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REVIEW ARTICLE

Sublingual Administration for Pain Control: Pharmacology, Clinical Applications and Future Directions

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Abstract

Sublingual (SL) drug delivery represents an important alternative route of analgesic administration, particularly in settings where rapid pain control is desired or oral and parenteral routes are limited. By enabling direct absorption through the oral mucosa, SL administration partially bypasses first-pass hepatic metabolism, potentially improving bioavailability and accelerating the onset of action for select medications. Historically, SL analgesia has been most closely associated with opioid formulations such as fentanyl, buprenorphine, and sufentanil. SL fentanyl has demonstrated efficacy in breakthrough cancer pain among opioid-tolerant patients because of its rapid absorption and potent analgesic properties, whereas buprenorphine remains widely utilized for chronic pain and opioid use disorder owing to its partial μ-opioid receptor agonism and ceiling effect on respiratory depression. More recently, SL sufentanil has gained interest for the supervised management of acute pain in perioperative and emergency settings. Beyond opioids, expanding interest in SL therapeutics has included ketamine, cannabinoids, α2-adrenergic agonists, and investigational nonsteroidal anti-inflammatory drug (NSAID) formulations. Ketamine has shown potential utility in neuropathic and refractory pain syndromes, while cannabinoids are being explored for chronic, inflammatory, neuropathic, and cancer-related pain. Clonidine and dexmedetomidine may also serve as opioid-sparing adjuncts in selected settings. This review summarizes currently available and emerging SL analgesics, emphasizing pharmacologic mechanisms, pharmacokinetics, clinical applications, safety considerations, and therapeutic limitations. Although SL delivery offers advantages, such as noninvasive administration and rapid systemic exposure, limitations including variable bioavailability, formulation challenges, adverse effects, and limited comparative clinical evidence continue to restrict broader adoption.

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Key Points

Placing a medication under the tongue allows it to enter the bloodstream quickly without being broken down by the liver, making sublingual delivery a practical option for rapid pain relief in patients who cannot swallow or do not have intravenous access.

Among currently available sublingual analgesics, opioids such as fentanyl, buprenorphine, and sufentanil have the strongest clinical evidence, while newer agents, including ketamine, cannabinoids, and anti-inflammatory drugs, show promise but remain supported by limited or early-stage data.

The effectiveness of sublingual drug delivery depends heavily on a medication's physical and chemical properties, and despite its advantages, challenges, such as inconsistent absorption, taste, and restricted prescribing programs, continue to limit its widespread use in pain management.

1 Introduction

Sublingual (SL) drug delivery can be used as an alternative route of administration in pain management, particularly in patient populations where traditional oral or parenteral routes are limited. The SL route offers several pharmacokinetic advantages, including rapid systemic absorption, partial avoidance of first-pass hepatic metabolism, and improved bioavailability for select compounds (Fig. 1). These characteristics make SL delivery especially attractive for the management of acute pain, breakthrough pain, and conditions requiring rapid onset of analgesia.

Over time, SL therapeutics have expanded beyond traditional opioid formulations to include a growing range of nonopioid and adjunctive agents investigated across diverse pain conditions, including neuropathic, musculoskeletal, inflammatory, cancer-related, mucosal, procedural, and chronic pain syndromes. However, evidence supporting SL therapies remains variable across disease states, and many applications remain investigational or supported by limited clinical data.

Accordingly, the primary aim of this review is not to provide an exhaustive disease-specific review of pain management, but rather to provide a comprehensive overview of currently available and emerging SL analgesics with an emphasis on pharmacologic mechanisms, pharmacokinetics, clinical utility, safety considerations, and therapeutic limitations (Table 1). By synthesizing available evidence across drug classes, this article seeks to clarify the current and evolving role of SL analgesia within multimodal pain management strategies.

2 Fentanyl

2.1 Pharmacology and Pharmacokinetics

Sublingual fentanyl is a highly potent μ-opioid receptor agonist, with analgesic effects approximately 50–100 times greater than morphine, mediated through activation of μ receptors at both supraspinal and spinal sites [1]. In addition to analgesia, μ-receptor activation contributes to dose-dependent respiratory depression, sedation, and euphoria, reflecting fentanyl's narrow therapeutic window. Its extreme lipophilicity promotes rapid penetration across biological membranes and facilitates efficient absorption through the SL mucosa, bypassing first-pass hepatic metabolism and achieving detectable plasma concentrations within minutes of administration [2, 3]. Early pharmacokinetic studies in healthy volunteers demonstrated that approximately half of an SL dose enters the systemic circulation, substantially greater than hydrophilic opioids such as morphine. This systemic uptake is reliable and predictable as it relies primarily on physicochemical properties rather than administration technique [2]. Following absorption, fentanyl rapidly distributes to highly perfused tissues, including the central nervous system, accounting for its fast onset of analgesia [3]. Subsequent studies evaluating SL fentanyl wafers confirmed high absolute bioavailability (79%) and a short time to peak plasma concentration, supporting SL delivery as an effective route for rapid-onset analgesia [4].

