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Buprenorphine: Place in Therapy for Chronic Pain

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Pain management is an important aspect of care for a variety of acute and chronic conditions. Evidence supporting specific non-pharmacologic and pharmaceutical therapy varies depending on the condition, but most guidelines, medical societies, and public health agencies recommend against routinely prescribing opioids for acute or chronic pain conditions due to increasing evidence of short-term adverse events and serious harms reported with long-term use in observational and epidemiologic studies.[1] However, there remains an urgent need to appropriately and effectively manage pain while mitigating risk for potential misuse.

While illicit opioids (such as heroin and non-prescription fentanyl) have been implicated in increased death rates over time, the American Medical Association has reported that nearly half of all heroin users started with an addiction to a prescription opioid medication before switching to heroin due to ease of access.[2] Thus, there is a need for safer options to treat chronic pain. This newsletter will describe available evidence for buprenorphine for chronic pain to evaluate whether it is a safer alternative compared to other opioids.

Buprenorphine for Pain

Unlike other opioids, buprenorphine is a partial mu opioid agonist and a schedule III-controlled substance. Buprenorphine may have potential advantages compared to full or pure opioid agonists (e.g., morphine, fentanyl, oxycodone, hydrocodone, oxymorphone, methadone) or opioids with a mixed mechanism (e.g., tramadol or tapentadol). However, advantages cited in the literature (such as decreased respiratory depression, improved safety in elderly and renal disease, increased efficacy for neuropathic pain, less development of tolerance, and lack of hyperanalgesic effect), are generally based on assumptions about mechanism and pharmacology, and not based on well-designed prospective studies.[3] Additionally, publications which cite these advantages often note manufacturer funding.[3]

Buprenorphine is available in several formulations and doses. Formulations for treatment of OUD usually provide substantially higher doses of buprenorphine than formulations with indications for pain. Formulations that are indicated for treatment of severe pain include buccal films (BELBUCA®; 75-900 mcg/film), transdermal patches (BUTRANS®; 5-20 mcg/hour), and intramuscular or intravenous injections (BUPRENEX®; 300 mcg/mL). Buprenorphine formulations that are FDA-approved for treatment of opioid use disorder (OUD) include subcutaneous injections (e.g., SUBLOCADE®; 200 mg/mL) and sublingual films or tablets with or without naloxone (SUBOXONE®, ZUBSOLV®, SUBUTEX®; 0.7-8 mg/unit). While prescription of buprenorphine for OUD has historically been regulated under the federal DATA-waiver program, recent changes to the program have removed these regulatory requirements.[4] A waiver has never been required to prescribe buprenorphine for pain.

Efficacy of Buprenorphine for Chronic Pain

A systematic review from Agency for Healthcare Research and Quality (AHRQ) published in 2020 and updated in March 2022 evaluated evidence of opioids used to manage chronic pain.[1] The review specifically evaluated evidence of effectiveness based on type of opioid (pure agonist, partial agonist, or opioids with a mixed mechanism). For pain relief, there was moderate quality evidence of no difference in efficacy outcomes between buprenorphine and pure opioid agonists. Direct comparative evidence was limited to 3 randomized controlled trials (RCTs) comparing buprenorphine to tramadol and fentanyl. Placebo-controlled data were also available from 38 trials of pure opioid agonists, 8 trials of buprenorphine (5 evaluated transdermal patch and 2 evaluated buccal formulation), and 16 trials evaluated mixed opioids (tramadol or tapentadol).[1] Subgroup analyses of the placebo-controlled data showed no correlation between type of opioid (full, partial, or mixed) and effects on pain, function, short form (SF)-36 health status, sleep or depression.

