

# PCSS Guidance Documents

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## **PCSS Guidance**

**Topic:** Buprenorphine Induction

**Author:** Paul P. Casadonte, MD

**Last Updated:** 10/27/09

**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 moments 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 their first withdrawal symptoms are and advise that it is at this time they 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 they absolutely need 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 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 in the medical record to document withdrawal. The COWS is available at [http://www.pcssmentor.org/pcss/resources\\_clinicaltools.php](http://www.pcssmentor.org/pcss/resources_clinicaltools.php).

Some physicians may choose to use buprenorphine mono (Subutex) 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 (Suboxone) 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 12-16 is observed.
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.). In this study, researchers provided significant patient education, including a detailed handout, that covered how and when to start buprenorphine/ naloxone. 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, alone 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.

### **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.

#### **References**

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>

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**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

**Author:** Paul P. Casadonte, MD

**Last Updated:** 08/09/06

**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 transfer 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 a transfer to 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, 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 their 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 their 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.

Alternatively, the patient may not be doing well on methadone, continuing to use opiates, stimulants (cocaine or methamphetamines) or benzodiazepines and wishing 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 lowered, 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) 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 they receive their first dose of buprenorphine.

With the long-acting agonist methadone, the timing of the first dose of buprenorphine may be perhaps more difficult to determine than when starting someone who is using a short acting-opiate. 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 for them to go into withdrawal while using heroin, they 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 maintain that dose for a week

or more. 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 they come for their 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 they report discomfort, and if withdrawal signs are observed by the practitioner, the patient can then be stated on buprenorphine with results similar to a taper to 30 mg methadone. (Breen, Harris, Lintzeris 2003)

A recent 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 day1, 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 of 15, it appears advisable to start at 2 mg, and continue to dose until the patient is comfortable 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 them to wait a bit longer, provide additional therapeutic support and/or increase ancillary medications.

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**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-



## **PCSS Guidance**

**Topic:** Pregnancy and Buprenorphine Treatment

**Author:** Judith Martin, MD

**Last Updated:** March 21, 2006

### **Guideline Coverage:**

This topic is also addressed in:

1. TIP 43: Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs, chapter 13, SAMHSA/CSAT, 2005.
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:**

Heroin 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. Prenatal methadone exposure may result in a neonatal withdrawal syndrome (sometimes called neonatal abstinence syndrome). This withdrawal syndrome is a generalized disorder characterized by signs and symptoms indicating dysfunction of the autonomic nervous system, gastrointestinal tract and respiratory system.<sup>1</sup> 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.<sup>2</sup> There

are case studies showing that buprenorphine is safe and effective.<sup>3,4</sup> A large non-randomized observational prospective study comparing methadone and buprenorphine showed similar neonatal outcomes with both medications.<sup>5</sup>

There are two small randomized, double-blind study comparing methadone to buprenorphine, showing comparable, or slightly better neonatal outcomes with buprenorphine.<sup>6,7</sup> There is a multi-site study in progress based on these results. The case reports and prospective studies of women maintained on buprenorphine indicate that neonatal withdrawal occurs in over half of the infants, peaking at roughly 72 hours after birth. Percentages requiring treatment are similar to methadone maintenance studies, between 40-55 percent. There are no specific studies examining maternal and neonatal outcomes following buprenorphine treatment during pregnancy using women who were dependent on prescription opioids.

Buprenorphine is pregnancy category C, because of limited data in humans. Physicians should use buprenorphine in pregnancy using a risk/benefit analysis, informing the patient about the still unproven status of buprenorphine treatment. 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.

**Recommendations:** Level of evidence: Low -based on case studies and two limited controlled trials

Pregnant patients should be offered methadone maintenance when available. If they refuse, or if methadone maintenance is not available, they should be informed that buprenorphine is not a proven treatment during pregnancy, and the clinician should get 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. In the case of unstable patients, smaller prescriptions, observed dosing, or more frequent visits are recommended, to avoid injection abuse of the mono product.

Most experts recommend breastfeeding for mothers who are on buprenorphine.

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*British Medical Journal*, 2004;328;1490-



## **PCSS Guidance**

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

**Author:** David Fiellin, M.D.

**Last Updated:** 11/10/05

### **Guideline Coverage:**

This topic is also addressed in Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction (TIP 40), page 75-76.

[http://www.pcssmentor.org/pcss/documents2/Training/Clinical%20Guidelines%20\(TIP%2040\).pdf](http://www.pcssmentor.org/pcss/documents2/Training/Clinical%20Guidelines%20(TIP%2040).pdf)

### **Clinical Question:**

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

### **Background:**

Buprenorphine is a partial agonist at the mu opioid receptor. As such, buprenorphine can provide analgesia, although the doses used generally for analgesia in other countries ranges from 0.2 to 0.6 mg., sublingually and the duration of effect is limited to 6-8 hours. No peer-reviewed published data is available to advise the appropriate dose of bup/nx for the management of acute or chronic pain. As a mu agonist, buprenorphine effectively blocks the analgesic properties of other opioids that could be used to treat acute pain. In addition, providing buprenorphine after a full mu agonist can result in precipitated withdrawal in a patient who has already taken an agonist opioid medication to treat acute pain.

