## **REVIEW ARTICLE**

# Opioid Use in the Elderly: A Narrative Review of Buprenorphine Use for Chronic Noncancer Pain

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## **ABSTRACT**

Chronic noncancer pain presents a significant challenge worldwide, particularly among the elderly population, where concerns of polypharmacy and additional morbidity and mortality risks exist. When nonopioid treatment approaches are deemed ineffective, the decision to use opioids requires a careful risk-benefit analysis. Our objective was to review recent literature in the use of opioid analgesics and opioid alternatives to analyze treatment protocol recommendations when prescribing pain medication for elderly patients. Databases such as PubMed, CDC, Embase, JAMA, and SCOPUS were used as primary sources for literature. Following a review of the literature, benefits and consequences of opioid use in the elderly were reviewed. Opioid use in the elderly continues to be a debated topic due to the systemic effects of the medication, risk of polypharmacy, and risk of opioid dependency. However, the use of buprenorphine may help with minimizing risk and maximizing relief of pain in the elderly, positioning it as a strong contender if not a replacement for first-line treatment for chronic noncancer pain in the elderly. Future research should focus on further analysis of drug combinations to provide optimal pain relief for elderly care with the goals of improving quality of life without risking patient health.

# INTRODUCTION

Chronic pain is a pervasive and debilitating health condition that affects millions of people worldwide, significantly impacting their quality of life and well-being. Defined as persistent or recurrent pain that lasts for more than 3 months, chronic pain represents a multifaceted challenge, particularly in the elderly population.<sup>1</sup> With the aging of societies globally, the prevalence of chronic pain among older adults has surged, posing considerable burdens on healthcare systems and underscoring the urgency for effective management strategies tailored to this unique demographic. The utilization of opioids as a primary pharmacologic approach to managing chronic pain in the elderly has seen a notable rise, yet it remains a topic of extensive debate and concern.<sup>2</sup>

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## Prevalence and Epidemiology

Various studies have reported differing rates of chronic pain in older adults, highlighting the complexity of accurately assessing its prevalence. Nevertheless, a consistent pattern emerges, indicating that the prevalence of chronic pain increases with age, reaching its peak in the oldest age groups. As older adults often experience age-related conditions like osteoarthritis, arthritis, fibromyalgia, musculoskeletal disorders, neuropathy, and neurodegenerative diseases,<sup>3</sup> the likelihood of experiencing chronic pain is significantly elevated. The presence of comorbidities and the interaction of chronic pain with other health issues further exacerbate the complexity of pain management in the elderly.<sup>4</sup>

Chronic noncancer pain has far-reaching health implications. Chronic pain in the elderly is associated with depression, Alzheimer's and other types of dementia, increased suicide risk, and substance use and misuse.<sup>5</sup> Chronic pain has been shown to have a direct effect on increasing risk of falls and an indirect effect on mediating disordered sleep.<sup>6</sup> The existing burden of increasing morbidity associated with increasing age is compounded by the presence of chronic pain. Likewise, the increasing use of opioids in elderly patients has raised concerns about their safety, efficacy, and potential for misuse and addiction.<sup>7</sup>

# Challenges With Opioid Use in the Elderly

The use of opioids in elderly patients presents unique challenges and risks that demand cautious consideration. Advanced age is associated with physiologic changes that affect drug metabolism and clearance, leading to an increased susceptibility to adverse drug reactions and drug interactions. As a result, elderly patients are at higher risk of experiencing opioid-related side effects such as sedation, respiratory depression, constipation, and cognitive impairment. Such adverse events can have severe consequences for the elderly, impacting their functional independence and overall health. Furthermore, the potential for opioid misuse and the development of tolerance pose significant concerns in this population. The growing opioid epidemic has shed light on the need for judicious opioid prescribing to mitigate the risks of addiction and abuse, particularly in vulnerable populations like the elderly.<sup>2</sup> Ultimately, by updating and refining current management practices, we can pave the way for improved pain management strategies, ultimately enhancing the guality of life for elderly individuals living with chronic pain.8

## **METHODS**

By critically examining the prevalence, epidemiology, and medications used in managing chronic pain, with a particular focus on opioids, this paper seeks to contribute to a deeper understanding of the complexities surrounding pain management in the elderly. Furthermore, it aims to highlight the potential risks associated with opioid therapy, as well as the need for evidence-based tailored approaches that prioritize the safety and well-being of older adults. To accomplish this, a narrative review was employed. Databases such as PubMed, Cochrane, Google Scholar, and others were used for primary literature.