2.2 Clinical Applications

Historically, SL fentanyl formulations have been indicated primarily for breakthrough cancer pain in opioid-tolerant adults, with limited use in other clinical pain states. These formulations include SL sprays and tablets. Fentanyl buccal tablets have also been administered sublingually, off label. Pharmacokinetic studies confirm comparable systemic exposure between buccal and SL placement [4]. These agents fall within the class of Transmucosal Immediate-Release Fentanyl (TIRF) formulations. Among these formulations, SL sprays demonstrate faster absorption, earlier peak plasma concentrations, and reduced interindividual variability compared with lozenge-based transmucosal tablets, while overall systemic exposure remains equivalent [6, 7]. Clinically, randomized trials and noninferiority studies show that SL fentanyl provides rapid and effective pain relief comparable to subcutaneous morphine for breakthrough cancer pain, with patients frequently preferring the SL route owing to its noninvasive administration [5, 6]. Additionally, palliative

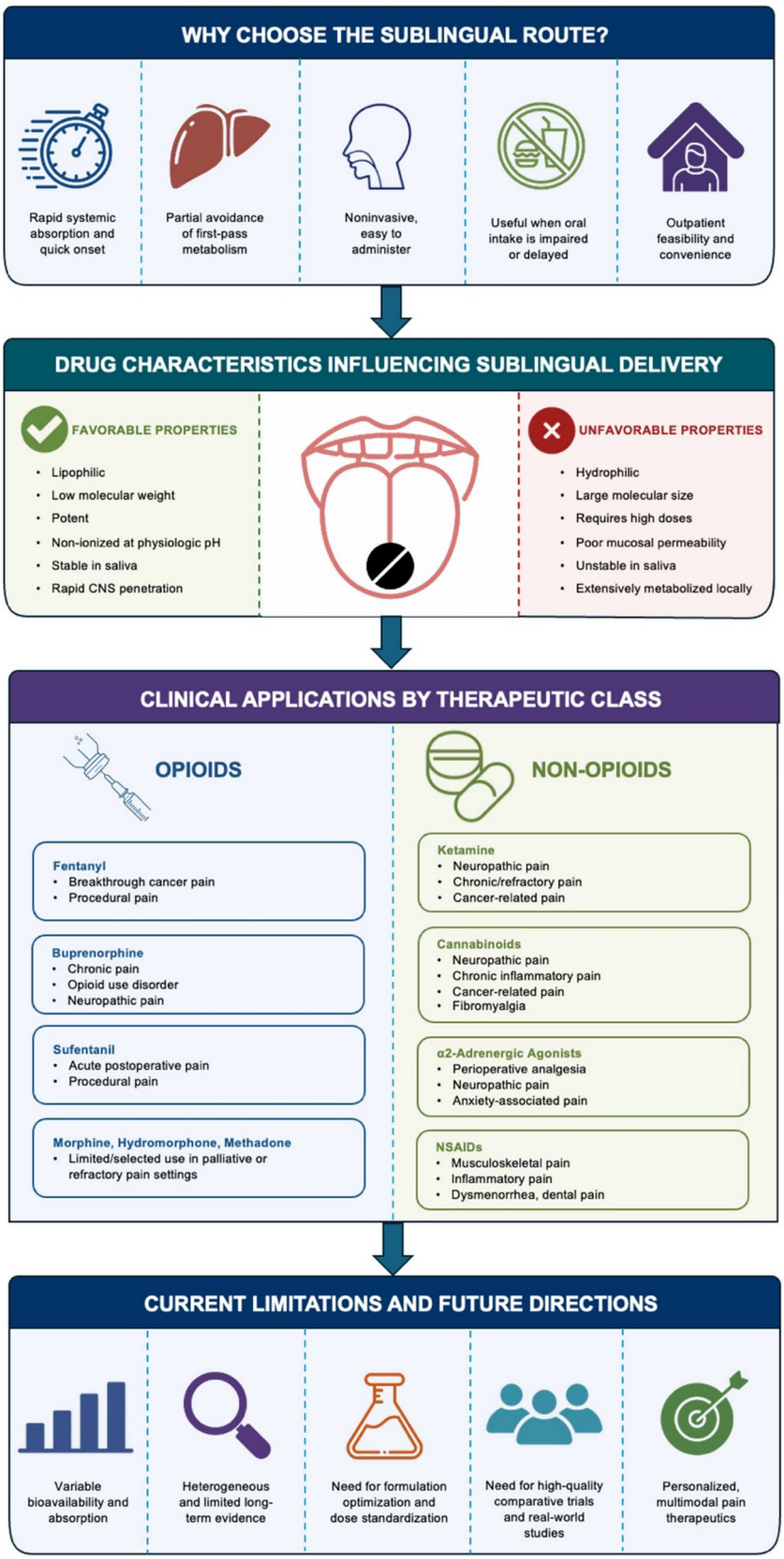

Fig. 1 Overview of Sublingual Analgesic Therapy. This figure summarizes the advantages of sublingual (SL) drug delivery, key physicochemical properties influencing SL absorption, representative opioid and nonopioid analgesic applications, and current limitations and future directions of SL therapeutics in pain management. *CNS* central nervous system