**General Principles:** Inform patient of your awareness of their addiction and provide reassurance that their addiction will not be an obstacle to 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 indicated. Maintenance opioids should not be expected to adequately treat new onset acute pain. Patient controlled anesthesia (PCA) can be used in opioid dependent patients with acute pain.

### **Recommendations:**

Level of evidence: **Very low – expert opinion/clinical experience**

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.
  - 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.
  - Re-induce patient onto bup/nx as per usual.

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**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-



## **PCSS Guidance**

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

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

**Last Updated:** 4/17/06

**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%20Guidelines.pdf> and in Methadone-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs (TIP 43), page36-42.

**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% (Brooner, 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 no 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. 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).

While it is common clinical practice to prescribe SSRI's 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. Bupirone, which has low abuse liability, 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.

**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](http://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 their 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.

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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**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-



## **PCSS Guidance**

**Topic:** Monitoring of Liver Function Tests and Hepatitis in Patients Receiving Buprenorphine/Naloxone

**Author:** Andrew J. Saxon, M.D.

**Last Updated:** 11/22/05

**Guideline Coverage:** This topic is also partially addressed in Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction (TIP 40), pages 33-34. <http://buprenorphine.samhsa.gov/Bup%20Guidelines.pdf>

### **Clinical Questions:**

1. How should I monitor liver function tests in patients with or without underlying chronic hepatitis who are receiving buprenorphine/naloxone (bup/nx) for the treatment of opioid dependence?
2. What should I do if a patient receiving bup/nx does develop evidence of acute hepatitis or worsening chronic hepatitis?

**Background:** An early report of adverse events related to buprenorphine treatment noted that some participants showed increases in serum aminotransferase levels, but these increases could not be directly attributed to buprenorphine.<sup>1</sup> That study was published prior to the availability of clinical testing for Hepatitis C so that the Hepatitis C status of the subjects was not known. A subsequent study obtained liver enzyme values on patients prior to initiation of buprenorphine and again after a minimum of 40 days of treatment with either 2, 4, or 8 mg/70 kg buprenorphine per day.<sup>2</sup> Patients with a history of hepatitis (but not those without such a history) exhibited statistically significant (but not necessarily clinically meaningful) increases in ALT (median increase=8.5 IU) and AST (median increase=9.5 IU). In this study, higher buprenorphine doses were associated with greater odds of an increase in AST. One series of cases reported from France described 4 individuals with Hepatitis C who injected buprenorphine intravenously and developed ALT elevations 13-50 times the upper limit of normal and 1 individual with Hepatitis C and HIV who became jaundiced and had panlobular liver necrosis and microvesicular steatosis after using only sublingual buprenorphine.<sup>3</sup> The intravenous users recovered after stopping intravenous injection, and 2 of them did not interrupt sublingual administration of buprenorphine. The HIV positive patient also recovered after stopping buprenorphine. A second series of cases from France included 7 patients who developed hepatitis while on buprenorphine.<sup>4</sup> Only 1 of these patients was injecting buprenorphine. The other 6 took it as prescribed by the sublingual route. Average ALT levels were 39 times normal. All patients had serologic evidence of Hepatitis C. Buprenorphine treatment was continued in all patients, although 3 had a dose reduction of 50%. All 7 patients recovered without apparent sequelae. An *in vitro* study with rat

hepatocytes suggested that buprenorphine is a proton donor that can interfere with mitochondrial respiration resulting in necrosis of hepatocytes.<sup>5</sup>

It thus appears that buprenorphine may have the potential to cause elevations in transaminases and reversible hepatic injury, particularly in individuals with Hepatitis C. The precise incidence of these types of event remains uncertain, though the serious hepatic injury appears to be quite rare considering that many thousands of individuals have been treated with buprenorphine in France with only a few reported cases of hepatic injury. The National Institute on Drug Abuse Clinical Trials Network will be conducting a prospective study that will systematically assess changes in liver tests over time in opioid dependent patients randomized to be treated with either buprenorphine/naloxone or methadone. Results from this trial should provide more information about the effects of buprenorphine/naloxone on the liver.

**General Principles:** Be aware of potential risk of liver injury with bup/nx and inform patients of risk prior to beginning medication and monitor appropriately. Intervene if evidence of liver injury occurs. Note that the clinical trials conducted in the United States with buprenorphine excluded patients with baseline transaminases greater than 3-5 times normal. Little information is available at this point to guide clinicians who are treating patients with baseline transaminases that are greater than 5 times normal.

