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REVIEW

Expanding Horizons of Buprenorphine: A Comprehensive Narrative Review of Its Pharmacological Properties and Clinical Applications in Chronic Pain

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ABSTRACT

Buprenorphine has gained significant attention for its unique pharmacological properties, making it a valuable tool in chronic pain management. Unlike traditional opioids, buprenorphine's partial and biased agonist actions at the μ-opioid receptor provide potent analgesia while minimizing risks such as respiratory depression, tolerance, and dependence. Its favorable pharmacokinetic profile provides the potential for expanding its clinical use in different patient populations. A literature search was conducted in PubMed, Web of Science, and Google Scholar to identify peer-reviewed studies on recent developments in the pharmacological features and new clinical applications of buprenorphine, including original research, reviews, and consensus statements. This comprehensive review explores the expanding clinical applications of buprenorphine, emphasizing its role in managing chronic pain in elderly patients, individuals with cardiac conditions, and those with renal impairments. Emerging evidence highlights its utility in addressing chronic pain in younger adults and its potential in mitigating side effects associated with aromatase inhibitor therapy in patients with breast cancer. Additionally, buprenorphine's lower endocrine side-effect profile and antidepressant properties open new therapeutic avenues for pain-associated depression. With its unique pharmacodynamics, transdermal formulations for sustained drug release, and reduced adverse effects, buprenorphine represents a promising option for tailored, multimodal pain management strategies, especially in populations with complex medical needs. Further studies are warranted to confirm its broad therapeutic potential.

Keywords: Buprenorphine; Chronic pain management; Buprenorphine transdermal formulation

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Key Summary Points

Buprenorphine is a partial agonist and a biased at μ-opioid receptors, and provides potent analgesia with reduced risks of tolerance, dependence, and side effects compared to traditional opioids.

Transdermal buprenorphine offers a non-invasive method for controlled drug delivery, reducing the risk of side effects.

Transdermal buprenorphine is particularly effective in chronic pain management, especially for elderly patients or those with renal and hepatic impairments.

Buprenorphine is effective for managing chronic pain in specific populations, including young adults, patients with cardiac conditions, women undergoing aromatase inhibitor therapy, and younger adults for whom it may help prevent hormone imbalance.

INTRODUCTION

Opioids are a class of analgesics employed in multimodal therapy for pain management [1–3]. These drugs are generally used for treating conditions such as chronic [4, 5] or cancer-related pain [6, 7]. However, there are three main limitations associated with the use of these drugs for chronic therapy: (1) side effects such as nausea, constipation, itching, dizziness and respiratory depression which may lead to treatment discontinuation [8, 9]; (2) the development of hyperalgesia and tolerance, which decreases the treatment's efficacy over time [10]; (2) the risk of developing opioid dependence, which creates social, economic, and public issues all over the world [11].

Buprenorphine is an opioid that provides a potent analgesia with reduced side effects that are commonly associated with these therapies [8, 12]. It is a synthetic molecule derived from thebaine, and its unique pharmacokinetic and pharmacodynamic profile makes it particularly advantageous for treating chronic pain [8, 13]. Buprenorphine has been widely used in clinical practice since the early 1980s [14]. However, this molecule holds potential for further applications.

This review aims to provide an updated overview of buprenorphine's pharmacological profile and the state of the art concerning its use in clinical practice. We aim to first describe the molecular mechanism of opioid analgesia, focusing on buprenorphine's partial agonist and biased agonism properties. Then, we discuss buprenorphine pharmacokinetics, with a focus on the transdermal formulation, and its interaction with P-glycoprotein. Finally, we summarize the clinical use of buprenorphine, highlighting its advantages in chronic pain management, particularly among specific populations, with particular attention to new perspectives on its clinical use—efficacy and safety in younger adults, role in reducing side effects associated with aromatase inhibitors in breast cancer therapy, and the reduction of endocrine side effects associated with opioid therapy.

METHODS

This study is a comprehensive descriptive thematic analysis to examine recent findings on the pharmacological properties and emerging clinical applications of buprenorphine. It is based on previously conducted studies and does not include any new research involving human participants or animals by the authors.