Table 1 Summary of established and emerging sublingual analgesics

Agent/class	Primary mechanism	Typical sublingual formulation	Main pain applications	Advantages of sublingual delivery	Key limitations/safety considerations	Overall clinical evidence
Fentanyl	Full μ-opioid receptor agonist	Spray, tablet, wafer	Breakthrough cancer pain, procedural pain, palliative pain	Rapid onset, high bioavailability, bypasses first-pass metabolism	Respiratory depression, misuse potential, REMS restrictions, reduced market availability	Strong
Buprenorphine	Partial μ-opioid receptor agonist	Tablet, film	Chronic pain, opioid use disorder, neuropathic pain, musculoskeletal pain	Ceiling effect on respiratory depression, favorable safety profile	Variable absorption, dosing variability, opioid-related adverse effects	Moderate–strong
Sufentanil	Full μ-opioid receptor agonist	Tablet	Acute postoperative pain, procedural pain, trauma-related pain	Rapid analgesia, predictable absorption, noninvasive administration	Restricted supervised use, sedation, respiratory depression risk	Moderate–strong
Morphine	Full μ-opioid receptor agonist	Dissolved tablet/liquid	Palliative pain, end-of-life care	Useful when swallowing is impaired	Poor sublingual absorption, unpleasant taste, delayed onset	Limited
Hydromorphone	Full μ-opioid receptor agonist	Crushed tablet (off label)	Palliative pain, hospice care	Alternative when oral intake is limited	Low and variable bioavailability, limited supporting evidence	Very limited
Methadone	Full μ-opioid receptor agonist and NMDA antagonist	Crushed tablet, liquid	Chronic pain, neuropathic pain, breakthrough cancer pain	Long duration of action, potential utility in neuropathic pain	QT prolongation, complex pharmacokinetics, limited sublingual data	Limited
Ketamine	NMDA receptor antagonist	Troche, lozenge, wafer	Neuropathic pain, chronic pain syndromes, refractory pain, cancer pain	Opioid-sparing effects, outpatient feasibility, rapid CNS penetration	Psychomimetic effects, dizziness, sedation, limited long-term data	Emerging–moderate
Cannabinoids (THC/CBD)	CB1/CB2 receptor modulation	Oils, sprays, wafers	Neuropathic pain, inflammatory pain, cancer-related pain, fibromyalgia	Noninvasive administration, multimodal effects, partial avoidance of first-pass metabolism	Sedation, cognitive effects, heterogeneous formulations and evidence	Emerging
α2-Adrenergic agonists	Central α2-adrenergic receptor agonism	Film, tablet	Adjunctive perioperative pain management, anxiety-associated pain, neuropathic pain	Opioid-sparing potential, anxiolytic and sympatholytic effects	Bradycardia, hypotension, sedation	Limited–emerging
NSAIDs	Cyclooxygenase inhibition	Investigational tablets/films	Musculoskeletal pain, inflammatory pain, dental pain	Potential rapid absorption and nonopioid analgesia	Limited clinical availability and evidence, formulation challenges	Investigational

The table summarizes representative sublingual (SL) analgesic agents and therapeutic classes, including mechanisms of action, common formulations, clinical pain applications, advantages of SL delivery, key limitations and safety considerations, and the overall strength of current clinical evidence

REMS risk evaluation and mitigation strategy, *THC* tetrahydrocannabinol, *CBD* cannabidiol, *NMDA N*-methyl-D-aspartate

care reviews note that SL fentanyl administration may offer superior analgesic efficacy over oral morphine for breakthrough cancer and noncancer related pain. SL fentanyl and has been commonly employed in hospice settings, particularly for patients with dysphagia or limited oral intake [7, 8].

Although SL fentanyl is primarily indicated for breakthrough cancer pain in opioid-tolerant adults, its use has been explored in other pain contexts [9]. For example, in patients with chronic musculoskeletal pain with a neuropathic component, SL tablets produced rapid and clinically meaningful analgesia and were generally well tolerated [10]. In investigations of procedural pain, such as during colonoscopy, SL administration was feasible, but doses low enough to be deemed safe did not provide significant analgesic benefit [11]. Higher or repeated dosing increases the risk of hypoxia, emphasizing the importance of careful patient selection and dosing [12]. Importantly, these controlled investigations represent only a small portion of the broader clinical use of transmucosal fentanyl formulations. The American College of Medical Toxicology has emphasized that these agents have been primarily studied in carefully selected, opioid-maintained populations, most commonly patients with cancer, and that data on adverse events and safety outside these settings remain limited [13]. These safety considerations have informed the implementation of strict prescribing programs, such as the TIRF Risk Evaluation and Mitigation Strategy (REMS) in the USA, which requires prescriber certification, patient education, and adherence to dosing guidelines to minimize risk and ensure safe use [12, 14].

2.3 Safety Considerations

It is important to note that in recent years, manufacturers have discontinued distribution of SL fentanyl formulations in several major markets, resulting in reduced commercial availability and clinical access [15]. Publicly available regulatory records indicate that, by late 2024, no SL fentanyl formulations remained widely marketed in the USA, while limited availability persists in select international settings [15]. This reduction in access appears to reflect a combination of market forces and increasingly restrictive risk-mitigation requirements rather than new clinical safety data [15]. Consequently, many clinicians have been advised to transition patients previously treated with SL fentanyl to alternative therapy strategies in accordance with local prescribing frameworks [15]. Despite this contraction in availability, the existing pharmacokinetic data, randomized trials, and observational studies continue to provide valuable insight into the clinical characteristics, potential utility, and safety considerations of SL fentanyl as a rapid-onset opioid analgesic.

3 Buprenorphine

3.1 Pharmacology and Pharmacokinetics

Buprenorphine is a semisynthetic opioid that exerts its analgesic effects through partial agonism of the mu opioid receptor. Buprenorphine's high receptor affinity and slow dissociation from the mu-opioid receptor contribute to prolonged receptor occupancy and reduced receptor internalization compared with full μ-agonists [16]. Another major benefit is its reduced potential for toxicity and overdose. When compared with other opioids, such as fentanyl, buprenorphine displays a dose-dependent ceiling effect on respiratory depression, making overdose less likely [17, 18]. Oral administration of buprenorphine yields low systemic absorption owing to extensive first-pass metabolism. However, SL administration allows for adequate plasma concentration for clinical use [19, 20].

3.2 Clinical Applications

Buprenorphine has also seen a significant increase in utilization for the treatment of addiction and chronic pain in the USA. One systematic review found that SL administration was effective in chronic treatment of a variety of conditions, including osteoarthritis and sickle cell disease [21]. Limitations in the effective use of SL administration typically surround the high variability in absorption. When taken under the tongue, a significant portion of the drug remains unabsorbed in the saliva, leading to a decreased plasma concentration [22]. Inconsistency in SL absorption leads to heterogeneity in dosing and research methodologies, as well as mixed outcomes in clinical practice [23].