**Recommendations:** Level of evidence: **Low – observational studies**

- 1) Obtain liver tests including transaminases, bilirubin, prothrombin time/INR, and albumin prior to initiating bup/nx treatment.
- 2) Obtain Hepatitis B and C panels prior to initiating bup/nx in patients whose serostatus is unknown and who have risk factors for these viral infections.
- 3) Periodically monitor liver tests during bup/nx treatment. There is no empirical evidence currently to guide the frequency of monitoring. Therefore, the frequency of monitoring may be determined by physician discretion.
- 4) Inform patients to contact physician immediately if they develop symptoms or signs of hepatotoxicity such as fever, malaise, nausea, vomiting, abdominal distress, dark urine, clay colored stools, or icterus.
- 5) If a patient does have clinical and/or laboratory evidence of hepatotoxicity (e.g. transaminases >5X upper limit of normal, abnormal bilirubin or abnormal prothrombin time)
  - All possible causes of liver injury should be evaluated.
  - Strong consideration should be given to consulting a gastroenterologist or hepatologist.
  - Consideration should be given to lowering the dose of bup/nx or discontinuing bup/nx.
  - The patient should be followed with serial clinical and laboratory monitoring until evidence of hepatic injury resolves.
- 6) It is recognized that in certain clinical situations such as urgent or brief medically supervised withdrawal, it may be impractical or impossible to obtain liver tests prior to

initiating treatment. Nevertheless, given the unpredictability of liver reactions, and to avoid inappropriately ascribing abnormalities to bup/nx, the best clinical practice when possible is to check liver tests and hepatitis testing prior to initiation of therapy.

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**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-



## **PCSS Guidance**

**Topic:** Opioid Therapies, HIV Disease and Drug Interactions

**Author:** Elinore F. McCance-Katz, MD, PhD

**Last Updated:** 2/28/08

**Guideline Coverage:** TIP #40, Special Populations: Patients with Medical Comorbidities (pgs. 67-68).

### **Clinical Questions:**

1. Do drug interactions of clinical significance occur between methadone or buprenorphine and HIV medications?
2. How can I determine whether an opiate-addicted patient with HIV disease should be treated with methadone or buprenorphine?

### **Background:**

Injection drug use is a risk factor for HIV infection. Many, if not most injection drug users are addicted to opiates. The treatment of choice for opioid dependence in these patients is opioid maintenance therapy available principally as either methadone or buprenorphine pharmacotherapy (Johnson et al. 2000).

Preclinical studies elucidating the clinical pharmacology of antiretroviral medications and opioids indicate that drug interactions are likely to occur (Kumar et al. 1996, Iribarne et al., 1998). Methadone and buprenorphine are primarily metabolized by hepatic cytochrome P450 enzymes (CYP 450), specifically CYP 450 3A4 (Moody et al., 1997, Iribarne et al, 1996). A number of antiretroviral medications are substrates of and have been shown in preclinical studies to inhibit the activity of CYP 450 3A4 leading to speculation of opioid toxicity and/or toxicity related to increased exposure to the HIV medications in those receiving maintenance therapies. Conversely, if an antiretroviral agent were to induce CYP 450 enzyme production, an opiate abstinence syndrome could result placing the patient at risk for relapse to illicit drug use and/or nonadherence to HIV medication therapies.

To date (February 2008), methadone has been associated with several clinically important, adverse drug interactions with HIV medications. Buprenorphine has been studied in combination with antiretroviral medications more recently. Table 1 summarizes drug interactions that have been identified between antiretroviral medications and either methadone or buprenorphine. The clinical importance of drug interactions lies in the associated adverse events that occur. Drug interactions that lead to reduced methadone concentrations in the blood have been associated with opiate withdrawal syndromes which themselves have been linked to non-adherence to HIV medications and to increases in illicit drug use including high risk behaviors such as

injection drug use. To date, reductions in buprenorphine concentrations resulting from drug interactions have not been associated with opiate withdrawal. Drug interactions that lead to low plasma concentrations of antiretroviral medications may produce subtherapeutic concentrations that may be clinically ineffective and risk the possibility of the development of viral resistance. Similarly, toxicities resulting from drug interactions that might increase plasma concentrations of opioids or antiretroviral medications include the risk of non-adherence or sporadic adherence to HIV regimens that may result in the development of viral resistance. These consequences underscore the need for clinicians to be familiar with the drug interactions of importance between opioids and antiretroviral therapies so that they can monitor patients for adverse events and intervene as needed as well as to educate their patients.