Literature Search Strategy

Between September 20, 2024 and October 10, 2024, a search was conducted using PubMed, Web of Science, and Google Scholar. To be eligible for inclusion, studies had to be peer-reviewed, empirical, or prospective investigations that addressed recent developments in the pharmacological features and new clinical uses of buprenorphine. Accepted formats included original research articles, reviews, and consensus statements, for which full-text access was required.

Studies were excluded if they did not align with the designated topic, lacked sufficient clarity in reporting objectives and conclusions, or were unavailable in full text. These inclusion and exclusion criteria were applied to ensure the selection of literature aligned with the study's objectives and focus. No specific publication date limits were set for the search, but older studies, published earlier than the last 5 years, were carefully assessed for relevance and excluded if their findings were outdated or no longer aligned with current pharmacological advancements and clinical applications of buprenorphine.

To ensure a comprehensive literature review on "Buprenorphine Pharmacology and Clinical Uses," keywords were chosen to capture the core concepts of the investigation, with a particular focus on "Buprenorphine pharmacology", "Buprenorphine in chronic pain treatment" and related terms. The initial search phrase was broadened to include synonymous expressions, variant terms, and alternative formulations to encompass all relevant material. References within identified articles and reviews were examined to identify additional relevant sources. All retrieved results were then manually screened to determine their relevance according to the previously established criteria.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic

Opioid receptors, μ, δ, κ, and the opioid-like receptor-1 (ORL-1) are part of the endogenous opioid system [2, 15]. The activation of these membrane proteins in the spinal cord inhibits the ascending pain pathways in the central nervous system via inhibitory G proteins (Gαi and Gαo) activation, reducing pain transmission [8, 15]. The modulation of ion channels is one of the most conserved pathways through which opioid receptors alter neuronal function, both at presynaptic and postsynaptic sites (Fig. 1). μ-opioid receptors, expressed at the spinal synapse between nociceptors and spinothalamic neurons, play a central role in pain control. The vast majority of opioid drugs used in clinical practice are agonists of these receptors [15].

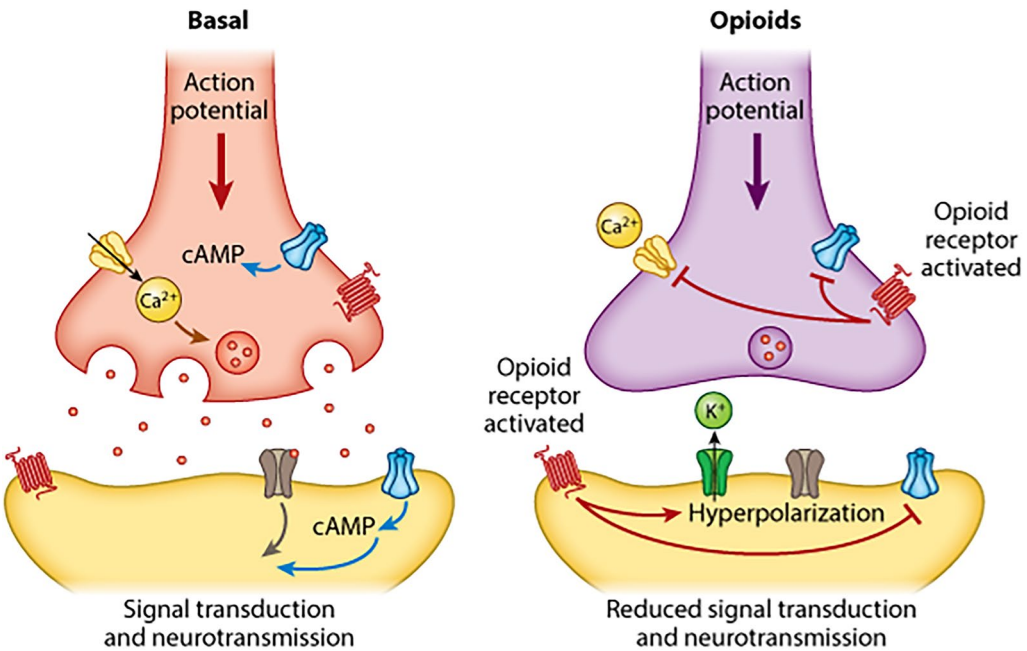

Fig. 1 Opioid mechanism of action involves both pre-synaptically and post-synaptically effects. Adapted from Ref. [2]. Ca^{2+} calcium ion, *cAMP* cyclic adenosine monophosphate, K^{+} potassium ion