3.3 Safety Considerations

Overall, the SL administration of buprenorphine is a safe and effective method for the treatment of opioid abuse disorder with a variety of clinical indications for chronic pain treatment. The literature proves that its excellent safety profile and efficacy in preventing opioid relapse make it useful in bridging the gap for chronic pain treatments in patients with opioid use disorder, while more evidence is required to solidify its role in the treatment of chronic pain disorders such as cancer, osteoarthritis, and sickle cell disease.

4 Sufentanil

4.1 Pharmacology and Pharmacokinetics

Sufentanil is a synthetic μ-opioid receptor agonist structurally related to fentanyl but with substantially greater potency, estimated at approximately 5–10 times that of fentanyl and 500–1000 times that of morphine, reflecting its high intrinsic efficacy and strong receptor-binding affinity [24]. Like fentanyl, sufentanil is highly lipophilic, which facilitates rapid transmucosal absorption. Sublingual administration bypasses first-pass hepatic metabolism and allows for predictable systemic exposure with rapid onset of analgesia while limiting gastrointestinal variability [25]. Sufentanil rapidly distributes to highly perfused tissues, including the central nervous system, accounting for its prompt analgesic effect, while its high potency permits effective analgesia at very small absolute doses [26].

Pharmacokinetic studies of SL sufentanil tablets in healthy volunteers demonstrated rapid absorption, dose-proportional systemic exposure, and a relatively short time to peak plasma concentration [27]. Importantly, despite its extreme lipophilicity, a controlled tablet formulation slows dissolution at the SL surface, producing a gradual rise in plasma concentrations rather than abrupt peaks associated with intravenous bolus dosing [25]. This controlled absorption profile has been proposed to reduce peak-related adverse effects, particularly respiratory depression, while preserving rapid analgesic onset [28]. Compared with fentanyl, sufentanil's higher potency and slower plasma rise following SL administration may contribute to a wider functional margin between analgesia and serious respiratory compromise when used within structured dosing protocols [29]. These pharmacokinetic characteristics, rapid absorption, controlled plasma rise, and high potency at small doses, make SL sufentanil particularly suited for controlled acute pain management rather than long-term or home use [25, 28].

4.2 Clinical Applications

Clinical development of SL sufentanil has focused on acute pain management, i.e., postoperative pain, trauma-related pain, and procedural pain, rather than breakthrough cancer pain, with two distinct tablet strengths (15 μg and 30 μg) evaluated in different clinical contexts [30]. Unlike SL fentanyl, sufentanil's use is strictly limited to supervised medical settings, with no allowance for home or unsupervised administration [31]. As with SL fentanyl, SL sufentanil is subject to a REMS program in the USA to ensure prescriber certification, patient education, and adherence to dosing guidelines [32].

The 15 μg SL tablet has primarily been studied in postoperative and inpatient settings using patient-controlled analgesia (PCA)-like systems [30]. Randomized controlled trials in patients undergoing major orthopedic procedures demonstrated that patient-controlled SL sufentanil 15 μg provided significantly improved pain control compared with placebo, reduced supplemental opioid requirements, and was generally well tolerated, with nausea and mild sedation being the most common adverse effects [33]. Subsequent prospective and real-world studies confirmed the feasibility and effectiveness of this system for managing moderate-to-severe postoperative pain, with high patient satisfaction and low rates of clinically significant respiratory depression when used under supervised conditions [34]. Additional randomized data in patients undergoing thoracic surgery showed that the 15 μg SL sufentanil provided effective postoperative analgesia comparable to traditional opioid strategies while facilitating early mobilization and avoiding the need for intravenous access [35].

The 30-μg SL tablet has been evaluated primarily as a clinician-administered analgesic for short-term treatment of acute pain. Reviews of clinical trial data emphasize that the fixed-dose, nontitrated nature of the 30-μg tablet simplifies administration while maintaining predictable pharmacokinetics [36]. Phase III trials and pooled safety analyses demonstrated that single or repeated doses of SL sufentanil 30 μg produced rapid and clinically meaningful reductions in pain intensity across a range of acute pain conditions, with onset often within 15–30 min and sustained analgesia lasting several hours [37]. Adverse events were consistent with known opioid effects and were generally mild to moderate in severity, with low rates of hypoxia or serious respiratory events when dosing limits were followed [37, 38]. More recently, randomized controlled data in trauma patients demonstrated that early administration of SL sufentanil 30 μg provided effective analgesia in prehospital and emergency settings, supporting its potential role as a noninvasive alternative to intravenous opioids for acute pain management [39].

4.3 Safety Considerations

Adverse effects associated with SL sufentanil are consistent with those of other μ-opioid agonists and include nausea, sedation, dizziness, and vomiting, which were among the most commonly reported events across clinical trials [33, 34, 37]. Clinically significant respiratory depression occurred at low rates when dosing protocols and monitoring requirements were followed, though the risk increases with dose escalation or deviation from structured protocols [37, 38]. Use of SL sufentanil is restricted to supervised medical settings and governed by a REMS program in the USA, reflecting the need for careful patient selection and close clinical oversight [31, 32].

Collectively, prior studies suggest that SL occupies a distinct clinical niche among rapid-onset opioid analgesics. Its high potency, controlled transmucosal absorption, and formulation-specific dosing strategies differentiate it pharmacologically and clinically from SL fentanyl. While its use remains largely confined to acute pain settings under structured protocols, the available evidence supports SL sufentanil as an effective and predictable option for short-term analgesia when careful patient selection and dosing oversight are applied [30].