<b>Table 1: Drug Interactions</b>		
<b>HIV Medication</b>	<b>Interaction with Methadone</b>	<b>Interaction with Buprenorphine (BUP)</b>
<b>Nucleoside Reverse Transcriptase Inhibitors</b>		
Zidovudine (AZT)	↑ AZT AUC by 40%, AZT toxicity observed requiring dose adjustment in several participants, no effect on methadone levels (McCance-Katz <i>et al.</i> , 1998)	Non-clinically significant ↓ AZT concentrations ; no need to adjust AZT dose (McCance-Katz <i>et al.</i> , 2001)
Didanosine (ddI) tablet	↓ ddI AUC by 63%, no effect on methadone levels (Rainey <i>et al.</i> , 2000)	Not studied
Didanosine (ddI) enteric-coated	No significant effect of methadone on ddI (this formulation should be used in patients with HIV/AIDS and who are methadone maintained (Friedland <i>et al.</i> , 2002)	No clinically significant interaction
Zalcitabine (ddC)	None	Not studied
Lamivudine (3TC)	None	No effect of lamivudine on buprenorphine concentrations
Lamivudine/zidovudine	None (Rainey <i>et al.</i> , 2002)	Not studied
Stavudine (d4T)	↓ d4T AUC by 25% (Rainey <i>et al.</i> , 2000)	Not studied
Abacavir (ABC)	↑ Methadone clearance, but no withdrawal, no clinically significant effect on ABC concentrations (Sellers <i>et al.</i> , 1999),	Not studied
Tenofovir	No significant interaction	No significant interaction
<b>Non-Nucleoside Reverse Transcriptase Inhibitors</b>		
Nevirapine	Withdrawal symptoms, need for increased methadone dose (Altice <i>et al.</i> , 1999), 40% decrease in methadone (Stocker <i>et al.</i> 2004)	Under study
Delavirdine (DLV)	↑ Methadone levels without toxicity (McCance-Katz, <i>et al.</i> 2006), no effect on DLV	↑ BUP concentrations without toxicity, no effect on DLV (McCance-Katz <i>et al.</i> 2006)
Efavirenz (EFV)	↓ Methadone levels, withdrawal symptoms, ↑ methadone dose necessary (up to 50%) (Clarke <i>et al.</i> , 2001, McCance-Katz <i>et al.</i> 2002)	↓ BUP levels, no withdrawal, no dose change needed, no effect on EFV levels (McCance-Katz, <i>et al.</i> 2006)

<b>Protease Inhibitors</b>		
Nelfinavir (NLF)	↓ Methadone levels, but no withdrawal symptoms observed (McCance-Katz <i>et al.</i> , 2004), increased NLF, decreased M8 metabolite, no clinically significant change in NLF exposure	No effect on BUP (McCance-Katz <i>et al.</i> , 2006), no significant effect of BUP on NLF
Indinavir	Not studied	Not studied
Ritonavir (RTV)	↑ Methadone levels, not clinically significant (McCance-Katz <i>et al.</i> 2003)	↑ BUP levels, not clinically significant, no effect of BUP on RTV
Saquinavir	↓ Methadone levels (S enantiomer), no withdrawal (Gerber <i>et al.</i> 2002)	Not studied
Amprenavir	↓ methadone, no withdrawal	Under study
Lopinavir/ritonavir (L/R)	↓ methadone, withdrawal may occur, methadone may need to be increased (McCance-Katz <i>et al.</i> , 2003)	No significant effect on BUP, no effect of BUP on L/R (McCance-Katz, 2006)
Atazanavir (ATZ) or Atazanavir/ritonavir (ATV/r)	No effect of ATZ on methadone, no effect of methadone on ATZ (Friedland <i>et al.</i> , 2005)	Significant increase in BUP and norbuprenorphine; sedation may occur (McCance-Katz <i>et al.</i> , 2007); clinical observation of sedation and cognitive impairment with ATV/r (Bruce, 2005)

**Patient Education:** When a patient with HIV disease 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 only been observed with certain antiretroviral medications and methadone) or opiate excess (this has been recently observed in several patients receiving the protease inhibitor combination atazanavir/ritonavir and buprenorphine). Buprenorphine has fewer adverse drug interactions with HIV medications than does methadone. Buprenorphine treatment may also be preferable to methadone for many patients in that physicians with appropriate training and qualifications can prescribe buprenorphine for opioid addiction; thus one physician may be able to provide both HIV care and treatment for opioid dependence. Demonstration projects of this model of care are currently underway (see [www.bhives.org](http://www.bhives.org)).

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

- 1. For the patient with HIV disease who is methadone-maintained and requires initiation of highly active antiretroviral therapy (HAART):** 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, opiate excess (sleepiness, impaired thinking), or symptoms of antiretroviral toxicity (such symptoms are specific to the medications being prescribed; thus far the only antiretroviral medication that has been associated with toxicity is zidovudine (AZT) and this appears to be a rare event). Patients should be encouraged to immediately report any adverse symptoms to their HIV treatment provider and to clinical staff at the methadone