# RESULTS

#### Long-Acting Opioids

Long-acting opioids, also referred to as extended-release opioids, are formulated to provide a sustained analgesic effect over an extended period, reducing the need for frequent dosing. These opioids are typically prescribed for chronic pain management, as they offer more consistent pain relief and can improve patient compliance with treatment regimens. Common examples of long-acting opioids include controlled-release morphine, methadone, oxycodone, and fentanyl patches.

While long-acting opioids may be advantageous for managing chronic pain, their use in elderly patients demands careful consideration. Due to age-related changes in drug metabolism and sensitivity, older adults may experience prolonged drug effects, heightening the risk of side effects and adverse events. Furthermore, long-acting opioids may have a delayed onset of action, making it essential to monitor patients closely during initial treatment and dosage adjustments.<sup>10</sup>

## **Buprenorphine Overview**

Buprenorphine, a unique opioid, has gained recognition for its role in opioid agonist therapy and pain management. Unlike traditional opioids, buprenorphine is a partial agonist at opioid receptors, meaning it has a ceiling effect on respiratory depression and a lower potential for overdose compared to full agonists like morphine or oxycodone. Buprenorphine is used in the treatment of opioid use disorder (OUD) and has been found effective in reducing opioid cravings and withdrawal symptoms.

Additionally, buprenorphine is utilized for pain management, especially in situations where other opioids may not be suitable due to the risk of adverse effects or drug interactions. The unique pharmacologic profile of buprenorphine may make it a safer alternative for elderly patients with chronic pain, particularly those with a history of substance abuse or a higher risk of opioid-related adverse events.

This review aims to provide an in-depth update and narrative expansion upon the previous systematic review conducted by Guerriero<sup>11</sup> on the use of opioids in the elderly with chronic pain, incorporating newer clinical data released since their review in 2017, to gain further insight into the potential benefits and risks of this treatment modality.

## **General Adverse Side Effect Summary**

The pharmacologic class that are opioids have their benefits but are not without their own unique challenges. While they are utilized for their ability to produce analgesia, there are also many side effects associated with opioid usage. Due to the relatively high concentration of opioid receptors in the enteric nervous system, opioid usage commonly causes gastrointestinal (GI) symptoms, such as nausea, vomiting, and constipation. Nausea and vomiting also occur through stimulation of the brain's chemoreceptor activating zone, sometimes called the brain's vomiting center. Fatigue and sedation are potentially concerning adverse side effects in the elderly that can increase the risk of falls. The sedation effect occurs primarily through acetylcholine inhibition in the medial pontine reticular formation, among other mechanisms.<sup>12</sup>

Dizziness is another potentially dangerous adverse side effect that can contribute to fall risk and increases morbidity associated with opioid use. Dizziness and nausea occur by altering neuronal excitability within the vestibular apparatus.<sup>13</sup>

Other common adverse side effects include sweating, pruritus, and hot flashes. These and the above-mentioned side effects have all been shown to be significantly associated with medium- and long-term opioid use.<sup>14</sup> A 2023 Cochrane review found no studies that met inclusion criteria in evaluating the efficacy and safety of high-dose opioids for chronic noncancer pain.<sup>15</sup>

Additional common adverse side effects include opioidinduced hyperalgesia from toxic metabolites, urinary retention from anticholinergic effects, dysphoria or euphoria, impaired host immunity,<sup>16</sup> and, most notably, respiratory depression, which is the target for naloxone in opioid overdoses. All adverse side effects that are not life-threatening should be managed by either: dosage reduction, symptomatic treatment, rotating medication choice, and/or changing administration method.<sup>17</sup>

Regarding delirium, in an analysis of critically ill patients with an average age of 60.9 years, use of any opiate was associated with a significant risk of delirium the next day if that patient was awake.<sup>18</sup> Whereas an observational study of emergency department (ED) patients ≥65 years found that pain was significantly associated with development of delirium and not opiate consumption.<sup>19</sup> These conflicting data bring into question the causes of delirium, suggesting pain and opioid usage may both contribute.

