



## **Medical and Rehabilitation Innovations**

Buprenorphine and Chronic Pain

## BACKGROUND

Buprenorphine is a powerful semi-synthetic opioid medication used primarily to treat opioid dependence or narcotic addiction in the United States since 2003. It is the active drug ingredient in such preparations as Butrans, Suboxone, Subutex and the recently studied Probuphine, a subdermal implant recently approved by the Food and Drug Administration's (FDA) Drug Advisory Committee in a 12-5 vote. According to the Substance Abuse and Mental Health Services Administration (SAMHSA) (September 25, 2015), the FDA has approved the following products for opioid addiction:

- Bunavail (buprenorphine and naloxone) buccal film
- Suboxone (buprenorphine and naloxone) film
- Zubslov (buprenorphine and naloxone) sublingual tablets
- Buprenorphine-containing transmucosal products for opioid dependency

According to Colameco et al., buprenorphine is now approved by the FDA for the treatment of chronic pain in low-dose transdermal patch formulations and for the treatment of addiction in high-dose sublingual tablets and films. Interestingly, clinicians often prescribe these high-dose preparations "off label" for chronic pain management even when there is currently no clear research evidence demonstrating increased benefit or heightened efficacy of buprenorphine on chronic pain as compared to other less expensive opioids. It is crucial to understand that physician prescribing practices do not automatically validate that it is actually effective.

The use of buprenorphine, like other opioids, must be considered in the context of the larger prescription opioid epidemic. Furthermore, in the workers' compensation setting, it is particularly important to consider the following factors such as:

- a) treatment for any co-occurring addiction, as well as pain;
- b) alternative approaches to therapy and any potential treatment side effects, such as opioid withdrawal prior to initiating buprenorphine treatment; and
- c) the anticipated duration of treatment.<sup>1</sup>

### What is Buprenorphine?

Buprenorphine is a partial mu receptor agonist with high affinity but low intrinsic activity at the mu opioid receptors (MOR). The drug also has an antagonist effect at the kappa and delta receptors in the central nervous system (CNS). Though its pharmacology is complex and not completely understood, buprenorphine has been marketed for addiction and more recently a potential drug for chronic pain (at low doses).

As an addiction treatment, it is promoted as being safer than illicit or prescription opioids due to its reported "ceiling" effect (at approximately 16 mg oral dose per day) where the high affinity for MOR leads to a quick saturation of the mu receptors by displacing and preventing the attachment of other opioids (e.g. morphine, oxycodone, methadone, etc.) on mu receptors which are responsible for the euphoria of opioids and for respiratory depression. The low intrinsic activity and the plateauing of effects at higher doses make it harder to have a fatal

overdose on buprenorphine alone, though not impossible. This potential safety feature does not necessarily hold if a person is on other medications that can suppress breathing, such as benzodiazepines. Buprenorphine's high affinity to MOR results in interference or blocking of therapeutic effects of other opioids in managing pain, and this may actually cause severe withdrawal symptoms unless treatment is induced cautiously by a trained physician.

## LITERATURE SUMMARY

### Treatment of Opioid Dependence

Currently, buprenorphine is well accepted in both the physician and academic communities as an effective treatment of opioid addiction. Many published studies confirm the reduction in illicit drug abuse during buprenorphine maintenance therapy. As a result, the best known preparations of buprenorphine, such as Suboxone or Subutex, are used in buprenorphine-certified addiction clinics.

However, the existence of significant and protracted buprenorphine associated withdrawal syndrome, even with a very gradual transition from maintenance therapy to abstinence, raises strong concern for addicted individuals' ability to effectively discontinue buprenorphine therapy. With no published literature guidance on standard of care buprenorphine taper, many buprenorphine clinics do not have the degree of oversight or counselling necessary to monitor the buprenorphine discontinuation process and achieve abstinence.

