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Mini Review

The Complexities in the Management of Chronic Pain with Co-Morbid Opiate Use Disorder: A Concise Review of Current Literature

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Abstract

Chronic Pain and Opioid Use Disorder are both often causes of significant decrements to social and occupational function, especially when found co-morbidly. Funding for and interest in research for both disorders are currently robust given the large numbers of opiate related deaths that continue to rise in the United States. A concise review of the literature within the last three years shows that use of buprenorphine in treatment of these conditions remains low despite its efficacy as an analgesic, as an FDA approved medication for treatment of OUD, and specific properties in assisting the reduction of opiate induced hyperalgesia. Current barriers include lack of waivered prescribers, lack of accessibility and support in rural communities for prescribers, and lack of specialty trained addiction physicians to provide mentoring and education in many underserved communities.

ABBREVIATIONS

CDC: Centers for Disease Control and Prevention; CNCRP: Chronic Non-cancer Related Pain; DOD: Department of Defense; MAT: Medication Assisted Treatment; MME: Morphine Milligram Equivalents; OUD: Opioid Use Disorder; VA: Veterans Affairs

INTRODUCTION

Chronic pain (cancer relation and non-cancer) and opioid use disorder represent challenging diagnoses to manage in any clinical setting, and new reviews and research within the last three years have helped to expand our knowledge base in how to approach this complex duality when these disorders overlap. Based on this expanded understanding, the newest CDC guidelines (August 2017) recommend transition to 20-50 Morphine Milligram Equivalents (MME) or less daily for all opioid pain medications to reduce the risk of sudden death [1,2], and prevention of longer term full agonist opiate complications such as sedative polypharmacy risk and opiate induced hyperalgesia. Doses over 90 MME daily carry a profound risk of sudden death [3], especially when sedative polypharmacy is present. Although opiates remain an effective option for pain relief, their use needs close monitoring and frequent in clinic follow ups. With current research showing equal analgesic effects with non-opiate pain medications and improvement with a multi-modal treatment approach the use of partial agonists such as buprenorphine in lieu of full agonists may represent a safer and equally effective alternative to full agonists in a patient population with chronic pain and opioid use disorder [4,5].

At present the vast majority of opiates dosed for chronic pain remains full opioid receptor agonists, with a large portion of chronic pain patients presenting with risks for or evidence of overmedication [6]. While buprenorphine falls within the opioid category and is an analgesic, its inherent differences in pharmacokinetics as compared to the related full agonists make it a potentially more suitable choice to minimize the number of sedatives dosed in treatment, and in providing a safer medication in a high risk population. Despite current pushes towards safer prescribing practices and recent lower rates of opiate prescription numbers, opiate related deaths continue to rise [7]. A recent Cochrane review including over 60 studies on opiate related harm events showed that the absolute rate for an adverse event was 78% when compared to placebo, and 7.5% for serious adverse events for patients with medium and longer term opiate use for chronic non-cancer related pain (CNCRP) [8]. Although earlier studies had reported that patients on opioid medications had a low risk of developing an opiate use disorder [9], current longer term research has shown that any patient on any chronic opiate treatment at any does has an increased risk of developing an opiate use disorder, for overdose, and for sudden death [10,11].

Given the significant overlap of these physically and socially impairing diagnoses [12], this article reviews the current research within the last three years and describes the current advancements in knowledge on the safety and tolerability of buprenorphine, its analgesic benefit, and current access to treatment issues with this FDA approved medication. The

limited focus of a three year review of current literature and recommendations was performed to highlight active advances in knowledge or new changes to treatment strategies that are of interest in this at risk patient population.

Safety and Tolerability

Buprenorphine represents a medication and treatment strategy for both pain (as buprenorphine formulation) and opioid use disorder (as the buprenorphine / naloxone combination medication) [13] which in the recent decade has received renewed interest and research in the United States. Originally approved for use in the US by the FDA in the 1980s, it didn't garner much interest until it had been used successfully in many European countries over that same time in the harm reduction model of addictions treatment. Unlike full agonists, buprenorphine has been shown to have no immunosuppressive effects, its breakdown and elimination are not altered in the geriatric population or in cases of renal dysfunction, and the risk for respiratory depression is much lower [14]. This is thought to be primarily due to its partial agonism at the opioid receptor sites, in addition to activity at the opioid-like receptor 1 (ORL1) and antagonism at the Kappa opioid receptor. As compared to a full agonist such as fentanyl, buprenorphine does have a ceiling, or plateau effect in regards to respiratory depression in human and animal studies - a potential benefit to any patient on doses of sedative analgesics [15].

Analgesic Benefit

The analgesic action of buprenorphine is due to partial agonism at the mu, kappa, and lambda opioid receptor sites, for which it has a high affinity bonding action [14,15]. Analgesic benefit has been shown in both acute [17] and chronic pain management [18,19], with additional benefit in treatment in reducing opiate induced hyperalgesia [20]. In the acute pain intervention trial cited above, 0.4mg buprenorphine sublingual was equally as effective as a 5mg morphine dose in acute pain reduction for bone fracture pain. Studies such as these continue to build on the body of evidence that buprenorphine is not just an adequate pain management strategy, but perhaps a better alternative given the reduced risks of use as compared to many other full agonist choices. In looking at specific benefit to the chronic pain management cases, elimination of the persistent kappa receptor agonism of other full agonists thought causal of the hyperalgesia [21] has been shown to over time reduce perceived pain and improve quality of life outcomes. This is significant in light of the body of research showing that the hyperalgesic response is more prevalent in the chronic pain population on chronic opioid therapies than previously thought [21].