A lesser-known consequence of chronic opioid use is opioidrelated endocrinopathy, which can manifest as OPIAD (opiateinduced androgen deficiency).<sup>20</sup> Morphine use can inhibit the secretion of gonadotropin-releasing hormone at the level of the hypothalamus and can induce peripheral androgen catabolism.<sup>21</sup> Chronic opioid use is associated with a higher risk of diagnosis of and treatment for hypogonadism compared to short-term use.<sup>22</sup> Additionally, there is an apparent dosedependent relationship between higher opioid doses and increased odds of developing OPIAD.<sup>23</sup> This is significant in light of the knowledge that the aging male is likely to have decreased levels of testosterone over his lifetime.<sup>24</sup>

Opioid withdrawal syndrome is of particular concern in chronic pain patients and the elderly. An observational study found that individuals who are older, have more severe substance use, are female, have chronic pain, and have more severe withdrawal symptoms at intake and across different timepoints.<sup>25</sup> Onset of withdrawal symptoms depends on the duration of effect of the opioid used. Withdrawal from opiates is subjectively severe but can cause death, primarily by way of dehydration or hypernatremia.<sup>26</sup>

While prevalence is not well understood, sensorineural hearing loss can occur with any opioid. Much of the data are scant and exist as case reports. A 20-year retrospective study in New Jersey found that most cases occurred with heroin. There were also multiple cases that occurred with hydrocodone, oxycodone, tramadol, fentanyl, and methadone.<sup>27</sup>

It is also worth noting that OUD is on the rise in the elderly population. OUD is associated with comorbid major depressive disorder, anxiety, and posttraumatic stress disorder (PTSD) in the elderly.<sup>28</sup>

# **General Opioid Usage**

For chronic pain patients, it is currently recommended that patients be trialed first on short-acting opioids while longacting opioids only be reserved for severe and intractable pain or once initial interventions have failed. A low dose is considered up to 40 MME (milligram morphine equivalents), a medium dose ranges from 41 to 90 MME, and a high dose is considered >90 MME per day.<sup>29</sup> CDC guidelines agree with these numbers. In 2009, the American Geriatrics Society (AGS) formulated treatment guidelines for persistent pain in the elderly that does not rank the utility of specific opioids.<sup>30</sup> In 2017, the American Society of Interventional Pain Physicians (ASIPP) constructed recommendations for specific opioid usage in chronic noncancer pain, although it is worth noting that these guidelines are for the public and not specifically for elderly individuals.

Chronic kidney disease (CKD) is a common concern in the elderly. Transdermal buprenorphine and fentanyl do not require dose adjustments in nondialysis CKD patients. Oral immediate-release (IR) hydromorphone seems to be more tolerable than morphine in nondialysis CKD patients. Tramadol, codeine, and morphine are cautioned against in nondialysis CKD patients.<sup>31</sup>

With regard to liver failure of any etiology, it is recommended that the lowest starting dose be used, or less, if opioids are deemed as the most appropriate therapy for analgesia. Generally, IR formulations with lengthy dosing intervals are preferable over alternatives in this population. A high degree of caution should be used when prescribing opioids in patients with liver failure, and frequent monitoring for side effects and further decompensation with appropriate dosage adjustment is necessary.<sup>32,33</sup>

Lastly, it is worth noting, there seems to be little clinical benefit in alleviating pain with usage of high-dose opioid regimens, though it is understudied.<sup>34</sup> Additionally, the pharmacokinetics of different opioids and how they interact with an individual's unique pharmacogenetics is not well understood but plays a significant role in how different opioids affect people differently.

#### Buprenorphine

Buprenorphine has promising benefits in treating pain and limiting adverse side effects, though it is considered thirdline treatment for severe pain by the ASIPP. Buprenorphine is most often given in the sublingual and transdermal form for chronic pain. Sublingual administration is preferred for its superior bioavailability. No dose reduction is required in renal impairment as the drug is metabolized extensively by the liver and is primarily excreted in the biliary system and in the feces. While hepatic impairment will prolong the halflife, the other metabolites have little activity.<sup>35</sup> Safety studies of buprenorphine use in patients with hepatic impairment are still lacking. Buprenorphine has also demonstrated clinically insignificant effects on the QTc interval when used at usual doses (0.006-0.03 mg/kg), but this may not be true at high or atypical doses, suggesting a safe cardiac profile.<sup>36</sup> A thorough overview of the unique pharmacologic profile was performed by Gudin and Fudin.<sup>37</sup>

According to 2022 CDC guidelines, buprenorphine is not considered in calculating daily MME. This is because it is primarily viewed as a treatment for opioid dependence; meanwhile, its unique partial agonist profile confers a ceiling on its potency and limits the extent to which respiratory depression can occur.<sup>29</sup> A retrospective, postmortem, toxicology study of overdose deaths in Rhode Island between 2016 and 2018 concluded that the small percentage of individuals who were found to have buprenorphine or its metabolites upon toxicology testing were not recently exposed and thus buprenorphine did not likely contribute to that decedent's death.<sup>38</sup> This shows promise in the context of the opioid epidemic and rising rate of overdose deaths.

