A Primer on the Use of Buprenorphine for Pain Management in Hospice
August 2023

For decades, the synthetic opioid buprenorphine has been primarily used in the treatment of opioid use disorder (OUD) rather than pain management. Today, however, regulatory changes making it easier to prescribe buprenorphine have spurred renewed interest in the drug among palliative care practitioners.

Buprenorphine has a long and storied history, starting in the 1960s when it was developed as an alternative to morphine. While the drug's analgesic properties were apparent from the beginning, the unique pharmacology of buprenorphine (specifically reduced sedation and euphoria) also made it a promising alternative to methadone for OUD treatment. The subsequent association between buprenorphine and substance abuse medicine led to stigma around its use for pain management and heightened regulatory scrutiny.[1]

While clinicians have always had the ability to prescribe buprenorphine for pain, the Drug Treatment Act of 2000 required physicians to complete specific training and registration to receive a waiver to prescribe buprenorphine for opioid use disorder. This, in turn, led to confusion and consternation among prescribers and pharmacies about prescribing and accepting prescriptions for buprenorphine for pain management.

This all changed on Dec 29, 2022, with the signing of the Mainstreaming Addiction Treatment (MAT) Act of 2023. This act eliminated the so-called "X" Waiver (because of the X that was added to the clinician's DEA registration number) that physicians had previously been required to obtain to prescribe buprenorphine for opioid use disorder. As a Schedule III drug, buprenorphine can now be easily ordered for pain and OUD by phone or fax, and refills can be included on the original prescription.

Why is Buprenorphine Being Used in Hospice?

Buprenorphine is gaining popularity for pain management due to its unique pharmacology. The main benefit of buprenorphine is that it provides pain relief comparable to more commonly used opioids with fewer side effects. Buprenorphine appears to exert its analgesic effects mainly on the lower CNS (spinal cord) rather than in the brain, which promotes analgesia while limiting adverse effects like respiratory depression and euphoria.[2]

Buprenorphine's unique properties are related to its pharmacology, namely the types of receptors where it exerts effects. Buprenorphine has effects at several different types of receptors, including mu, kappa, delta, and opioid-receptor-like 1 (ORL-1). At the mu receptor, the partial agonist properties provide a "ceiling effect" for respiratory depression, euphoria, and constipation. However, there does not appear to be a similar "ceiling effect" to analgesia.

As an antagonist at the kappa and delta receptors, buprenorphine provides potential antidepressant effects and causes blunted dysphoria and opioid craving, as well as decreased incidence of sedation and hyperalgesia. As an ORL-1 agonist, buprenorphine provides some additional analgesic effects with lowered opioid adverse effects such as constipation. Additionally, because buprenorphine does not occupy all types of mu receptors, it leaves some of them open for other full agonists (such as morphine) to have effect.[2]

A systematic review of ten trials involving 1190 patients demonstrated sublingual buprenorphine is effective as an analgesic and 23 of 24 studies showed buprenorphine is as effective as morphine fentanyl, and oxycodone for pain treatment.[3] When compared across clinical studies, the efficacy of buprenorphine buccal film was similar to that of the extended-release versions of hydromorphone, hydrocodone, and oxymorphone.[4] Depending on the formulation, buprenorphine is approximately 25-100 times more potent than morphine, which makes it nearly as potent as fentanyl.

How is Buprenorphine Administered in Palliative Care?

Oral bioavailability of buprenorphine is low because of extensive first-pass hepatic metabolism. However, the administration of buprenorphine by the sublingual and buccal routes bypasses this. Transdermal administration of buprenorphine has also proven effective and offers a valuable option for hospice patients who are unable to swallow, as well as for those with mouth or bowel lesions (who might be unable to utilize oral or rectal formulations), or who have persistent nausea and vomiting precluding the use of oral medications.[2]

One barrier to buprenorphine initiation is that current practice guidelines recommend a period of mild-to-moderate withdrawal from opioids which may be intolerable for palliative care patients currently treated with a full agonist. A possible alternative to this route is low dose initiation: overlapping smaller doses of buprenorphine with the current full opioid agonist. Recent research indicates comparable safety and effectiveness for a variety of traditional and low-dose initiation methods, suggesting an individualized approach based on the needs and previous opioid use of each patient.[5]

Is Buprenorphine Safe for Pain Management?

