Providers Clinical Support System

PCSS Guidance

Topic: Adherence, Diversion and Misuse of Sublingual Buprenorphine

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Guidelines Coverage:
Tip 43, MAT of Opioid Addiction in Opioid Treatment Programs, pages 81-85 (http://www.kap.samhsa.gov/products/manuals/index.htm)
Tip 40, Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction (http://www.kap.samhsa.gov.products/manuals/index.htm)
Draft, Physician's Guide to Opioid Agonist Medical Maintenance Treatment, Center for Substance Abuse Treatment, chapter 4 and 5.

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

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

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

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

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

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

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

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

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

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

Buprenorphine/naloxone to minimize misuse:

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

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

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

Types of monitoring:

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

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

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

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

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

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

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

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

Criteria for unobserved dosing:
The federal regulations governing methadone treatment (42CFR Part 8.12) specify eight clinical considerations that the physician must take into account when allowing unobserved dosing (take-home medication). Although not formulated for office-based practice with buprenorphine, the listed criteria are consistent with markers of improvement in treatment of addictive disorders:
.. ."(i) Absence of recent abuse of drugs (opioid or nonnarcotic), including alcohol; (ii) Regularity of clinic attendance; (iii) Absence of serious behavioral problems at the clinic; (iv) Absence of known recent criminal activity, e.g., drug dealing; (v) Stability of the patient's home environment and social relationships; (vi) Length of time in comprehensive maintenance treatment; (vii) Assurance that take-home medication can be safely stored within the patient's home, (viii) Whether the rehabilitative benefit the patient derived from decreasing the frequency of clinic attendance outweighs the potential risks of diversion."[15]

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

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

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

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

Recommendations:
Level of evidence: **Low to Moderate**

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

References:

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PCSS Guidances use the following levels of evidence*:
High = Further research is very unlikely to change our confidence in the estimate of effect.
Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may
change the estimate.
Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is
likely to change the estimate.
Very low = Any estimate of effect is very uncertain.

Type of evidence:
Randomized trial = **high**
Observational study = **low**
Any other evidence = **very low**

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