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Opinion Article

Off Label Use of Buprenorphine for Chronic Pain

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Abstract

Buprenorphine, a partial agonist synthetic opioid is both an excellent treatment for opioid withdrawal symptoms and as an analgesic. It is widely used in sublingual form as a Medication for Opioid Use Disorder (MOUD) but only relatively expensive forms are approved by the US Food and Drug Administration (US FDA) for the treatment of non-cancer chronic pain.In this paper we analyze why the sublingual form may not be more widely used in the US as an analgesic.

Keywords:Buprenorphine; Opioid use disorder; Chronic pain

Discussion

Opioid Use Disorder (OUD), previously referred to as "opioid addiction" is defined in the DSM-5 as a problematic pattern of opioid use leading to clinically significant impairment or distress [1].The attempt to relieve acute or chronic pain is a common reason for use and/or misuse of full agonist opioids and can lead to OUD. SAMHSA TIP 54, managing chronic pain in adults with or in recovery from substance use disorders, outlines methods for managing such pain [2]. Obviously, full agonist opioids, if utilized at all, must be carefully monitored in patients with OUD.

But, in addition to non-opioid and non-pharmacologic treatment of chronic pain, there is an opioid that is safe and effective to use for the treatment of chronic pain, *viz*. buprenorphine.Buprenorphine is a thebaine derivative that is a partial agonist at the mu opioid receptor, has strong binding to the receptor [3], and, by itself, has a ceiling effect on respiratory depression, so it is much safer than full agonists, such as oxycodone or fentanyl [4].

However, only three formulations of buprenorphine are approved by the US Food and Drug Administration (US FDA) as an analgesic for the indication of pain: IV/IM injectable formulation (Buprenex®), transdermal patch formulation (Butrans®), and buccal film formulation (Belbuca®).However, these medications are expensive for patients who do not have health insurance or who have a high out-of-pocket deductible.

Fortunately, there are relatively inexpensive alternative formulations, the Sublingual (SL) tablet (mono-product), previously marketed as Subutex®, and the SL film containing both buprenorphine and naloxone previously marketed as Suboxone® (combo-product), but now are both generic.Although the use of SL buprenorphine is considered off-label by the USFDA, such uses are common and legal in clinical practice in the US [5].

The idea of off-label use of the SL forms for chronic pain is not new. Malinoff et al. [6] in an open label study in 2005 concluded that SL buprenorphine and buprenorphine/naloxone were well tolerated and safe, and appeared to be effective in the treatment of chronic pain in patient's refractory to Long Term Opiate Analgesic (LTOA).

A clinical trial, registered in 2008 and using the combo-product [7], was designed to develop and pilot test clinical guidelines for the use of buprenorphine for the treatment chronic pain among patients with substance abuse histories. The final report for that study was not published until 2012 [8]. The authors had intended to enroll 40 patients in the open label study but were able to enroll only 12 patients. Of those, 6 had adverse events, 2 withdrew, and 4 completed the 3 months trial. Encouragingly, for them, the average and worst pain decreased after the switch to Bup/Nx (the combo product).Another clinical trial registered in December 2013 using the combo product was terminated because of "low recruitment yield" (6 patients) [9].

In a review of available data, Cote et al. [10] in 2014 concluded that "Preliminary trials suggest a plausible role; however, due to a paucity of high-quality trials, the current evidence is insufficient to determine the effectiveness of sublingual buprenorphine for thetreatment of chronic pain. Rigorous further trials are warranted". Rosen et al. [11], that same year, conducted a survey among prescribers and non-prescribers and concluded that sublingual buprenorphine is indeed being used to treat chronic pain; however, the circumstances when this occurs are not entirely clear.A clinical trial registered in October 2021, calledTreating Opioid Patients' Pain and Sadness (TOPPS) appears designed to (hopefully) answer the questions that have arisen from the reports so far published [12].

Interestingly, it appears that the doses required for analgesia are generally lower than those required to block withdrawal symptoms in opioid dependent patients. Butrans®, for instance, releases 5 mcg, 10 mcg, or 20 mcg per hour, or a maximum daily dose of 480 mcg (1/2mg) per day. Medication Assisted Treatment (MAT) with buprenorphine generally requires a daily SL dose of 16 mg to 24 mg, with absorption of approximately 30%- yielding a daily dose 10 to 15 times higher than the transdermal dose! Aside from the pharmacologic aspect of a relatively steady blood level from the transdermal application, it would also appear that the antinociceptive action at the mu receptor is stronger than the withdrawal blocking effects. See Khanna and Pillarisetti [13] for a more detailed discussion.

Having read these studies, and inconclusive clinical trials, I

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became confused about why the off-label use of SL buprenorphine for chronic pain management has not generally caught on in American clinical practice. A clinic with which I am associated has been using SL buprenorphine with success for several years.

On re-reading the clinical trials it struck me that the investigators may have not been aware of 2 potential problems that could affect both enrollment and retention: (1) The studies were designed to administer the combo-product, i.e. the tablets contained naloxone, falsely believed to deter diversion [14], and (2) they may have been unaware of a reaction called Precipitated Withdrawal (PW).Although not studied in a controlled manner, the combo-product is notorious for frequently causing intolerable side effects (such as headaches and dysphoria) and PW can occur if buprenorphine of any formulation is administered to a patient who is not experiencing significant withdrawal [15]. Many patients are aware of such problems and may have declined enrollment because of knowledge of or experience with, such effects.

Investigators who are inexperienced in the treatment of OUD with buprenorphine might have been unaware of these 2 confounding factors.The solution to those problems is to (1) Study the administration of only the mono-product, i.e. without naloxone and (2) Understand how to properly transition a patient from full agonist opioids to buprenorphine [16].

Conclusion

Buprenorphine, in sublingual form, is an extremely safe opioid that is currently underutilized in the US for the treatment of chronic pain.We speculate that such underutilization is multifactoral: (1) Medical providers are unfamiliar with the basic drug itself, (2) They are unaware of the problems of transitioning from full agonists to buprenorphine, and (3) They are unfamiliar with the common side effects of the combo-product, i.e., formulations that include naloxone. All of these potential problems can be overcome with proper education of both provider and patient.

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