At the presynaptic level, μ-opioid receptors inhibit N-type voltage-gated calcium channels [2]. Since the release of neurotransmitters is a calcium-dependent process, receptor stimulation causes a blockade of synaptic transmission and a reduction of pain [2]. At the postsynaptic level, receptor activation facilitates potassium efflux from the cell and the hyperpolarization of the neuronal membrane. As a result, the neuron becomes less responsive, preventing action potential generation [1, 16]. μ-opioid receptors can also inhibit the adenylyl cyclase, thus decreasing cAMP production, with additional effects on neurotransmission [2].

Buprenorphine has a peculiar pharmacodynamics as it interacts with all the receptors of the endogenous opioid system [8, 12, 13]. The molecule acts as a partial agonist at μ receptors, antagonist at δ receptors, inverse agonist at κ receptors, and as a partial agonist with low affinity to the ORL-1 [13]. Interactions with δ, and κ receptors may limit the adverse effects such as constipation, respiratory depression, anxiety, and addiction, which are the typical side effects of prolonged opioid treatment [8, 14]. Buprenorphine is a potent partial agonist at the μ-opioid receptor, characterized by high binding affinity, low intrinsic activity, and slow dissociation constant [14]. These features allow for the provision of potent analgesia at low doses [17]. Although buprenorphine exhibits lower intrinsic activity compared to full μ-opioid agonists, it activates the signaling pathway required for getting enough analgesia in many clinical settings [12]. Buprenorphine demonstrates both tonic- and use-dependent sodium (Na^+) channel-blocking activity, resembling the effects of local anesthetics [18]. Moreover, its slow dissociation constant prolongs this effect and enables the drug to displace other opioids from the μ receptor, a property usually employed to treat opioid dependence [8]. In vivo studies indicate that buprenorphine also interacts with the arylepoxamide receptor (AEAr), a 6-transmembrane protein derived from the μ-opioid receptor gene (Oprm1) that may contribute to its analgesic effects [12]. Receptor/ligand definitions are reported in Table 1 [12].

An important clinical advantage of buprenorphine over other opioids is its lower risk of inducing side effects such as respiratory depression, tolerance, and constipation, typically associated with prolonged opioid treatment [12, 14]. These events are attributed to the concomitant activation of G protein and β-arrestin pathways via the μ-opioid receptors by full agonists [2, 12, 13, 19]. Buprenorphine, a G protein-biased agonist at the μ receptor [14, 20], preferentially stabilizes the receptor conformation associated with G protein signaling. This reduces β-arrestin pathway activation thereby minimizing adverse effects [21–23], as confirmed by recent in vivo and in vitro findings [24, 25].

β-arrestin family plays a crucial role also in receptor downregulation and internalization, both associated with the development of opioid tolerance [15, 17]. Under physiological conditions, internalization maintains the appropriate number of receptors on the cell surface [2]. However, during prolonged opioid use, increased internalization reduces the number of available receptors, contributing to opioid tolerance [11,

Table 1 Receptor/ligand definitions adapted from reference [12]

Pharmacological terms	Definition
Potency	The quantity of a drug required to achieve a specific level of response intensity
Affinity	The ability of a molecule to bind to its receptor, expressed as a binding constant (K_i)
Intrinsic activity	The ability of a molecule to activate the receptor and initiate downstream signaling
Partial agonist	A compound with lower intrinsic activity compared to a full agonist
Dissociation constant	The propensity of a drug to separate reversibly from its receptor

12]. Buprenorphine's low activation of β-arrestin pathway may be responsible for its lower risk of tolerance and cross-tolerance compared to full μ agonist [8, 13, 26, 27].

