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Treating Chronic Pain: Is Buprenorphine the (or even an) Answer?

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The opioid epidemic in the United States continues to impose a significant mortality and morbidity burden. For example, life expectancy at birth in the United States fell from 78.9 to 78.8 years between 2014 and 2015, the first year-over-year decline since 1993¹, and was reduced further to 78.6 years in 2016, with deaths from opioid overdose being hypothesized to play a role in these decreases.² While not all opioid overdose is related to prescription opioids for the treatment of chronic pain (e.g., opioid use disorder), nearly 40% of opioid overdose deaths involve a prescription opioid.³ As such, finding safe and effective therapies for patients with chronic pain is paramount. A staggering 11% U.S. adults have chronic, daily pain which is moderate to severe.⁴ This population is more likely to have decreased health, require more medical care, and to be disabled.⁴ Thus, in addition to relieving the burden of pain, the improved care of chronic pain patients could also result in significantly decreased costs to the United States healthcare system. In an effort to provide guidance and to improve the treatment of chronic pain, the United States Centers for Disease has released guidelines for opioid prescribing for chronic pain, and a key recommendation of the guidelines is a focus on minimizing the use of traditional opioids.⁵

Ideally, an alternative to traditional opioids (primarily mu-opioid receptor agonists) would (a) provide adequate treatment of pain and (b) be associated with a low risk profile. Buprenorphine may hold the potential to be a “silver bullet” for treating chronic pain—or at the very least, another tool in the arsenal. While buprenorphine was initially used to treat patients with opioid use disorder, its unique structure as a mixed opioid receptor agonist/antagonist holds the promise of providing pain relief with a lower risk of adverse events. As

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a result, buprenorphine is increasingly being used for the treatment of chronic pain.^{6,7} Buprenorphine is available in several formulations; two crucial distinction are the route of administration (transdermal vs. sublingual) and whether the formulation contains naloxone, with naloxone-containing formulations typically being used for opioid use disorder as opposed to chronic pain.

However, whether buprenorphine lives up to its promise is an empirical question.⁸ In their recently published paper, Aiyer et al. performed a systematic review to address this issue.⁹ The authors identified 25 randomized controlled trials examining the effectiveness of buprenorphine in treating chronic pain from a wide variety of sources, including pain from cancer and lower back pathology. Because of the wide variety of endpoints and patient populations across these studies, a formal meta-analysis that might have obtained a summary result was not possible. However, the authors found that 14 of these 25 studies demonstrated an association between buprenorphine and improved pain scores. Because most of the studies with positive findings tested the transdermal formulation of buprenorphine, the authors concluded that buprenorphine in this formulation is an effective analgesic for patients with chronic pain, and that the buccal formulation also holds promise.

In the face of the opioid epidemic, any additional evaluation of potential therapies for chronic pain is useful. However, from a policy perspective, the findings of this paper are mainly instructive because they demonstrate the limitations of the current literature on buprenorphine and point to important avenues for further research. In particular, while the studies in this systematic review did examine side effects, none appears to have been designed or sufficiently powered to identify whether buprenorphine is safer than potential alternatives (e.g., traditional opioid agonists), particularly with regards to serious adverse events. Along these lines, as the authors note, the vast majority of studies they considered evaluated buprenorphine against a placebo, and its performance was mixed when compared against active agents such as oral morphine.

As such, the results the authors find are a good starting point, but are not sufficient to recommend the use of buprenorphine over other alternatives such as traditional opioid agonists, nor are they sufficient to guide policymakers and payers in designing incentives to favor (or disfavor) buprenorphine over these alternatives. Going forward, what is most helpful from a policy and a clinical decision-making perspective is a comparative evaluation of the relative risks and benefits of buprenorphine compared to other alternatives for the management of chronic pain. These trials should be designed to test the non-inferiority of buprenorphine compared with traditional opioids. In addition to efficacy, future studies should aim to address whether buprenorphine is indeed safer than potential alternatives. Since serious adverse events from buprenorphine (e.g., respiratory depression, withdrawal) are reasonably rare, conventional randomized trials may not be sufficiently powered to precisely estimate the safety profile of buprenorphine. In this regard, well done retrospective trials using administrative claims data may be helpful. This view is consistent with the conclusion from the work of Aiyer et al. that we need more data to evaluate whether buprenorphine can play an important role in chronic pain management and reducing morbidity and mortality from opioid use.

These findings also have implications for the vast majority of anesthesiologists who are not trained in pain medicine and provide care in the operating room setting. Given a growing body of literature, including this study, suggesting that buprenorphine is effective for the treatment of chronic pain, we can expect an increase in the percentage of surgical patients presenting with buprenorphine use. The perioperative management of patients using buprenorphine raises many critical questions that have not been definitively answered and for which there is no widespread consensus.¹⁰ In another recently published paper, Ward et al. discuss perioperative management strategies for patients who present for surgery and are taking methadone and buprenorphine formulations as treatment for opioid use disorder.¹¹ Generally clinicians are in agreement about, and evidence supports, continuing methadone perioperatively along with additional analgesics to manage acute postsurgical pain. Unfortunately, the best perioperative analgesic strategy for patients presenting for surgery on buprenorphine has not yet been determined. It is likely that the most effective strategy will be based on the reason for buprenorphine use (chronic pain vs opioid use disorder), the expected amount of postoperative pain, and whether or not regional anesthesia can be used to control postoperative pain. High level evidence, such as randomized controlled trials, is greatly needed. The traditional standpoint of discontinuing buprenorphine preoperatively is based on single patient case reports and hypotheses driven from buprenorphine pharmacokinetics. However, while reports are heterogeneous and retrospective patients on buprenorphine are more likely to experience adequate analgesia when buprenorphine is continued during the perioperative period. Additionally, it is important to weigh the risk of having suboptimal postoperative pain control if buprenorphine is continued versus the risk of substance use relapse if buprenorphine is discontinued. While Ward et al. are cautious about making strong recommendations, they correctly point out that the perioperative period is a high risk time for opioid use disorder relapse, and clinicians should be careful about instituting broad recommendations that include the preoperative discontinuation of buprenorphine for all patients who are taking it. The risks from relapse after buprenorphine discontinuation are grave; in one study 18% of patients in a single large healthcare system with opioid use disorder died within the study period and there was an even higher risk of serious morbidity.¹²

Both of these studies raise one final issue. Without doubt, the identification and use of better clinical therapies has the potential to make a meaningful impact on this population and perhaps the opioid epidemic. However, it should be noted that patients with chronic pain and/or opioid use disorders have numerous interactions with the health care system across multiple providers. In this setting, policies and changes at the system-level—such as the increased use of multidisciplinary teams for the treatment of chronic pain—may have just as large or perhaps an even larger effect in improving the health and welfare of these patients. Simply put, a pain physician may come up with the perfectly correct management plan for the patient, but any implementation of the plan is highly dependent on varying levels of coordination from a variety of healthcare providers, such as the patient's primary care provider as well as local emergency room physicians. For example, prescribing buprenorphine may not provide the expected benefit to patients if they can easily obtain traditional opioids from their primary care provider or the emergency room. As clinicians, perhaps our “blind spot” is the belief that better therapies are sufficient to treat chronic pain

and to address the opioid epidemic. However, it very likely that accomplishing both of these goals is a policy, and perhaps political, issue as much as it is a clinical one.

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