>
(\$125 members, \$200 non members)

APA

<http://www.apaeducation.org/ihtml/application/student/interface.apa/index.htm?dvar=1>
(free APA members-in-training, \$100 APA members, \$200 non members, 8 CMEs)

ASAM

<http://www.buppractice.com/>
(\$200 and 9 CMEs)

Other Useful links:

<http://pcssmat.org/>

link to PCSS-MAT (Providers' Clinical Support System for medication assisted treatment)

<http://pcssmat.org/opioid-resources/clinical-tools/>

within PCSS-MAT, link to buprenorphine specific reference materials

<http://www.naabt.org/> (general info about buprenorphine, formulations, finding provider; and for providers, resources including links to certifications)

DEA regulations on buprenorphine

<http://www.buppractice.com/node/12246> (updated aug 2015)

http://www.deadiversion.usdoj.gov/drug_chem_info/buprenorphine.pdf
(updated 2013)

Urine Drug Testing Guidelines (2015, Gourlay/Heit/Caplan)

<http://www.udtmonograph6.com>

COWS Clinical Opiate Withdrawal Scale

<https://www.drugabuse.gov/sites/default/files/files/ClinicalOpiateWithdrawalScale.pdf>

Registration for the California Prescription Drug Monitoring Program (PDMP CURES)

https://pmp.doj.ca.gov/pmpreg/RegistrationType_input.action#

ICD-10 codes for Opioid Dependence

<http://www.icd10data.com/ICD10CM/Codes/F01-F99/F10-F19/F11-/F11.2>