5 Morphine

5.1 Pharmacology and Pharmacokinetics

Morphine acts primarily as a full μ-opioid receptor agonist, with weaker activity at kappa receptors and minimal delta receptor contribution. Agonistic interactions with these receptors result in analgesia, sedation, euphoria, respiratory depression, and gastrointestinal smooth muscle contraction [40]. Owing to various mechanisms, including increased dopamine release and chronic desensitization of opioid receptors, chronic morphine use can lead to physical and psychological dependence and is considered a drug of abuse [41].

Sublingual administration of morphine is a less effective pathway for drug delivery than traditional parenteral routes. Morphine exists predominantly in its ionized form at physiological pH, making it a highly water-soluble drug. This largely inhibits SL administration, which is better suited for lipophilic opioids [42, 43]. Weinberg et al. found that morphine had an SL absorption of around 18%, compared with more lipophilic opioids, such as buprenorphine and fentanyl, that had absorption rates around 50% [2].

5.2 Clinical Applications

Even with limitations in SL morphine administration, it is often still utilized in palliative care for patients who have lost the ability to swallow. Multiple studies have reported that plasma morphine concentrations were comparable between SL and oral administration. Much of the observed analgesic effect likely reflects gastrointestinal absorption of swallowed drug rather than true transmucosal uptake. Oral administration was preferred by patients owing to the unpleasant taste of the dissolved SL tablet [44, 45]. Because of this, SL morphine administration is still primarily reserved for palliative care in patients who are unable to swallow morphine in the oral formulation. Future research is unlikely owing to these pharmacologic limitations in SL administration.

5.3 Safety Considerations

Adverse effects of SL morphine mirror the full μ-opioid agonist class profile, including respiratory depression, sedation, nausea, constipation, and risk of physical and psychological dependence with repeated use [40, 41]. The low and variable SL bioavailability (~18%) may limit peak analgesic effect but does not eliminate opioid-related risks, as a substantial portion of the dose may still be absorbed via gastrointestinal swallowing [42–45]. Standard precautions for opioid administration, including monitoring for respiratory depression and sedation, apply regardless of route.

6 Hydromorphone

6.1 Pharmacology and Pharmacokinetics

Hydromorphone is a μ-opioid receptor agonist, with analgesic potency roughly 5–7 times that of morphine. It has high aqueous solubility and relatively low lipid solubility, reflecting a hydrophilic chemical profile that limits passive transmucosal absorption compared with more lipophilic opioids [46]. In a comparative pharmacokinetic study of multiple opioids, hydromorphone demonstrated substantially lower SL bioavailability than fentanyl and sufentanil [2]. Systemic exposure following SL administration is therefore low and highly variable, precluding predictable analgesia. No widely approved SL formulation exists, and its use has been largely restricted to small case series or compassionate-use scenarios in patients unable to swallow oral medications [47, 48]. These pharmacologic limitations underscore why SL hydromorphone is rarely employed clinically, with no established guidelines for use in specific pain states [49]. Dedicated pharmacokinetic studies evaluating SL hydromorphone bioavailability are lacking.

6.2 Clinical Applications

Sublingual hydromorphone has occasionally been used in palliative care for patients who cannot swallow, but evidence indicates that absorption is limited and unpredictable [7]. In these situations, SL administration is largely a pragmatic choice rather than one supported by robust pharmacokinetic or clinical trial data. When the oral route is unavailable, subcutaneous or intravenous administration is generally preferred over SL use for hydrophilic opioids [47]. Standard clinical practice continues to rely on oral, subcutaneous, intravenous, and rectal routes, with SL hydromorphone reserved for exceptional circumstances in homebound or hospice patients [48, 49].

6.3 Safety Considerations

Hydromorphone carries a full μ-opioid agonist adverse effect profile, including respiratory depression, sedation, nausea, and constipation, with a potency approximately 5–7 times that of morphine [46, 48]. The unpredictable SL absorption may lead to inadequate initial analgesia and prompt repeated dosing, increasing the risk of cumulative toxicity and delayed respiratory depression [47–49]. When used in palliative or hospice settings where parenteral access is unavailable, close monitoring for oversedation remains essential, as the gastrointestinal absorption of a swallowed drug may contribute to systemic exposure [47, 48].

7 Methadone

7.1 Pharmacology and Pharmacokinetics

Methadone is a full agonist at the μ-opioid receptor and is also a weak antagonist of the Glutamate *N*-methyl-D-aspartate (NMDA) receptor. This unique mechanism of action has proven useful in treating neuropathic pain in addition to chronic, non-neuropathic pain, and opioid use disorder [50, 51]. Methadone has an extended half-life of 6–80 hours, allowing for longer-lasting daily doses. Sustained μ-receptor occupancy produces cross-tolerance, reducing the euphoric effects of shorter-acting opioids. Longer-lasting doses also decrease severe symptoms of withdrawal [52]. There is also evidence that methadone can be used as a second-line drug for both acute and chronic pain treatment if analgesia is no longer adequate with morphine [47]. Clinicians prescribing methadone should be aware of the potential risk of QTc interval prolongation and Torsades de Pointes [53–55].

7.2 Clinical Applications

Methadone is a highly lipophilic molecule, indicating the potential for SL administration [2]. Nonetheless, little research has been conducted regarding the efficacy of SL methadone administration. A formal feasibility study showed that SL methadone was a safe and effective analgesic for breakthrough pain in patients with cancer [56]. Methadone has also been shown to be effective and well-tolerated when switching from oral to buccal mucosal administration in end-of-life, palliative care patients [57]. A single case study described the use of SL methadone in a patient with chemotherapy/radiation-induced mucositis, where the patient was able to achieve adequate pain relief by allowing a crushed methadone tablet to dissolve under the tongue [58].

