“Treating Chronic Pain in 2024 - Let’s Refocus on Buprenorphine”

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Physicians are increasingly aware of the risks, both clinical and legal, for treating pain with opioids. Fearful of regulatory scrutiny, faced with reluctance of pharmacists at the large chains, and surrounded with rising stigma and misunderstanding, the pace of prescribing for opioids has dropped considerably. Despite this, the rate of illicit and dangerous opioid use, outside of medical care, has brought the death rate of overdoses and morbidity to an all-time high.

Our medical practice has been in the fields of addiction and pain medicine for three decades. We were early adopters of buprenorphine for pain in the 1990's and for addiction after FDA approval in 2002. We have introduced and published several innovations regarding the uses of this versatile medication and lectured on buprenorphine both locally and nationally. For the patient population with pain that is unresponsive to non-pharmacologic and non-opioid interventions, we have seen this medication be transformative in hundreds of situations.

Furthermore, buprenorphine is quite effective in discouraging and preventing the emergence of addictive behavior and to a significant degree, can also directly prevent overdose deaths by blunting the activity of other administered opioids. Relevant to pain medicine, buprenorphine is recognized for efficacy against opioid induced hyperalgesia, as well as in neuropathic pain, which is often unresponsive to other opioids.

Although recent regulatory changes at the federal level have removed barriers to prescribing buprenorphine for addiction, it is not clear that there is any such momentum in the treatment of pain with

buprenorphine. Despite decades of review papers in highly placed peer reviewed journals highlighting buprenorphine's remarkable efficacy and safety in treating chronic pain, neither pain specialists nor primary care physicians in our community often propose or even mention buprenorphine.

For example, few physicians are prescribers of the two FDA approved forms of buprenorphine for chronic pain: transdermal buprenorphine (Butrans and generic) - and - mucoadhesive/buccal buprenorphine (Belbuca). Fewer still are skilled at repurposing the more available and affordable forms of buprenorphine that are approved for addiction towards pain conditions.

Buprenorphine, like other opioids, induces a physiological dependency, but much more so than other opioids, is particularly suited to a gradual tapering process. In those with or highly vulnerable to addiction, or with a high level of severity of symptoms, buprenorphine can be maintained indefinitely. Much more or in contrast with other opioids, buprenorphine is associated with relief of depression, anxiety, and other psychiatric syndromes, rather than the exacerbation of these co-occurring disorders. In this regard, treatment with buprenorphine can facilitate tapering patients off of unnecessary or harmful medications including benzodiazepines, zolpidem like drugs, anti-psychotics, and SSRI's, when appropriate. For those who stay on buprenorphine over time, the benefits in pain and symptom management are often seen to increase, while the side effects remain stable or decrease.)

Like other opioids, buprenorphine is associated, but less so, with hypogonadism and constipation. Both of these conditions are highly responsive to thoughtful intervention. Buprenorphine, compared to other opioids, is not thought to contribute to immunodeficiency, nor to complications when used in renal and hepatic dysfunction.)

Since the publication by the CDC of the 2016 Guidelines for Prescribing Opioids for Chronic Pain, millions of patients with chronic pain have undergone opiate dose reductions or eliminations.

Although the risk of addiction and overdose were undoubtedly reduced for many, at least for the short run, a significant minority of these patients suffered setbacks, including turning to street drugs, rather than experiencing better outcomes.

Large numbers of other patients with more recently diagnosed chronic pain , irrespective of severity, have been denied both standard opioid pharmacotherapy as well as a consideration of buprenorphine.

If clinicians are even aware of the availability of buprenorphine for chronic pain, there are more often than not misconceptions, five of which are listed:

Common Misconceptions Among Providers Surrounding Buprenorphine
1) Buprenorphine is often thought of as too powerful, as it is also used in addiction, but this is based on either stigma or inexperience in reducing the initial dosing.
2) Buprenorphine is alternatively thought of as too weak as it is a "partial agonist," but this conception is considered outdated for pain and applies more directly to respiratory depression.
3) Buprenorphine is expected to interfere with the actions of other opioids that would be given for post surgical or breakthrough pain, but in practice, adjusting the dose upwards under careful monitoring is quite successful.
4) Buprenorphine is often not "liked" by patients, but this is often a function of "euphoric recall" of the regular opiate. With tincture of time and careful dose calibration, patients learn to appreciate and "like" the steady support of the buprenorphine, as opposed to the roller coaster of previous opiate prescriptions.
5) Buprenorphine should not be used for chronic pain as it is associated with physiological dependence and is hard to taper from. Misconceived, notwithstanding the surface truth of these observations, is that the patients who would benefit from buprenorphine are often already being managed with dependency producing medications, such as opioids or benzodiazepines, with negative outcomes. With poorly managed pain, these patients and others face significant morbidity and mortality, sometimes from suicide, that make the cost/benefit ratio favorable. With experience, buprenorphine prescribers can develop skills at tapering and discontinuing the medication. Due to its long duration of action and tight binding properties at the mu opioid receptor, buprenorphine is uniquely suited to dose reductions.

The adoption of buprenorphine in pain medicine has likely been slowed by other factors. At the highest level of government science, unlike the case with buprenorphine for addiction, the potential of this medication for pain is rarely discussed. A case in point can be found in the pages of the NIH Pain Consortium, where buprenorphine is mentioned only once in a pediatric context (*2020 NIH Pain Consortium Symposium Summary*, 2020).

Another instance is the otherwise excellent 2018 *Neuropsychopharmacology* review article on opioid mechanisms, co-authored by Nora Volkow, Director of the National Institute of Drug Abuse (Valentino & Volkow, 2018). She and her co-author describe the two primary intracellular second messenger pathways activated by classical opiates, the G protein pathway that leads to the desired analgesic effect of opiates and the β-arrestin pathway that leads to less desirable effects such as respiratory depression, euphoria, withdrawal, and addiction. Experimental drugs have shown potential or "bias" in favoring the beneficial G protein pathway. The authors, like others, see this as an opportunity for industry to patent new drugs. Not mentioned, however, even by such an erudite author is time tested buprenorphine, that displays the desired G protein bias.

In the last year, there has also been much publicity about the novel non-opioid molecule “VX-548” developed by Vertex Pharmaceuticals to target the sodium channel in peripheral nerves. It was favorably studied in a postoperative acute pain model, and Vertex plans to submit it for review by the FDA this year. It is being hailed as the long sought after alternative to standard opioids and the possible answer to our opioid dilemma. Not mentioned in the media coverage, is buprenorphine's currently availability and FDA approval and how extensively it has been studied. For example, there are over 10,000 Pub Med entries for buprenorphine.

In retrospect, it may have been the proprietary marketing of such products as OxyContin and Duragesic (sustained release oxycodone and transdermal fentanyl) in the late 1980's and 1990's that drove out consideration of the better studied buprenorphine, already known for analgesia and lower abuse potential.

We need innovation and the pharmaceutical industry. Buprenorphine itself was an invention of the private sector. But let's not let the vision of a new crop of theoretical and expensive drugs eclipse the need for public health funding and guidance to further study and implement buprenorphine therapeutics for severe pain.

References

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