One of the main safety concerns about opioids, in general, is respiratory depression. Buprenorphine appears to be significantly safer than other opioids regarding respiratory depression. No cases of respiratory depression were reported in any clinical trials of buprenorphine buccal film. In a post-marketing survey of 13,179 patients receiving transdermal buprenorphine, only one patient experienced respiratory depression. At only 0.01 percent, this is approximately 80 times less than what was observed in a separate study of transdermal fentanyl.[4]

The safety profile of buprenorphine prompted the US Department of Health and Human Services to state the following as part of a task force report: “Buprenorphine, an opioid medication that the FDA has approved for clinical use, is a partial agonist at the mu opioid receptor and therefore has a reduced potential for respiratory depression; it is thus safer than full agonists such as morphine, hydrocodone, and oxycodone.”[6]

Buprenorphine is also safe for use in mild to moderate liver failure and in all stages of renal failure. This is because it does not produce active metabolites that can accumulate in chronic kidney disease. Buprenorphine is a Schedule III drug with less potential for abuse than Schedule II drugs (e.g., morphine,

oxycodone, fentanyl). The risks of drug dependence and analgesic tolerance are also lower for buprenorphine than for conventional opioids.[4]

Is Buprenorphine Well Tolerated?

While it does cause adverse effects (e.g., constipation, respiratory depression, dizziness) that are typical of all opioids, buprenorphine may have more of an effect in spinal receptors compared to brain receptors, which appears to limit its overall adverse effect profile. Constipation was reported in only 4% of patients receiving buprenorphine buccal film. Only one percent of more than 130000 patients in a post marketing surveillance study of transdermal buprenorphine experienced constipation.[4] In addition, a comparison of adverse events reported in clinical trials for buprenorphine buccal film and ER formulations of oxycodone, hydromorphone, and oxymorphone showed that the proportion of patients who experienced nausea, vomiting, constipation, headache, dizziness, somnolence, anxiety, and dry mouth was lower with buprenorphine buccal film than with conventional opioids.[4]

Buprenorphine is metabolized to norbuprenorphine, and CYP3A4 plays a significant role in its metabolism. As such, exposure to buprenorphine is increased following concomitant administration with strong CYP3A inhibitors such as ketoconazole. Pharmacodynamic interactions can occur with the coadministration of buprenorphine with benzodiazepines, both of which can cause respiratory depression. Unlike methadone, buprenorphine has not been found to cause significant prolongation of the QT interval.[2]

Should Hospices Offer Buprenorphine?

There have been fewer studies on buprenorphine for pain management compared to other opioids but the safety and side effect profile of buprenorphine makes a compelling case for use in end-of-life care. Buprenorphine may be particularly well suited for the elderly patient, where the long duration of action, relative safety profile and ability to use in the presence of renal failure make it an attractive choice. In addition, the absorption of transdermal buprenorphine does not appear to be significantly affected by age.[7] Buprenorphine is also appropriate for palliative care patients with a history of OUD.

Buprenorphine has the potential to become a drug of choice in hospice and palliative care, but barriers to adoption remain. For hospices, the higher cost of buprenorphine is an important consideration. The stigma associated with a drug primarily used for substance abuse may also lead to resistance among patients and caregivers. Many prescribers and pharmacists also remain wary of legal and regulatory issues due to the rapid pace of change and longstanding confusion around the differing rules for its use in OUD vs. pain management. Additionally, at least 15 states have restrictions that do not align with loosening of restrictions at the federal level.[8]

Despite these barriers, buprenorphine is increasingly acknowledged as a first line pain management treatment. For example, recent updates to VA/DoD clinical practice guidelines recommend buprenorphine instead of full agonist opioids for patients receiving daily opioids for the treatment of chronic pain.[9] Hospices should be deliberate about educating their teams on the pros and cons of buprenorphine and developing guidelines for its use in order to provide the safest and most effective symptom management for each patient.

Further Reading

In addition to the references provided for this article, Enclara recommends the following Palliative Care Network of Wisconsin (PCNOW) Fast Facts and Concepts:

- #221 Treatment of Pain in Patients Taking Buprenorphine for Opioid Use Disorders
- #268 Low-Dose Buprenorphine Patch for Pain
- #441 Sublingual Buprenorphine Initiation: The Traditional Method
- #457 Buprenorphine Initiation – Low Dose Methods

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