7.3 Safety Considerations

A key safety concern with methadone is its propensity to prolong the QTc interval, increasing the risk of potentially fatal ventricular arrhythmias including Torsades de Pointes. Baseline and periodic electrocardiographic monitoring is therefore recommended in all patients [53–55]. Methadone's long and unpredictable half-life (6–80 h) increases the risk of drug accumulation and delayed respiratory depression, particularly during dose titration or when combined with other central nervous system depressants [52]. These risks are compounded in the SL setting by variable absorption, underscoring the importance of careful patient selection and close clinical monitoring [56, 57].

Beyond these preliminary trials and observations, there is limited research in SL delivery of methadone. Initial research shows that it may be a viable route of delivery for rapid pain relief in patients with difficulty swallowing or in patients with direct oral pain. While the overall research on SL administration is still inadequate, these initial feasibility studies provide a starting point for the potential benefits for use in pain relief for cancer pain, mucositis, and other chronic pain conditions, especially in the palliative setting.

8 Ketamine

8.1 Pharmacology and Pharmacokinetics

Ketamine, a phencyclidine derivative with anesthetic and analgesic effects, acts primarily as a noncompetitive antagonist at transmembrane NMDA receptors in the spinal cord and brain with no affinity for GABA receptors [59, 60]. Ketamine is a chiral molecule consisting of two optical enantiomers: S(+)-ketamine and R(−)-ketamine. While most studies have evaluated racemic ketamine, the use of S(+)-ketamine has increased as recent evidence suggests it is approximately twice as potent as the racemic mixture and four times as potent as R(-)-ketamine [61].

Owing to extensive first-pass metabolism, ketamine exhibits low oral bioavailability (approximately 8–24%), while SL administration yields modestly improved systemic bioavailability (approximately 27–31%) [62]. Ketamine undergoes N-demethylation to form norketamine via cytochrome P450 enzymes 3A and 2B6. Norketamine is a pharmacologically active metabolite with NMDA receptor antagonist properties, although its overall contribution to ketamine's clinical effects appears limited owing to differences in its potency and pharmacokinetic profile. Studies have demonstrated that inhibition or induction of CYP3A and CYP2B6 significantly alters ketamine exposure, indicating that its metabolism is largely mediated by the cytochrome P450 system [63, 64]. Given its high

lipophilicity, ketamine readily crosses the blood–brain barrier after entering the systemic circulation, resulting in rapid distribution to the brain and other tissues.

8.2 Clinical Applications

Although intravenous ketamine remains the most extensively studied and established route of administration, SL formulations may offer a practical balance between analgesic efficacy, outpatient feasibility, and relatively rapid onset. Available evidence suggests that SL ketamine can be an effective and generally well-tolerated analgesic. Reported adverse effects do not appear to correlate consistently with treatment duration or total daily dose, supporting its use in selected patients with chronic pain [65]. A single study evaluating outpatient ketamine use for chronic low back pain reported significant reductions in severe pain and disability scores, along with high medication adherence, which was attributed to the generally mild side effects associated with SL administration [66].

In a prospective study of patients with chronic, nonmalignant pain, subanesthetic subcutaneous ketamine was administered, followed by subsequent treatments of SL ketamine lozenges. The initial infusions resulted in significant reductions in pain severity and opioid requirement, with mild but manageable adverse effects. The SL treatments that followed, initiated at 25 mg three times a day, produced a prolonged period of analgesic effect and longer opioid discontinuation, ultimately supporting a promising approach for long-term pain management [67]. Preliminary research suggests that SL ketamine, administered as a 25-mg SL wafer up to a maximum of 75 mg/day, may be effective and well-tolerated for pain relief in advanced cancer; however, significant feasibility challenges remain for conducting such trials [68]. Additionally, a randomized, double blind crossover trial of inpatients with acute pain aimed to compare oral and SL ketamine found that a 50-mg SL lozenge produced a faster onset of pain relief and a higher incidence of adverse events [69].

Beyond acting as an analgesic agent, ketamine has been shown to be effective for anesthetic induction, sedation, and treatment of several psychiatric conditions, including depression, anxiety, and PTSD [70, 71]. At anesthetic doses, it is used for procedural sedation and induction in hemodynamically unstable patients given its sympathomimetic properties. At subanesthetic doses, it serves as an opioid-sparing adjunct in perioperative and emergency department pain management [72]. As such, ketamine dosing is highly dependent on the desired clinical effect [73].

8.3 Safety Considerations

In the context of SL administration for pain management, relatively low doses and systemic exposures are typically used to achieve effective analgesia while minimizing dissociative and anesthetic effects. With other routes of administration, ketamine is generally contraindicated in patients with poorly controlled hypertension, severe hepatic dysfunction, elevated intracranial or intraocular pressures, pregnancy, and other systemic diseases [73–75]. Common adverse effects of ketamine include nausea, drowsiness, double vision, and confusion. Less frequent but more severe adverse events may include psychomimetic symptoms, renal or hepatic toxicity, and cardiac arrest. However, currently available studies of SL ketamine report minimal adverse effects and a favorable tolerability profile, with drowsiness being the most frequently observed adverse event and no consistent evidence of renal or hepatotoxicity [65].