Respiratory depression is a major reason for discontinuation of opioid treatment [28–30]. Recent animal studies are challenging the theory that attributes this effect to β-arrestin activation [31, 32]. Moreover, emerging evidence suggests that μ-opioid receptor modulation of GIRK channel can inhibit rhythmic breathing and may be responsible for these adverse effects [33]. As a partial agonist, buprenorphine has a ceiling effect also on respiratory depression [8, 12], with a reduced risk of respiratory depression compared to other opioids [12, 34, 35]. Moreover, a placebo-controlled crossover study in healthy volunteers and opioid-tolerant patients suggests that sustained high concentrations of buprenorphine may reduce fentanyl-induced respiratory depression, making it potentially useful in treating fentanyl overdoses [36].

Pharmacokinetics

Buprenorphine's unique pharmacokinetics provide a good level of analgesia, reducing the risk of common side effects associated with prolonged use of full μ agonist opioids [37].

Intravenous administration of buprenorphine achieves 100% bioavailability [38], while oral administration results in 46–51% [39], sublingual administration yields 28–51% [40, 41], and transdermal administration offers approximately 15% [13].

The low oral absorption of the drug is attributed to the first-pass metabolism [42, 43]. The molecule has a high volume of distribution and penetrates all tissues, including the central nervous system [14]. The drug is approximately 96% bound to α and β globulins in the plasma, which reduces the amount of free drug available to interact with receptors thereby extending its duration of action [42, 44]. Buprenorphine can be especially beneficial for elderly patients as globulin levels are generally less affected by age [42, 45].

Buprenorphine formulations include transdermal patches, which offer several. Transdermal delivery systems are non-invasive and provide the drug's controlled release, ensuring constant and predictable serum drug levels for a prolonged period with a single dose [46]. These formulations allow for a steady state to be achieved upon first application, while plasma concentrations remain relatively constant over the following 7 days without peaks [37, 47]. As a result, the area under the curve (AUC) [48], increases in a dose-proportional manner [47], providing several advantages in terms of pharmacokinetics, dose adjustment, and safety.

The drug is mainly metabolized into the liver by CyP3A4, which mediates *N*-dealkylation to obtain norbuprenorphine [49, 50]. In vitro studies show that this metabolite has a high affinity for all four opioid receptors, and preclinical studies confirm its low analgesic effect [51, 52]. Buprenorphine and norbuprenorphine are further metabolized by UDP glucuronosyl transferase to obtain buprenorphine-3-glucuronide and norbuprenorphine-3-glucuronide, respectively [43, 53]. Preclinical evidence suggests that buprenorphine-3-glucuronide induces low-potency analgesia, whereas norbuprenorphine-3-glucuronide has sedative effects [53].

Buprenorphine and its metabolites are excreted mainly via the biliary system, and only a small fraction (10–30%) is eliminated in urine and feces [42, 54, 55], making buprenorphine use advantageous for patients with renal impairment [14, 37].

Buprenorphine and its metabolite norbuprenorphine inhibit P-glycoprotein [56]. This membrane efflux transporter plays a critical role in removing drugs and toxins from cells [57, 58]. At the blood–brain barrier, P-glycoprotein limits the entry of drugs into the central nervous system (CNS) [57]. Chronic exposure to opioids can lead to overexpression of this protein in different brain regions, resulting in the enhanced extrusion of these drugs from the CNS and contributing to opioid tolerance [59–61]. This effect is not seen with buprenorphine, as P-glycoprotein inhibition ensures an increased accumulation of the drug in the CNS, potentially enhancing its therapeutic effects [56].

CLINICAL USE OF BUPRENORPHINE

Chronic Pain Management

Chronic pain affects more than 30% of people worldwide and is the outcome of various biological, psychological, and social factors, including CNS alterations, distress, and depression [20, 62–68]. This condition is marked by heightened sensitivity of the nervous system and is commonly managed with CNS depressants such as opioids [69]. Additionally, psychological factors significantly influence its development and persistence, as highlighted by the Fear-Avoidance Model [70]. Emotional and behavioral responses to pain, such as fear and avoidance, contributing to developing and maintaining chronic pain [71]. Indeed, the fear of pain can lead to avoiding physical activities, resulting in physical deconditioning and increased disability [72]. Moreover, negative beliefs can further hamper a patient's recovery [72]. Depression, which is closely linked to chronic pain, affects an average of 52% of individuals with this condition [65].