maintenance program. It should be recognized that patients receiving HAART and methadone may require methadone dose adjustments. A trough methadone level prior to initiation of HAART and when a patient experiences symptoms thought to be opiate withdrawal/excess may be helpful. A significant decrease or increase in trough methadone concentration with antiretroviral treatment would indicate a need for increasing/decreasing the methadone dose. In patients experiencing acute, severe symptoms; the methadone dose should be addressed immediately. In a patient showing evidence of acute onset of opiate withdrawal, the methadone dose will need to be increased immediately to prevent non-adherence to HIV medications and/or abuse of illicit drugs. The methadone dose can be increased by up to 10 mg every 2-3 days until the patient is restabilized. An additional challenge for patients with HIV/AIDS and who are methadone-maintained can occur when the patient requires a change in antiretroviral medication necessitating discontinuation of the inducing HIV therapeutic. 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 complication is cardiac arrhythmia due to increased methadone exposure when an antiretroviral medication that can induce methadone metabolism is discontinued resulting in increased methadone exposure (Krantz et al. 2003). Once the medication that is inducing CYP 450 3A enzymes 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 with HIV disease who is buprenorphine-maintained and requires initiation of highly active antiretroviral therapy (HAART):** Patients should continue on their current buprenorphine/naloxone dose. Patients should be informed of the potential for drug interactions with HIV medicines that may cause them to experience symptoms of opiate excess (sleepiness, impaired thinking) (this has been observed only with atazanavir/ritonavir to date) or potentially, opiate abstinence (this has not been observed between buprenorphine and any antiretroviral medication studied to date). Patients should be encouraged to report any adverse events experienced which should be clinically evaluated and if necessary, buprenorphine dose adjustment should be made.
3. **For the opiate-addicted patient with HIV disease 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 antiretroviral medications than does methadone. However, patients 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, 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 HIV physicians who can provide buprenorphine treatment may be best treated by that physician for both disorders. Patients needing HAART may benefit from a trial of buprenorphine treatment due to the reduced likelihood of adverse drug interactions as compared to methadone. Any patient treated with HAART and initiating opioid therapy warrants clinical observation to determine whether adverse interactions occur and, if so, how to address these interactions.

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**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-

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## **PCSS Guidance**

**Topic:** Treatment of opioid dependent adolescents and young adults using sublingual buprenorphine

**Authors:** Geetha Subramaniam, M.D. and Sharon Levy, M.D.

**Last Updated:** 3-27-2010

### **Guideline Coverage:**

None current

### **Clinical Questions:**

1. What is the research evidence for the treatment of opioid dependent youth with buprenorphine?
2. What special issues should be considered when treating adolescents with buprenorphine?

### **Background:**

While the use of heroin has remained low and stable (at approximately 1%), the use of non-heroin opioids, the second most commonly used illicit drug among youth has almost doubled over the past decade. (5 to 9%)<sup>1</sup>. Correspondingly, there has been a ten-fold increase in adolescent admissions to publicly funded substance abuse treatment programs for non-heroin opioid use problems during the same period (0.2 to 2.2%)<sup>2</sup>. Further, treatment-seeking opioid dependent youth, with short histories of dependence on any type of opioid, present with complex co-occurring treatment issues such as psychiatric disorders, injection-drug use and sexual behavior related HIV risk, abscesses, Hepatitis-C infection, school-drop out, legal problems, etc.<sup>3,4</sup>. Currently, most youth who enter treatment receive usual care consisting of brief detoxification followed by psychosocial treatments, commonly in outpatient and sometimes in residential settings, even though these interventions have not been well studied.

Buprenorphine, a partial opioid agonist, with Food and Drug Administration (FDA) approval for the treatment of opioid dependence for those 16 years and older has

been well established as an effective treatment of opioid dependent adults. However, the empirical evidence for treatment of opioid dependent youth with buprenorphine is emerging and it has been shown to be effective when combined with psychosocial treatments. In one study, 36 opioid dependent adolescents ages 13-18 years were randomly assigned to a 28-day outpatient treatment with either sublingual buprenorphine or oral clonidine; both groups received 3 times weekly behavioral counseling and incentives contingent on opiate abstinence. Those who received buprenorphine compared to those on clonidine had higher rates of treatment retention, opiate negative urines and higher rates of transfer to oral naltrexone<sup>5</sup>. In the second study (a NIDA Clinical Trials Network sponsored multisite study), 152 opioid dependent youth aged 15-21 were randomized to either sublingual buprenorphine/naloxone (longer treatment condition) for 12-weeks or a 14-day buprenorphine/naloxone taper (detoxification condition), with each arm being offered weekly group and individual drug counseling. During weeks 1-12, those in the longer treatment condition compared to the detoxification condition had significantly fewer opioid-positive urines, better retention, less self-reported opioid use and less injection drug use. Buprenorphine/naloxone was well tolerated (up to a maximum dose of 24mg/day) and no medication-related serious adverse effects were reported in either study.

### **General Principles:**

The following general principles are based on clinical experiences guided by current research with youth and the information available from the use of buprenorphine/naloxone in the treatment of opioid dependent adults. Most adolescents that have developed opioid dependence will be not able to remain abstinent without treatment. No single approach is suitable for all individuals; treatment should be comprehensive, and tailored to meet individual needs. In most cases, treatment should include both opioid agonist medication as well as behavioral therapies.

Prior to beginning medication-assisted therapy, all adolescents should have a complete evaluation including a thorough substance use history to confirm the diagnosis of opioid dependence, medical, mental health, vocational and psychosocial histories and physical exam, and all active problems should be addressed so that they do not interfere with recovery. Routine laboratory tests, particularly urine toxicology tests to confirm opioid use and to evaluate concomitant benzodiazepine dependence (because of its potential for death from overdose), and liver enzymes to assess hepatic function are recommended. Clinicians treating adolescents should take advantage of the availability of parents or guardians for authority and structure whenever possible to improve adolescent treatment adherence, allow for prompt intervention when a relapse occurs and minimize diversion risk.<sup>6</sup> However, most states have laws that allow adolescents to seek treatment for substance use disorders without parental consent; in these cases the adolescents confidentiality should be respected.<sup>7</sup>

