PCSS Guidance

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

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

Last Updated: 11/29/13 (Maria A. Sullivan, M.D., Ph.D.) **Reviewed and Re-released:** May 2022

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

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

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

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

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

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

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

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

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

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

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

General Principles:

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

Recommendations:

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

References:

1. Heit HA, Gourlay DL. Buprenorphine: new tricks with an old molecule for pain management. Clin J Pain 2008;24(2):93-7.
2. Center for Substance Abuse Treatment. Treatment Improvement Protocol 40: Clinical guidelines

for the use of buprenorphine in the treatment of opioid addiction. Rockville, MD: 2004.
3. Malinoff HL, Barkin RL, Wilson G. Sublingual buprenorphine is effective in the treatment of chronic pain syndrome. Am J Ther 2005;12(5):379-84.
4. Baron MJ, McDonald PW. Significant pain reduction in chroinc pain patients after detoxification from high-dose opioids. Journal of Opioid Management 2010;2(5):277-82.
5. 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): 1442-8.
6. Jones JD, Sullivan MA, Manubay J, Vosburg SK, Comer SD. The subjective, reinforcing, and analgesic effects of oxycodone in patients with chronic, non-malignant pain who are maintained on sublingual buprenorphine/naloxone. Neuropsychopharmacology 2011; 36(2): 411-22.
7. Berland DW, Malinoff HF, Weiner MA, Przybylski R. When opioids fail in chronic pain management: the role for buprenorphine and hospitalization. Am J Ther 2013; 316-21.

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 Joumal. **2004:328:1490-**