Safety of Buprenorphine for Chronic Pain

Short-term studies (with follow-up over 16 months) comparing buprenorphine directly to full opioid agonists found similar harms in people with chronic pain (moderate quality evidence).[1] Compared to placebo, opioids of all types were associated with increased rates of adverse events.[1] Adverse events which were more common than placebo in short-term trials are listed in **Table 1**. Pruritus was the only adverse event which demonstrated a statistical difference based on type of opioid with higher risk associated with pure agonists and mixed mechanism opioids compared to buprenorphine.[1]

Table 1. Adverse event rates associated with opioids in short-term RCTs compared to placebo

Adverse Event (AE)	RR (95% CI)	NNH
Discontinuation for AEs	2.25 (1.86 to 2.73)	10
Somnolence	2.97 (2.44 to 3.66)	11
Nausea	2.46 (2.17 to 2.80)	7
Vomiting	3.57 (2.98 to 4.34)	14
Constipation	3.38 (2.96 to 3.92)	7
Dizziness	2.66 (2.37 to 2.99)	12
Pruritus	3.51 (2.47 to 5.16)	14

*Number needed to harm (NNH) = the number of people who need to be treated in order for one person to experience an adverse event

Because RCTs are not powered or designed to evaluate long-term harms, evidence on serious long-term adverse events is based primarily on observational studies.[1] Most long-term observational studies in patients with chronic pain have not included buprenorphine, but have shown an increased risk of adverse events with opioids compared to matched populations without opioid use. Low quality evidence shows that compared to matched cohorts, opioids are associated with increased risk for:[1]

- abuse, dependence, overdose, addiction
- myocardial infarction, fracture, falls
- endocrine dysfunction (erectile dysfunction, female reproductive dysfunction, androgen deficiency)
- mortality

Risk of overdose increases when opioids are combined with a benzodiazepine (especially with short-term use) or gabapentinoid (particularly at higher gabapentinoid doses).[1] Risk for adverse events also increases with higher opioid doses compared to lower doses, although there is no dose threshold for which there is no risk.[1] In some studies, risk for falls and fractures was highest at the start of therapy and decreased with longer-term use.[1]

Overall, there is insufficient data evaluating long-term safety of buprenorphine for chronic pain and comparing buprenorphine to other opioids for long-term, serious adverse events. One observational study (n=9,500) reported data on buprenorphine compared to other opioids. An increased risk of hip fracture was identified for patients prescribed opioids (age-adjusted incidence 3.47 vs. 1.94 per 100 person-years, hazard ratio [HR] 1.96, 95% CI, 1.27 to 3.02).[1] Risk was not statistically significant for patients prescribed codeine or dihydrocodeine (HR 1.70, 95% CI, 0.89 to 3.26) but was statistically significant for patients prescribed buprenorphine (HR 1.98, 95% CI, 1.33 to 2.95) and other full opioid agonists (HR 2.72, 95% CI, 1.25 to 5.93) compared to no opioid use.[1] There is insufficient evidence to determine if buprenorphine has lower risk of abuse, misuse, or development of OUD compared to other opioids. Pharmacokinetic studies of buprenorphine have documented a plateau effect for respiratory depression, and this may theoretically decrease risk of overdose.[5,6] However, the real-world implications of this effect have not been confirmed in clinical studies. It is currently unknown whether buprenorphine has lower risk of respiratory depression or overdose compared to other opioids.

Guideline Recommendations

Guidelines from the Department of Defense and Department of Veterans Affairs (DOD/VA) and National Institute for Health and Care Excellence (NICE) continue to recommend against initiation of opioids (including buprenorphine) for chronic pain.[2,7,8] Updated guidelines on the use of opioids from the Centers for Disease Control (CDC) recommend initiation of opioids only when:[9]

- alternative therapies including nonpharmacologic and non-opioid pharmacologic therapies are maximized,
- clinician and patient have discussed realistic benefits and risks of treatment and established goals of therapy,
- potential benefits outweigh risks, and
- there is an established plan to reassess therapy and discontinue treatment if benefit is not established.