### **Induction, Dosing and Duration of Treatment:**

We recommend observed induction for adequate dosing, education regarding adherence and parental monitoring of medication adherence and adverse effects of sedation, drowsiness, etc. The relative long half-life of buprenorphine permits once- daily dosing, though, if preferred, doses may be given 2-3 times a day. In studies, maintenance dosing has ranged from 2-24mg/day with 59% of patients stabilized on 9-16 mg/day.<sup>4</sup> It is considered optimal to dose until the youth no longer reports withdrawal symptoms or craving for opioids. Since there is no scientific evidence on the optimal duration of buprenorphine treatment we recommend that there be no hurry to wean these youth off buprenorphine and that the length of treatment (up to a year or longer) be determined based on progress and in collaboration with patients and in the case of minors, their legal guardians. Medications should be tapered slowly to avoid withdrawal symptoms and/or resurgence of cravings.

### **Recommendations:**

Level of evidence: **Low - clinical experience and limited research**

1. Confirm the diagnosis of opioid dependence through history and urine drug testing. Screen for potentially confounding conditions such as benzodiazepine abuse or dependence, elevated liver enzymes, need for ongoing pain management, etc.
2. Provide education about the role and effectiveness of buprenorphine in the treatment of opioid dependence. Establish a set of expectations for patients beginning medication-assisted therapy, i.e. medication compliance, participation in psychosocial treatments, risks of concomitant alcohol and/or benzodiazepine abuse/dependence. Encourage patients to commit to abstinence from all psycho-active substances including alcohol which can be dangerous in combination with buprenorphine, and provide or refer ancillary treatments to patients who are unable to achieve abstinence.
3. The optimal length of opioid agonist treatment for adolescents with opioid dependence has not been well established. Available research suggests that continued sublingual buprenorphine/naloxone for at least 12 weeks significantly improves outcomes. Even patients with short histories of opioid dependence (i.e. 1-2 years) prior to starting medication may rapidly relapse after medication cessation.
4. Involve parents in treatment whenever possible. In many cases, parents may already be aware of their child's drug use and the adolescent may give permission to involve their parents. Ask the adolescent for permission to discuss diagnoses, treatment recommendations and progress with parents. In order to protect the therapeutic relationship with the adolescent, avoid sharing details that do not impact treatment. In some states written parental consent may be required prior to starting medication; prescribers should be cognizant of the laws in their state.

5. Follow patients regularly to monitor for side effects, adherence, lack of diversion and continued cravings and adjust the dosing accordingly.
6. Refer patients for psychosocial support to develop relapse prevention skills.
7. Monitor patients with random drug tests to assure that they are taking their medication and evaluate the risk from use of other illicit substances.
8. Screen for co-occurring psychiatric disorders. Symptoms of mild depression or inattention may improve with abstinence and can be monitored if not debilitating; more significant co-morbidities should be treated simultaneously using pharmacological and non-pharmacological treatments.
9. Address or refer to the appropriate agencies/provider for concomitant social issues that may hinder the progress of treatment such as unstable living arrangements, conflicts and/or substance use within the family home, academic disengagement, employment issues and legal problems, etc.
10. Be aware that buprenorphine and buprenorphine/naloxone are approved by the Food and Drug Administration for individuals aged 16 and up, due to lack of data available in those younger than 16.

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**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:** Psychosocial Aspects of Treatment in Patients Receiving Buprenorphine/Naloxone

**Author:** Andrew J. Saxon, M.D.

**Last Updated:** 2/22/08

**Guideline Coverage:** This topic is also partially addressed in Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction (TIP 40), pages 63-64. <http://buprenorphine.samhsa.gov/Bup%20Guidelines.pdf>

### **Clinical Questions:**

1. Do my patients who are receiving buprenorphine/naloxone (bup/nx) for the treatment of opioid dependence need additional psychosocial treatment?
2. What type of psychosocial treatment should they get?
3. How much psychosocial treatment should they get?

### **Background:**

Many patients with opioid dependence do not fully respond to buprenorphine treatment alone. They may continue some degree of illicit opioid use, they may continue problematic use of other substances, or they may continue to struggle with core life issues such as relationships and employment. It makes sense that some patients would benefit from psychosocial interventions directed at the areas in which difficulties persist, although some uncertainty remains as to the optimal intensity or modality of psychosocial treatments for these patients.