Given the multifactorial nature of chronic pain, treatment involves multimodal therapies such as medications, physical rehabilitation, lifestyle changes, and psychological interventions [69]. The analgesic trolley model expands on traditional frameworks like the WHO analgesic ladder, offering a personalized strategy for chronic pain management [63]. The model organizes the treatment into categories of pharmacological agents and therapeutic techniques, including both non-invasive and invasive treatments [63].

The pharmacological management of chronic pain often involves analgesics, a class of drugs that offer prolonged pain relief and help enhance the patient's quality of life [69]. In the context of a pharmacological treatment within a multimodal therapy, opioids represent one of the most effective drugs [26]. However, the European clinical practice guidelines suggest the use of these analgesics only when non-opioid drugs are ineffective, intolerable, or contraindicated [73]. Indeed, long-term use of this class of drugs may lead to tolerance, addiction, an increased risk of developing substance use disorder, and other side effects [4, 26, 29]. Numerous scientific studies have demonstrated that transdermal buprenorphine is an effective analgesic for treating moderate to severe chronic pain. Even at low doses, it offers efficacy comparable to other opioids like morphine, oxycodone, and fentanyl, but with a lower risk of side effects [14, 20, 26, 46, 47, 74]. The transdermal formulation of low-dosage buprenorphine offers several advantages in the management of chronic pain, particularly for elderly patients and those with renal impairment. These benefits include once-weekly administration and no need for dosage adjustments, which improve patient compliance and reduce side effects [8, 47]. Indeed, transdermal buprenorphine has been found to be noninferior to tramadol for treating osteoarthritis and musculoskeletal pain in clinical studies [75, 76]. A systematic review supports the statistically significant reduction of non-cancer pain, with particularly strong evidence for low back pain management [77]. A recent study has highlighted the benefits of low-dosage buprenorphine transdermal patches in managing chronic arthritis pain [26]. Over a 36-month period, patients experienced a mean reduction of 1.19 points in pain severity from baseline, measured by the Numeric Rating Scale (NRS) score. Additionally, improvements were observed in quality of life and patient satisfaction, assessed using the PGIC test [26].

While the FDA has not approved buprenorphine specifically for depression, the molecule has shown antidepressant effects [78–80], suggesting it might be beneficial in addressing both chronic pain and its associated depressive symptoms. This dual effect can be attributed to its interaction with two opioid receptor subtypes involved in mood regulation. Specifically, by modulating the μ receptor, buprenorphine impacts serotonin neuron activity, and through the κ receptor, it directly inhibits dopamine release [80].

Buprenorphine Uses in Specific Populations

Buprenorphine is indicated for the treatment of non-malignant moderate pain in adults

when an opioid is needed to achieve adequate analgesia [81]. The drug is particularly beneficial for elderly patients and those with renal impairment, as no dose adjustment is required [81]. Indeed, specific groups of patients may benefit from using this opioid treatment for chronic pain.

Elderly Patients

Opioid treatment in elderly patients is a significant challenge due to age-related metabolic changes that increase the risk of these patients developing side effects and overdose when receiving analgesics [82]. Indeed, alterations in pharmacokinetics, pharmacodynamics, and drug distribution narrow the therapeutic index in this population. These individuals, often subjected to polypharmacy, face an increased risk of toxicity, drug–drug interactions, and accumulation of active opioid metabolites [82, 83]. Several studies have demonstrated the effectiveness and safety of transdermal buprenorphine for treating chronic pain in elderly patients [84–87]. This formulation offers continuous drug release for up to 7 days, minimizing peak-trough fluctuations and providing a gradual increase in serum concentration [47, 88]. The transdermal formulation reduces the risk of adverse events, particularly in elderly patients who often have altered metabolic function, decreased renal clearance, and ensures constant drug clearance, which is unaffected by age [82, 89]. These features are compliant with WHO guidelines for chronic pain management, which recommend formulations that reduce the possibility of sudden drug peaks in serum to minimize adverse effects [82]. A study involving 9489 patients with non-cancer-related pain demonstrated that transdermal buprenorphine patches are both effective and safe for older adults [85], with 80% of the patients reporting significant and stable pain relief [85]. Another study involving patients with a mean age of 81.6 years suffering from chronic pain found that transdermal buprenorphine effectively relieved pain regardless of the starting dose, and improved patients' quality of life [84].

