



PCSS Guidance

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

Original Author: David Fiellin, M.D.

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

Guideline Coverage:

This topic is also addressed in:

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

Clinical Question:

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

Background:

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

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

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

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

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

General Principles:

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

Recommendations:

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

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

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

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

References:

- Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2004. Available online at <http://www.ncbi.nlm.nih.gov/books/NBK64245/pdf/TOC.pdf>
- Center for Substance Abuse Treatment. Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Treatment Improvement Protocol (TIP) Series 43. HHS Publication No. (SMA) 12-4214. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2005. Available online at <http://www.ncbi.nlm.nih.gov/books/NBK64164/pdf/TOC.pdf>
- Daitch J, Frey ME, Silver D, Mitnik C, Daitch D, Pergolizzi J Jr. Conversion of chronic pain patients from full-opioid agonists to sublingual buprenorphine. *Pain Physician* 2013; 15(3 Suppl):ES59-66.
- Gatti A, Dauri M, Leonardis F, Longo G, Marinangeli F, Mammucari M, Sabat AF. Transdermal buprenorphine in non-oncological moderate-to-severe chronic pain. *Clinical Drug Investigation* 2010; 30 Suppl 2:31-38.
- Lee JD, Grossman E, DiRocco D, Gourevitch MN. Home buprenorphine/naloxone induction in primary care. *Journal of General Internal Medicine* 2009; 24(2): 226-232.
- Likar R, Kayser H, Sittl R. Long-term management of chronic pain with transdermal buprenorphine: a multi-center, open-label, follow-up study in patients from three short-term clinical trials. *Clinical Therapeutics* 2006; 28(6):943-952.
- Macintyre PE, Russell RA, Usher KA, Gaughwin M, Huxtable CA. Pain relief and opioid requirements in the first 24 hours after surgery in patients taking buprenorphine and methadone opioid substitution therapy. *Anaesthesia and Intensive Care* 2013; 41(2):222-230.
- Neumann AM, Blondell RD, Jaanimagi U, Giambone AK, Homish GG, Lozano JR, Kowalik U, Azardfard M. A preliminary study comparing methadone and buprenorphine in patients with chronic pain and coexist opioid addiction. *Journal of Addictive Disorders* 2013; 32(1):68-78.
- Rosen K, Gutierrez A, Haller D, Potter JS. Sublingual buprenorphine for chronic pain: a survey of clinician prescribing practices. *Clinical Journal of Pain* 2014; 30(4): 295-300.
- Rosenblum A, Cruciani RA, Strain EC, Cleland CM, Joseph H, Magura S, Marsch LA, McNicholas LF, Savage SR, Sundaram A, Portenoy RK. Sublingual buprenorphine/naloxone for chronic pain in at-risk patients: development and pilot test of a clinical protocol. *Journal of Opioid Management* 2012; 8(6):369-382.
- Rosenblum A, Joseph H, Fong C, Kipnis S, Cleland C, Portenoy RL. Prevalence and characteristics of chronic pain among chemically dependent patients in methadone maintenance and residential treatment facilities. *JAMA* 2003; 289: 2370-2378.
- Roux P, Sullivan MA, Cohen J, Fugon L, Jones JD, Vosburg SK, Cooper ZD, Manubay JM, Mogali S, Comer SD. Buprenorphine/naloxone as a promising therapeutic option for opioid abusing patients with chronic pain: Reduction of pain, opioid withdrawal symptoms, and abuse liability of oral oxycodone. *Pain* 2013; 154(8):1442-1448.
- Wasson M, Beirne OR. Buprenorphine therapy: an increasing challenge in oral and maxillofacial surgery. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology* 2013; 116(2):142-146.
-

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-

The Verification Community is eager to answer your UVM, SystemVerilog and Coverage related questions. We encourage you to take an active role in the Forums by answering and commenting to any questions that you are able to. For the Easier UVM guidelines that relate to coverage-driven verification, see Functional Coverage. Verification planning and management involves identifying the features of the DUT that need to be verified, prioritizing those features, measuring progress, and adjusting the allocation of verification resources so that verification closure can be reached on the required timescale. The mechanics of verification can be accomplished using static formal verification (also known as property checking), simulation, emulation, or FPGA prototyping.