These recommendations are based on data that opioids generally provided a small improvement in pain and function compared to placebo, but were also associated with short-term harms with evidence of pain attenuation with longer-term use between 3-6 months. No difference in pain or function was found between opioids and non-steroidal anti-inflammatory drugs (NSAIDs) for multiple chronic conditions.[9]

For people who are already established on daily opioid therapy, guidelines recommend careful reassessment of risks and benefits including shared decision making for discontinuation of opioids or risk mitigation for continued therapy.[2,8-10] Withdrawal symptoms have been documented with abrupt discontinuation of opioids (including buprenorphine) during post-marketing studies. The 2022 DOD/VA guideline for the treatment of chronic pain includes a suggestion for use of buprenorphine instead of full agonist opioids for patients prescribed daily opioids for chronic pain (weak recommendation for therapy).[2] The systematic literature review supporting this recommendation found low quality evidence that buprenorphine was equally effective at controlling pain compared to other opioids and insufficient evidence evaluating safety of buprenorphine compared to other opioids. In the absence of any evidence, guideline authors note that the theoretical safety profile of buprenorphine based on the mechanism of action as a partial agonist and status as a schedule III substance may decrease long-term risks compared to full opioid agonists (which are classified as schedule II substances and have known overdose risks).[2] However, potential benefits should be weighed against the lack of evidence for improved safety outcomes compared to other opioids.

Switching to Buprenorphine

Switching between opioid products typically requires careful monitoring for withdrawal symptoms, breakthrough pain, respiratory depression, and overdose. Many protocols describing transition from other opioids to buprenorphine require patients to exhibit mild withdrawal symptoms before initiation of buprenorphine therapy with the goal of avoiding precipitated withdrawal. There are a wide variety of protocols used to switch patients, and uncertainty about buprenorphine dose conversion ratios, variable pharmacokinetics among formulations, and inter-patient variability in opioid potency make standardization of protocols difficult.[11,12] A 2021 systematic review evaluated feasibility, efficacy, and safety of transition to buprenorphine in patients prescribed long-term

opioids for chronic pain.[12] Overall, authors did not identify any studies that evaluated whether switching to buprenorphine impacts important long-term outcomes such as overdose, mortality, and development of OUD. No studies evaluated healthcare utilization, and follow-up periods were generally short (<6 months).[12] In the absence of OUD, it is unclear whether transitioning to buprenorphine is safer than maintenance of current opioid therapy for people with chronic pain. However, many people have chronic pain and concurrent OUD, and switching to sublingual buprenorphine to manage OUD remains one of the first-line treatment option for this population.

Conclusion

Available data indicate that buprenorphine has similar rates of adverse events when compared to other opioids for short-term treatment of chronic pain (moderate quality evidence).[2,9] There is insufficient evidence to determine if buprenorphine is associated with lower risk for long-term safety outcomes of respiratory depression, overdose, and development of OUD compared to other opioids. All formulations of buprenorphine have warnings for abuse, misuse, addiction, respiratory depression, overdose, neonatal opioid withdrawal syndrome, withdrawal symptoms, adrenal insufficiency, and hepatic adverse events in the FDA labeling.

Most chronic pain guidelines do not recommend buprenorphine over other opioids. Instead, alternative therapies should be maximized before initiation of any opioid. Guidelines recommend that patients and providers discuss realistic expectations before initiating opioid treatment. Studies show that opioids generally provide only small improvements in pain and function compared to placebo and they can be associated with significant harms. Before prescribing or increasing the dose of an opioid, providers and patients should have a specific plan in place to assess therapy within 1 to 4 weeks and discontinue the opioid if benefit is not established. In patients already established on opioid treatment, providers and patients should work together to reassess risks and benefits including shared decision making for discontinuation of opioids or risk mitigation for continued therapy. Switching to buprenorphine is an option for providers to consider, but it is currently unknown whether switching therapy will decrease long-term risks of opioid therapy.

Pain Resources for Providers

- Tools for screening, tapering & risk benefit evaluation
- Health and Human Services Guidelines for appropriate dosage reduction
- Pain Education Toolkit for Patients
- Medication Toolkit for Patients

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