Overall, SL ketamine combines the well-established analgesic mechanisms of ketamine with the practicality of outpatient administration and a generally favorable tolerability profile, representing a promising and clinically distinct approach to pain management. Further prospective studies are needed to define optimal dosing strategies and to clarify long-term safety across diverse patient populations.

9 Cannabinoids

9.1 Pharmacology and Pharmacokinetics

The SL administration of cannabinoids, especially delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), has been gaining interest as an optimized mechanism in systemic delivery for therapeutic purposes, including pain management. In pain medicine, cannabinoids are most often studied or considered for chronic pain conditions, including neuropathic, cancer-related, inflammatory, musculoskeletal, and multiple sclerosis-associated conditions [76]. By contrast, their role in procedural, postoperative, and other acute pain settings remains less clearly defined. Clinically, THC exerts psychoactive effects and provides analgesic, antiemetic, and appetite-stimulating properties that support its use in conditions such as chemotherapy-induced nausea, cachexia, and chronic pain [77, 78]. By contrast, CBD is nonintoxicating and demonstrates broad therapeutic potential, including anxiolytic, antiepileptic, anti-inflammatory, neuroprotective, and analgesic properties, alongside a generally favorable safety profile in preclinical and clinical studies [77, 79–82].

Cannabinoids produce analgesic effects primarily through the modulation of the endocannabinoid system, particularly through the activation of cannabinoid type 1 (CB1) receptors as well as cannabinoid type 2 (CB2).

CB1 receptors are G protein-coupled receptors that can be found in the brain and peripheral nerves, where they reduce neurotransmitter release and modulate pain, mood, appetite, and motor control [83–86]. CB2 receptors are expressed predominantly on immune cells and some neural cells and are involved in the regulation of inflammation and immune responses [81, 83, 85, 86]. THC acts as a partial agonist at both CB1 and CB2 receptors, triggering Gi/o signaling. This cascade inhibits adenylyl cyclase, decreases cAMP, modulates ion channels, and alters both neuronal excitability and immune cell activity [84–87]. By contrast, CBD has low orthosteric affinity for CB1 and CB2 but acts as a negative allosteric modulator and inverse agonist. This allows CBD to dampen CB1/CB2 signaling in response to endocannabinoids and THC, while also engaging other targets, such as TRPV1 and 5-HT1A receptors, that contribute to its analgesic, anxiolytic, and anti-inflammatory effects [81, 86–89].

Sublingual administration of cannabinoids allows for rapid absorption directly into the systemic circulation and partial bypass of hepatic first-pass metabolism, a major limitation of oral cannabinoid formulations [90–92]. This results in a more rapid onset of action when compared to oral ingestion. However, absolute bioavailability appears to remain modest and is variably influenced by factors such as mucosal permeability, saliva production, how the patient administers the dose, and formulation properties [90, 91, 93–95]. Thus, the SL route may be most useful when patients need a non-inhaled and noninvasive cannabinoid formulation. It may offer more predictable administration than inhaled cannabis and faster absorption than standard oral products. However, it should not be viewed as the preferred route for all pain conditions.

Pharmacokinetic studies in both humans and animal models have shown that SL or oromucosal cannabinoid products (such as wafers, sprays, and tablets) achieve peak plasma concentrations (C_{max}) around 1–4 h after administration, with the elimination half-life ranging from 6 to 24 h, depending on the formulation and the utilized cannabinoid [90, 92, 93]. In a phase I trial that compared SL CBD wafers with oil solutions and oromucosal sprays, there were comparable C_{max} values (9.4–11.9 ng/mL for CBD), T_{max} around 4 h, and similar area under the curve [90]. This data indicates that there is similar systemic exposure between these different transmucosal routes. In animal studies, SL administration of THC/CBD combinations resulted in maximal plasma concentrations at 1–2 h, with evidence of progressive accumulation after multiple dose treatment [96]. Further studies in rabbits have elucidated formulation strategies, such as cyclodextrin complexes or nanoemulsions, that can enhance solubility and mucosal permeation. This led to improved bioavailability over standard ethanolic or oil-based formulations [97–99].

9.2 Clinical Applications

The pharmacological properties of SL formulations have prompted investigation as therapeutic options for chronic and neuropathic pain. Nabiximols (an oromucosal spray that contains a standardized 1:1 ratio of THC and CBD) is the most studied SL formulation and has been assessed in numerous randomized controlled trials as well as real-world cohort studies. Clinical evidence indicates that SL cannabinoids may provide modest improvements in pain severity, sleep quality, and overall function for patients with chronic pain, including those with neuropathic pain, fibromyalgia, cancer-related pain, and multiple sclerosis-related spasticity [100–106]. In patients with advanced cancer with poorly controlled pain, adjunctive treatment with nabiximols alongside optimized opioid therapy has been associated with greater analgesia at low to medium doses compared with placebo, including improvements in sleep disruption and overall quality of life [106, 107]. Similarly, registry-based studies of SL cannabis oils have reported significant improvements in patient-reported outcomes related to pain interference, sleep quality, and health-related quality of life over periods up to 6 months [102, 103].

9.3 Safety Considerations

Despite these encouraging findings, the overall analgesic effect is generally small to moderate and often accompanied by a higher incidence of adverse events such as dizziness, sedation, somnolence, and mild cognitive effects [100, 104, 105]. As a result, the combination of adverse events and inadequate analgesia may result in patient discontinuation. Comparative studies suggest that while SL administration may offer advantages in dosing consistency and patient acceptability over inhaled routes, especially for those seeking to avoid smoking, its effectiveness for pain conditions such as low back pain may be less pronounced than THC-rich inhaled therapies [108]. Of note, the clinical utility of SL cannabinoids appears to be the most relevant for chronic neuropathic pain populations, as evidence for their efficacy in acute or postoperative pain remains limited or inconclusive [109–112].