Studies of various intensities of psychosocial services in licensed methadone programs do offer some illumination on this point: patients who receive minimal psychosocial services do not fare as well as those who receive moderate or high levels of services.<sup>1-3</sup> However, the lower cost-effectiveness of more intensive services may nullify any slight advantage they hold over moderate services.<sup>3,4</sup> A study evaluating different doses of buprenorphine for combined opioid and cocaine dependence did find that more frequent attendance at weekly individual psychotherapy appointments was associated with better outcomes.<sup>5</sup> The one study that has so far rigorously addressed the question of intensity among buprenorphine treated patients supports the idea of providing a moderate intensity of psychosocial services. The study examined the efficacy of weekly extended medical management counseling (45 minute sessions) compared to weekly standard medical management counseling (20 minute sessions) and demonstrated no advantage of the extended counseling.<sup>6</sup>

In regard to modalities of psychosocial treatments, the accumulated general knowledge on modalities of psychotherapy indicates that individual therapist skill at creating a

therapeutic alliance has more effect on outcomes than the particular type of therapy practiced.<sup>7</sup> More specifically, the therapeutic alliance has a strong effect on outcomes in psychosocial interventions for substance dependence.<sup>8</sup> Nevertheless, a variety of specific modalities have been applied to patients with opioid dependence such as individual drug counseling,<sup>9</sup> cognitive-behavioral therapy,<sup>10</sup> supportive-expressive psychotherapy,<sup>9</sup> relapse prevention,<sup>11</sup> contingency management,<sup>12</sup> and medical management.<sup>6</sup> A recent meta-analysis of psychosocial interventions for substance use disorders that included interventions for opioid dependence found that both cognitive-behavior therapy and contingency management had positive moderate effects with a slight advantage for contingency management.<sup>13</sup> Psychotherapy performed better than drug counseling for patients with high psychiatric symptomatology.<sup>10</sup> There is some evidence that targeting psychosocial services specifically to address patient problem areas is beneficial.<sup>1</sup>

A third point pertains to the use of self-help groups such as 12 step programs. Such groups are widely attended and generally encouraged or even required by many addiction treatment programs. A large body of literature has addressed the benefit of self help groups for alcohol dependence with methodological limitations precluding firm scientific validation of their value.<sup>14</sup> There has been very little study of use of such groups for opioid dependence. In the past and probably currently many of these groups tend to stigmatize patients on agonist therapy. Nonetheless, these groups do offer readily available psychosocial treatment at no cost.

**General Principles:** The majority of opioid dependent patients treated with buprenorphine will benefit from some amount of psychosocial treatment in addition to pharmacotherapy. Treatment providers should encourage engagement in psychosocial treatment. The quality of the therapeutic alliance between psychosocial therapist and patient is probably more important than the type of therapy applied. A modest “dose” of psychosocial treatment is probably sufficient for most patients.

**Recommendations:** Level of evidence: **High – randomized trials**

- 1) Refer patients receiving buprenorphine/naloxone for some type of psychosocial intervention (or provide these services onsite)
- 2) For most patients weekly or monthly psychosocial intervention is an adequate frequency.

**Recommendation:** Level of evidence: **Moderate – observational studies**

- 3) Since therapeutic alliance is a good predictor of benefit from psychosocial treatment, seek referral sources with whom patients report substantial positive rapport early in the course of psychosocial treatment.

**Recommendation:** Level of evidence: **Low – expert opinion/clinical experience**

- 4) Do not require patients to attend self-help groups but encourage those with an interest to try such groups and to find a particular group where they feel accepted.

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**The following links may be helpful in locating professional counseling services or locations of self-help meetings:**

<http://findtreatment.samhsa.gov/>

[http://www.alcoholics-anonymous.org/en\\_find\\_meeting.cfm](http://www.alcoholics-anonymous.org/en_find_meeting.cfm)

<http://portaltools.na.org/portaltools/MeetingLoc/>

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Type of evidence:

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Observational study = **low**

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\* Grading quality of evidence and strength of recommendations

*British Medical Journal*, 2004;328;1490-

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## **PCSS Guidance**

**Topic:** Adherence, Diversion and Misuse of Sublingual Buprenorphine

**Author:** Judith Martin, MD

**Last Updated:** January 5, 2010

### **Guideline Coverage:**

Tip 43, Medication-Assisted Treatment for 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 Medial Maintenance Treatment, Center for Substance Abuse Treatment, chapters 4 and 5.

### **Clinical Question:**

1. 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. This 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 mis-used 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 prevalence of these mis-use behaviors in office-based treatment of opioid dependence using sublingual buprenorphine. It makes sense 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 US 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]

**General Principles:**

Buprenorphine is available as a buprenorphine only (mono) compound and a more common (in the U.S. market) buprenorphine/naloxone combination compound. In the fall of 2009 generic sublingual buprenorphine became available in the US. So far there are no generic tablets with naloxone. 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 their clinical state and the route of administration as outlined below:

<b>Patient</b>	<b>Effect Buprenorphine-only</b>	<b>Effect Buprenorphine/naloxone</b>
Opioid naïve	Buprenorphine agonism, reinforcing	Buprenorphine agonism, reinforcing
Opioid tolerant with full agonist opioids on receptors	Buprenorphine induced withdrawal, aversive. If injected, buprenorphine precipitated withdrawal, aversive.	Buprenorphine induced withdrawal, aversive. If injected, naloxone-precipitated withdrawal, aversive.
Opioid tolerant with no opioid agonist on receptors	Buprenorphine agonism, relieves withdrawal	Buprenorphine agonism, relieves withdrawal
Opioid tolerant with buprenorphine/naloxone on receptors	Primary buprenorphine effect, could be reinforcing	Primary buprenorphine effect, could be reinforcing