Buprenorphine has exhibited benefits in various situations. In a single-blinded study of 60 elderly patients with severe pain from osteoarthritis, there was significant relief when treated with transdermal buprenorphine, while the lower doses of 8.5 and 17.5 mcg/h resulted in fewer side effects than a starting dose of 35 mcg/h. Seven of the eight patients who did not complete the study were in the high-dose buprenorphine group, and the most reported side effect was confusion.39 This suggests that starting with a low dose and titrating up as needed should be safe and efficacious in the elderly where delirium is highly concerning. Low-dose transdermal buprenorphine has been shown to cause no central nervous system side effects when combined with low-dose oxycodone in elderly patients. Transdermal buprenorphine has also shown lower rates of constipation.40 A 2021 article described the effectiveness of buprenorphine in managing musculoskeletal pain and promising effects in managing diabetic neuropathy.<sup>41</sup>

Only one Cochrane review in 2015 has been performed evaluating buprenorphine in the use of noncancer patients and only included one article in the final analysis.<sup>42</sup> This highlights the paucity of high-quality evidence surrounding buprenorphine for chronic noncancer pain. A systematic review of sublingual buprenorphine in 2014 resulted in qualitative analysis due to wide-spread methodologic weakness of the studies. This team cited literature that buprenorphine shows safety in the elderly and the renally impaired, shows less immunosuppression, exhibits an antidepressant effect, and shows less development of tolerance and less hyperalgesia while on sublingual buprenorphine.<sup>43</sup>

Buprenorphine is used in a tapering fashion for management of opioid withdrawal syndrome. Since it is a partial agonist but is highly potent, it can precipitate withdrawals if an individual has been using opiates regularly.<sup>44</sup> In treating OUD, it is advised to wait until withdrawal symptoms emerge to administer buprenorphine. This also raises concern if cross-tapering from any other opioid with agonist action to buprenorphine. Buprenorphine formulated with naloxone (Subutex, Suboxone) is FDA approved for treating OUD. It is occasionally used off label for chronic pain management in high-risk OUD patients.

Transitioning from other opioids to buprenorphine has been investigated. A retrospective study to evaluate transitioning from high-dose therapy to buccal buprenorphine found nearly 90% of patients were stabilized on buccal buprenorphine. A higher average dose was utilized among those who were directly converted to buprenorphine compared to those who were titrated to a lower MME before switching. These results favor an aggressive titration schedule that results in lower MMEs than manufacturer recommendations (reducing to  $\leq$ 30 MMEs). There were also patients safely using other full opioid agonists for breakthrough pain while still using the buccal buprenorphine without reports of withdrawal.<sup>45</sup>

## DISCUSSION

As with any study, there were limitations inherent to this present design. As this was not a systematic review, this is not an exhaustive review of the literature. We also chose to exclude animal studies and as such could have excluded valuable data. This review did not include all opioids currently on the market.

In the process of this review, there were potential areas for future research uncovered. There is some evidence that intraoperative methadone may be superior to morphine for pain relief, but further controlled trials are needed.<sup>46</sup> There is further research needed regarding the safe rotation to and from methadone. There is also a lack of high-quality controlled studies evaluating and describing high-dose opioid use and its efficacy. There is a need for controlled studies to examine the use of buprenorphine for the management of chronic pain of different etiologies. There is also further work needed in formulating guidelines for opioid prescribing in elderly patients with CKD or impaired hepatic function.

## CONCLUSION

Pain management in the elderly is complicated by the presence of comorbid conditions that increase mortality and provide contraindications for certain treatment regimes. In the elderly, who already have a high burden of disease, with chronic pain, the investigation of safe and effective pain management methods for aging and associated disease states is crucial for the effective and judicious use of opioid pain medications. In our review of the literature, we found evidence that while there are risks associated with its use, buprenorphine appears no more hazardous and is likely safer and more efficacious than other opioids for chronic noncancer pain management in the elderly. There is a sincere lack of high-quality randomized controlled trials investigating long-term use of buprenorphine for chronic pain management that likely accounts for its relatively lower standing in clinical guidelines. We urge clinicians and medical societies alike to consider buprenorphine as a potential first-line agent in opioid-centered chronic pain management.

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