Access to Treatment

Two important access issues are present in treating this population: availability of a knowledgeable prescriber, and the patient being willing to access care available when opiate dosing continues to increase, or a concern for opioid use disorder is present with their chronic pain treatment.

A recent study found that among those on high dose opiates for CNCRP, only 26% sought treatment for their concerns for substance use disorder, and only 4.8% sought assistance through buprenorphine or methadone for treatment of their co-morbid conditions [22]. The stigma of seeking care, and the fear of the physician stopping all pain treatment were cited by the patients as the main barriers to accessing additional care. Given the complexity of the nature of these diagnoses [23], and the fear of repercussions for seeking treatment, new studies support use of multi-modal strategies such as active patient education, ensuring a good doctor patient relationship, and primary care based counselling to decrease patient barriers to care and to improve treatment outcomes [24]. Additional benefit to reduction of chronic pain scores over time with integration of alternative or complementary medical approaches such as acupuncture, meditation, and relaxation techniques [25] have been shown to improve quality of life scores. Unfortunately buprenorphine treatment along with many of the alternative strategies that have shown benefit may not be covered on individual insurance plans, are cost prohibitive, or represent a significant time-cost to the patient to engage in treatment - all of which are barriers shown to decrease access to care [26]. While retention can be problematic, patient preference tends to lean towards buprenorphine formulations when approaching treatment for any opiate use disorder due to ease of use and reduced side profile as opposed to alternatives [27]. Both providers and patients report increased ease of use with regards to intervals between monitoring and follow up visits once stable when in treatment for opioid use disorder and on the approved buprenorphine/naloxone combination.

On the provider side, we know that buprenorphine induction in the office setting requires more clinical monitoring than using the routine full agonists. Even among buprenorphine waivered providers statistics show that panels are not completely filled or that waivered providers are not accepting patients due to concerns over perceived lack of addiction specialist support, concerns over reimbursement, and concerns of potential legal or legislative difficulties [28-30]. Whatever the actual reasoning behind providers individual motivations to not prescribe buprenorphine, the fact remains that there is a nationwide shortage of waivered prescribers to fill the current and future need for this type of medication.

DISCUSSION & CONCLUSION

There have been significant recent shifts in recommended prescribing practices as outlined in the current CDC guidelines, in the DOD and VA joint treatment guidelines for CNCP, and recommendations from the American Society of Addiction Medicine and related addiction management organizations. Despite reduction to the total number of opiates prescribed patient deaths attributed to opioid overdoses continue to remain high [31] despite physician and patient education and shift in these recommendations. One treatment option that is able to address both pain relief and assist as in medication assisted treatment (MAT) for opioid use disorder is Buprenorphine/Naloxone. FDA approved for both pain management and in its buprenorphine/naloxone formulation for medication assisted treatment of opiate use disorder, and has unique pharmacologic and pharmacokinetic benefits to its use not seen in other full agonist opiates.

Those patients with opioid use disorder taking buprenorphine (or methadone) for medication assisted treatment of opiate use disorder have a high rate of comorbid chronic pain complaints, and typically report a greater incidence of pain complaints while in treatment. Given that the presence of increased pain is itself an indicator of risk of relapse, this population warrants prompt evaluation for multi-modal treatment strategies that address all areas of that patient's biopsychosocial formulation. Given the review of the current evidence, treatment of Opiate Use Disorder with co-morbid Chronic Pain should include a full pain and addiction medicine assessment, with initiation of buprenorphine/naloxone for both control of pain and medication assisted treatment of the OUD. Augmentation of medication treatment with therapy is also recommended. If approaching the treatment of both disorders from the pain management viewpoint, a shift to buprenorphine from full agonist opiates enables use of a medication that can blunt the effects of any unwanted supplementary short half-life full agonist opiates the patient may seek out for self-augmentation of a prescribed treatment regimen. It can as well improve patient outcomes by reduction or elimination of any active opiate induced hyperalgesia. Additional supplementary treatment options may include acupuncture, biofeedback, meditation, chiropractic manipulation as well as talk therapy such as cognitive behavioral therapy and motivational interviewing.

Although well designed, many of the recent studies showed low power and potential for high dropout rates or lack of follow up, issues which have been noted as well in many studies among this population outside the more recent 3-year window. Past studies focused on 12 weeks follow up and abstinence or firm medication dose compliance as an outcome measure may accurately report the data, but miss the longer-term positive outcomes of illicit use reduction, reduction in polypharmacy use, or improvements of social functionality. Larger multi-site studies may have a role in developing improved outcome data on pain relief and improvement of quality of life sought by a harm reduction model of treatment rather than the short-term trials with a focus on abstinence rates. The study of the overlay between these two diagnoses, and on how buprenorphine can benefit them in treatment remains an interesting and important area for research.

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