**Types of aberrant use of buprenorphine**

- Sharing or selling prescribed pills, or stockpiling medication for later use.
- Insufflating (snorting) or injecting 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 sublingual buprenorphine (mono) in Europe and New Zealand prompted the development of a buprenorphine/naloxone combination sublingual pill in the US (Suboxone®). The naloxone component is not significantly bio-available when orally or sublingually consumed, but is known to 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-naïve injector, and one study showed that recently detoxified heroin-dependent volunteers were unable to distinguish between injections of the buprenorphine-only preparation and the buprenorphine/naloxone preparation. [9] In addition, research demonstrates that the injection of the buprenorphine/naloxone combination in patients maintained on buprenorphine does not precipitate withdrawal.[10]

### **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. Patients may be diverting the prescribed buprenorphine in trade or as a cash source to buy other drugs. 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, monitor the bathroom door so that only one person can go in, and testing the temperature of the urine within four minutes of 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 helps to monitor the rate at which the pills are being consumed.

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 pill is observed to gradually shrink under the patient's tongue until it completely disappears. Some physicians use this type of observation during induction to assure that the patient knows how to take the sublingual pill 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 dissolving, or whether active medication is being wasted 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. 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). 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 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 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 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 until the patient begins to improve. One easy form of intensifying treatment is more frequent visits with shorter prescription spans. 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.
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.

### **References**

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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:

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-

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## **PCSS Guidance**

**Topic:** Drug Enforcement Administration Requirements for Prescribers and Dispensers of Buprenorphine and Buprenorphine/Naloxone

**Authors:** Edwin Salsitz MD, Martha J Wunsch MD

**Last Updated:** January 25, 2010

### **Guideline and Federal Document Coverage:**

Additional information on this topic is available at:

**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 B and 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](http://www.deadiversion.usdoj.gov/pubs/docs/dwp_buprenorphine.htm)

SAMHSA/CSAT Information on Record Keeping:  
<http://www.buprenorphine.samhsa.gov/faq.html#A9>

### **Clinical Questions:**

1. What regulations govern Drug Enforcement Administration (DEA) review of practices prescribing and/or dispensing buprenorphine or buprenorphine/naloxone?
2. What paperwork should be maintained?
3. How should medication be stored?
4. What has been the experience of providers who have undergone DEA visits?

### **Regulations:**

Congress passed the Drug Addiction Treatment Act (DATA) on October 17, 2000. This act permits qualified practitioners 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 and buprenorphine/naloxone tablets 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.

**Paperwork:** Physicians prescribing buprenorphine and buprenorphine/naloxone should maintain records 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 and C 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. It is not necessary for physicians to produce copies of their certification letters from CSAT.

**Patients:** Waivered physicians may treat up to 30 patients at any one time during the first year, and thereafter may submit a second notification to CSAT to increase their patient limit to 100. Notification forms are available at: <http://www.buprenorphine.samhsa.gov/howto.html>. The physicians' DEA certificate of registration indicates 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 physicians' DATA 2000 identification number (which begins with the prefix X) must be included on the prescription [See 21 CFR 1301.28 (d)(3)].

**Storage** For those physicians dispensing medication directly from their office, CFR 1301.75 stipulates that buprenorphine/naloxone and buprenorphine should be stored in a securely locked, substantially constructed cabinet. 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.

**Dispensing:** For those physicians dispensing medication directly from their office, CFR 1301.75 stipulates that buprenorphine and/or buprenorphine/naloxone should be stored in a securely locked, substantially constructed cabinet and 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 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. (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.

**Information based on past DEA inspections:**

DEA inspections usually last 1-2 hours. The physician has the right to refuse consent for the inspection. If the physician refuses consent for the inspection, DEA can obtain an Administrative Inspection Warrant which will allow the investigators to gain entry without consent. Anything of an incriminating nature may be seized and used against the physician in an administrative, civil and/or criminal prosecution.

**Information based on past DEA investigations:**

As of 9/10/2009, there had been 593 investigations out of 17,139 waived physicians (3.4%). In these 593 investigations, no problems were cited in 62% of prescribers. Of the 17% in which problems were cited, 54 physicians received verbal warnings related to record keeping and dispensing violations, 34 received letters of admonition addressing record keeping, security violations, or dispensing violations, 10 surrendered their registration for cause, there were 2 Show Cause proceedings, 1 revocation of registration and 1 resulted in a civil action. 14% had not prescribed buprenorphine products.

**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 B and 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](http://www.deadiversion.usdoj.gov/pubs/docs/dwp_buprenorphine.htm)

SAMHSA/CSAT Information on Record Keeping:  
<http://www.buprenorphine.samhsa.gov/faq.html#A9>

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## **Physician Billing for Office-Based Treatment of Opioid Dependence**

Office-based treatment is regular medical care provided in regular settings by regular physicians. Therefore, billing procedures are regular 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 chose to use regular psychiatric CPT codes

- Outpatient New Patient (90801)
- Outpatient Consultation (99251-55)
- Outpatient Medication Management (90862)
- Outpatient Psychotherapy (90804-09)
- 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.