



PCSS Guidance

Topic: The off-label use of sublingual buprenorphine and buprenorphine/naloxone for pain

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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://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 Questions:

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

Background:

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

The sublingual formulation of buprenorphine (buprenorphine SL and buprenorphine/naloxone SL) 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 contrasts with buprenorphine's effectiveness as a medication for the treatment of opioid dependence (addiction) on a daily or less-than-daily basis.[2] There is no evidence that buprenorphine or buprenorphine/naloxone SL provide better analgesia than oral opioids. In addition, there is no evidence that buprenorphine or buprenorphine/naloxone SL prevents opioid dependence (addiction) when used as a primary pain medication. 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 preclude 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 incur more 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 is no methodologically rigorous literature 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 a 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]

General Principles:

1. Sublingual tablet formulations of buprenorphine and buprenorphine/naloxone are only FDA approved for the treatment of opioid dependence (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 dependence (addiction) who have an acute or chronic pain condition (See PCSS guidance: Treatment of acute pain in patients receiving buprenorphine/naloxone).
3. 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 chronic pain patients after detoxification from high-dose opioids. Journal of Opioid Management 2010;2(5):277-82.

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:

Randomised trial = **high**

Observational study = **low**

Any other evidence = **very low**

* Grading quality of evidence and strength of recommendations

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