### Opioid Use for Non-Malignant Pain

Over the past 20 years in the United States there has been an increased liberalization of opioid use for non-malignant pain. This is believed to have resulted from the combination of aggressive development and marketing of new opioid pain relievers and a regulatory move to treat all pain, including chronic pain, more aggressively. The result has been what the CDC calls a prescription opioid epidemic causing in excess of 16,000 overdose deaths nationally per year. *The New York Times* notes that "deaths from drug overdoses have jumped in nearly every county across the United States, driven largely by an explosion in addiction to prescription painkillers and heroin."<sup>2</sup>

Despite the liberalization of opioid use for chronic pain, there is a paucity of any randomized, controlled research demonstrating the efficacy of long-term and/or high dose prescription opioids for chronic non-malignant pain.<sup>3</sup> Yet development and FDA approval of new opioid preparations has continued unabated despite the numerous, often disabling, opioid side effects, including severe constipation, nausea, hypogonadism, osteoporosis, periodontal disease, opioid-induced hyperalgesia, dependence, overdose and death.

## Buprenorphine for Treatment of Chronic Pain

Buprenorphine is promoted, and FDA approved, for the treatment of chronic pain only with the relatively low dose transdermal patch delivery system (e.g. Butrans patch). It is important to keep in mind that numerous other opioids are FDA approved for chronic pain, despite the fact they have not been proven to be efficacious in long-term management of chronic pain, all while other drug forms are being promoted off-label. For instance, Butrans is promoted and FDA approved for pain, yet buprenorphine’s effectiveness for non-malignant pain is still not proven. A systematic review on the use of sublingual buprenorphine concluded that “due to a paucity of high-quality trials, the current evidence is insufficient to determine the effectiveness of sublingual buprenorphine for the treatment of chronic pain.”<sup>4</sup> A small study comparing transdermal buprenorphine and transdermal fentanyl showed poor long-term efficacy of either after 6 months, 11 and 13 percent respectively, with common use of additional opioids.<sup>5</sup> Likewise, for neuropathic pain, buprenorphine is equally unproven; per a Cochrane review published September 30, 2015, “There is no evidence to support or refute the suggestion that buprenorphine works in any neuropathic pain condition. Large, properly conducted new clinical trials would be needed to provide evidence that buprenorphine worked in neuropathic pain conditions.”<sup>6</sup>

## PARADIGM POSITION

Buprenorphine is clearly indicated for use as a medical assistance opioid detoxification or maintenance treatment. There is no substantial published evidence to suggest that buprenorphine is superior to other opioids available to addiction clinicians. Long-term opioid treatment has not proven to result in clinical benefits past six months nor has it been proven to result in increased or improved function. Opioids, including buprenorphine, carry with them a considerable risk profile.

### For Treatment of Chronic Pain

Paradigm Outcomes does not recommend the use of buprenorphine in injured workers with chronic non-malignant pain due to the lack of proven long-term efficacy. Paradigm has a preference for non-opioid management because it significantly mitigates the medical risk profile of chronic opioids of any type.

Paradigm may support the use of low-dose buprenorphine products (e.g. Butrans patch) when there is a concurrent acknowledged addiction, but such clients would need to receive ongoing addiction treatment. However, it would be the carrier’s decision whether to provide coverage.

### Summary

The use of opioids in the treatment of chronic non-malignant pain has been disappointing due to the overall ineffectiveness of opioids in chronic pain, as well as the resultant major national medical crisis in addiction and opioid overdose related deaths. In addition, treating pain with

chronic high dose opioids causes a number of physical medical complications in addition to opioid use disorder. For this reason, Paradigm Outcomes does not support the use of long-term opioids, including buprenorphine, in the management of chronic non-malignant pain.

**Help:** Low doses may help pain, but probably no more than very low doses of other opioids. Buprenorphine may help opioid induced hyperalgesia, and it may be a replacement drug (medically assisted treatment) for opioid addicts as a means of weaning or as a replacement drug in patients who cannot maintain abstinence.

**Hope:** Buprenorphine is a safe alternative to methadone in the treatment of opioid addiction that requires less monitoring and achieves higher rates of abstinence from opioid dependence.

**Hype:** It is an opioid that can stabilize the chronic pain related prescription opioid and heroin crises without the risks and other adverse effects, including constipation, hypogonadism, sedation, addiction and diversion, associated of other opioids.

## ENDNOTES

### References

1. Colameco, MD, Stephen. Buprenorphine in the workers' compensation setting. *Journal of Opioid Management*. July/August 2014; pages 277-283.
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6. Buprenorphine for neuropathic pain in adults. *The Cochrane Library*. September 30, 2015.
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