Patients with Cardiac Issues

Buprenorphine may also be considered for patients with cardiac conditions who require long-term pain management. Indeed, it has been found that opioids, such as methadone and fentanyl, can inhibit the human ether-à-go-go-related gene (IhERG) current [90], which regulates the repolarization of the ventricular action potential, leading to QT prolongation [91]. This can cause Torsade de Pointes (TDP) [92], an arrhythmia characterized by prolonged intervals between ventricular depolarization and repolarization [92], which can be found in patients undergoing long-term opioid maintenance therapy [93–95]. Research indicates that buprenorphine does not significantly impact the QT interval [96–100], which may offer a safer alternative to other opioids [101]. In a randomized, placebo and positive-controlled clinical trial on healthy adults, transdermal formulation of buprenorphine at 10 mcg/h showed no significant effect on the QT interval [102]. Doses of 40 and 80 mcg/h caused only modest QTc prolongation, associated with minimal clinical risk [102]. These findings were further supported by a five-year follow-up study, which confirmed buprenorphine's cardiac safety profile, suggesting that transdermal buprenorphine may be a safer maintenance treatment for patients with heart disease [101]. Figure 2 summarizes the benefits of buprenorphine on different anatomical regions.

New Perspective for Buprenorphine Use

Recent research on buprenorphine suggests that its unique pharmacological properties may be particularly beneficial across diverse patient populations. According to a recent ISTISAN report, 41.8% of individuals experiencing chronic pain in Italy are aged between 18 and 54 years [103], highlighting the importance of addressing chronic pain treatment in this population as well. The report also emphasizes that younger patients tend to respond better to pain therapy with respect to older adults, pointing out the need for tailored pain treatments across different age groups [103]. While studies on

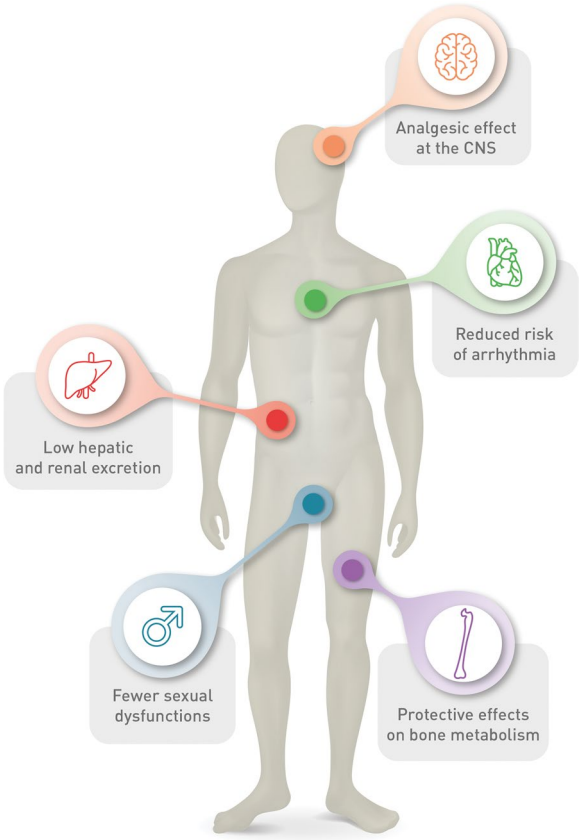

Fig. 2 Summary of the beneficial clinical effects of buprenorphine. *CNS* central nervous system

buprenorphine's effectiveness in young adults are still limited, two studies have compared pain reduction in patients treated for chronic pain with the transdermal formulation between younger and older patients, with cutoff ages of 65 and 74 years. These studies found similar outcomes for both age groups, suggesting that buprenorphine may effectively manage pain also in younger populations [86, 104]. Additionally, the molecule may offer unique benefits for younger patients: unlike other opioids, buprenorphine does not cause hormone imbalances, which can lead to reduced sexual function, decreased libido, and infertility, impacting the patient's quality of life in particular in young patients [105–108]. These benefits, along with related considerations, will be discussed in depth in the following sections.

Buprenorphine may also be considered for treating side effects associated with the aromatase inhibitor therapy in women of all ages. Aromatase inhibitors are antitumor drugs widely used in the treatment of breast cancer [109]. By blocking the enzyme aromatase, which converts androgens into estrogens, they are particularly effective against estrogen-sensitive tumors [88]. However, the resulting low estrogen levels can lead to side effects such as musculoskeletal pain, which affects more than half of the patients, and bone density loss observed in 14–15% of the subjects [109–112]. Robust evidence supports the effectiveness of buprenorphine in treating chronic musculoskeletal pain [75, 76]. In these studies, patients experienced significant reductions in pain levels, as measured by the NRS-11 and the Visual Analog Scale (VAS), with 44% of patients achieving good or very good pain relief [75, 76]. Recently, it has been proposed that opioids with dual mechanisms of action as buprenorphine may reduce the impact of opioids on bone density [113]. Additionally, an animal model study confirms that buprenorphine can reduce osteoporotic changes in the skeletal system, indicating protective effects on bone metabolism in estrogenic deficiency conditions [114]. Although these results are promising, they still require confirmation through clinical studies.

Endocrine Effects

Another side effect of chronic opioid treatment concerns endocrine imbalance. Opioid-induced androgen deficiency (OPIAD) is a condition in which the levels of sex hormones, particularly testosterone, are reduced by opioid suppression of the hypothalamic–pituitary–gonadal axis [115, 116]. Moreover, long-term opioid use can also increase levels of growth hormone, thyroid-stimulating hormone, and prolactin [117]. The resulting hormonal imbalance potentially leads to reduced libido and erectile dysfunction in men [118], oligomenorrhea or amenorrhea in women, and alteration of bone metabolism or infertility in both sexes [119]. In addition, other physiological changes such as fatigue, muscle wasting, and osteoporosis are reported [120]. The opioid hormonal side effects can lead to the

discontinuation of therapy. Common clinical practice recommends initiating hormone replacement therapy if opioid withdrawal cannot be achieved and the patient exhibits symptoms of endocrine dysfunction [116].

Many studies have examined the sexual effects of opioids in patients with opioid use disorder or addiction and have found that buprenorphine is associated with lower levels of sexual dysfunction symptoms compared to other opioids [105]. A meta-analysis reviewing 16 studies comparing methadone and buprenorphine for sexual dysfunction indicates a significantly higher odds ratio of sexual dysfunction in the methadone group compared to the buprenorphine group [105]. Two other studies highlighted the effects of buprenorphine on sexual function in patients treated for pain. One examined the effects of transdermal buprenorphine on pain and hormonal stability in 18 women with chronic noncancer musculoskeletal pain, split into pre-menopausal and post-menopausal groups. Over 6 months, participants reported significant and sustained pain relief. Unlike other opioids, buprenorphine maintained hormonal stability: testosterone levels slightly increased, and cortisol levels normalized, particularly in pre-menopausal women, without causing hypogonadism [106]. The second one measured the plasma testosterone levels in patients with acute persistent pain treated with buprenorphine over 6 months. Hormone levels were assessed at 1, 3, and 6 months after starting the treatment. In females, testosterone levels showed no decline over time; whereas in males, free testosterone remained below baseline [120]. In conclusion, these clinical studies suggest that buprenorphine administration is an effective, long-term option for pain management [105, 107], with a reduced risk of developing sexual dysfunctions associated with the treatment [121].

CONCLUSIONS

Buprenorphine is an opioid with unique pharmacological properties. The drug provides potent analgesia at low doses, reducing tolerance and side effects. Its low renal clearance and enhanced CNS penetration make it a safe and effective option for pain management, particularly in patients with renal impairments and in older patients. Recent studies also confirm its safety and efficacy in younger adults, with the added benefit of its antidepressant effects in managing pain-associated depression.

Emerging clinical applications include its use in patients with cardiac dysfunction and women undergoing therapy with aromatase inhibitors, and its lower risk of endocrine side effects paves the way for new therapeutic uses.

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Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. Diego Fornasari and Arturo Cuomo declare that they have no competing interests.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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