Variation in cannabinoid formulations (including differing THC:CBD ratios), dosing strategies, study designs, and patient populations complicates direct comparisons across trials and limits the generalizability of results. Furthermore, most studies only report short-term outcomes (1–6 months), are not powered to detect rare adverse events, and often lack standardized outcome measures. Further research is needed to clarify optimal dosing strategies, long-term safety, how SL cannabinoid formulations compare with other routes of administration, and which chronic pain populations are most likely to benefit from therapy.

10 α2-Adrenergic agonists

10.1 Pharmacology and Pharmacokinetics

Alpha agonists used in analgesia are largely α2-adrenergic receptor agonists, principally clonidine and dexmedetomidine. Through presynaptic inhibition of norepinephrine release and downstream modulation of pain processing, α2-agonists can attenuate nociceptive transmission at both supraspinal and spinal levels, while also reducing sympathetic hyperarousal that amplifies pain perception. Clinically, these agents are best characterized as opioid-sparing adjuncts, well established in perioperative multimodal analgesia and selected neuropathic pain states, rather than primary analgesics in isolation [115–119]. Beyond the perioperative setting, α2-agonists have also been explored in chronic pain syndromes, cancer-related pain, opioid withdrawal-associated hyperalgesia, procedural sedation with analgesia, and intensive care settings where analgesia, anxiolysis, and sympatholysis may provide synergistic benefits [113]. Dexmedetomidine in particular has gained interest in enhanced recovery pathways, regional anesthesia adjunct protocols, and pain phenotypes characterized by autonomic dysregulation or heightened central sensitization [114].

From a delivery standpoint, the SL route is appealing in pain medicine because it enables nonparenteral systemic exposure, may partially bypass first-pass metabolism, and can be used when oral intake is compromised, such as in nausea/vomiting, dysphagia, or perioperative NPO status. However, whether SL dosing meaningfully accelerates onset depends heavily on the drug and formulation [115]. Additionally, transmucosal exposure is sensitive to administration techniques. Patients should avoid chewing or swallowing the medication and should minimize food or drink immediately after dosing, as these factors may contribute to variability in absorption in clinical settings.

10.2 Clinical Applications

Data directly evaluating SL clonidine for analgesia are limited. The most relevant evidence supporting this route is derived from pharmacokinetic comparisons [116]. These studies demonstrated that SL clonidine does not substantially accelerate onset compared with oral administration. Pharmacokinetic and hemodynamic profiles are broadly similar, suggesting that the primary advantage of SL delivery is route feasibility rather than enhanced analgesic kinetics. Consequently, SL clonidine should be viewed primarily as a practical alternative route when swallowing or gastrointestinal absorption is unreliable, rather than a strategy for rapid analgesia.

By contrast, dexmedetomidine has a validated SL platform through an FDA-approved orally dissolving film formulation (IGALMI) for acute agitation [117]. The FDA label provides robust pharmacokinetic support for transmucosal delivery, reporting absolute bioavailability ~72% via SL (82% buccal), with plasma drug detection generally within ~5–20 min, a time to peak concentration (T_{max}) ~2 h, and terminal half-life ~2.8 h. Notably, early systemic exposure may occur within minutes, but peak concentrations occur later, suggesting that clinical effects may precede T_{max} while the maximal pharmacodynamic effect may not be immediate.

Similar to SL clonidine, direct evidence for pain-specific outcomes with SL dexmedetomidine remains limited. One early study reported improved pain intensity among patients with chronic low back pain receiving the SL formulation [118]. However, randomized agitation trials and FDA labeling establish its pharmacokinetic and safety profile, supporting its potential as a noninvasive opioid-sparing adjunct in pain settings where anxiolysis and sympatholysis are beneficial (e.g., perioperative pain with delirium risk, opioid-sensitive patients, or pain phenotypes characterized by heightened sympathetic arousal) [119].

10.3 Safety Considerations

Adoption of SL α2-agonists in pain care must account for class-limiting adverse effects, including hypotension, bradycardia, sedation/somnolence, dizziness, and xerostomia [120]. In clinical studies of SL dexmedetomidine film, hypotension and clinically meaningful reductions in heart rate were observed [119]. The FDA label also notes dose-related QTc effects [117]. Furthermore, one recent case report described an 88-year-old patient with hypertension who experienced profound hypotension after receiving SL dexmedetomidine for agitation [121]. These physiologic liabilities necessitate careful patient selection and monitoring, particularly in older adults, hypovolemic patients, those with conduction disease, or individuals receiving other bradycardic or sedating agents, such as beta-blockers, benzodiazepines, and gabapentinoids. Although α2-agonists generally preserve respiratory drive compared with opioids and benzodiazepines, clinically relevant additive sedation may occur when combined with opioids and other CNS depressants [120]. Overall, SL α2-agonists represent a potentially useful noninvasive adjunct platform. Currently, SL clonidine is best positioned as a feasibility-driven route substitution, while dexmedetomidine SL film represents the clearest proof-of-concept for scalable transmucosal α2-agonist delivery and a candidate for further pain-specific investigation.

For SL medications, clinical considerations include patient compliance, correct administration technique, and the properties of the drug. Sublingual delivery is ideal for situations requiring rapid analgesia or when oral intake is

compromised; however, it is not universally applicable. Research continues to explore novel formulations and permeation enhancers to optimize this route.

11 Nonsteroidal Anti-inflammatory Drugs

11.1 Pharmacology and Pharmacokinetics

Nonsteroidal anti-inflammatory drugs (NSAIDs) are of the most widely used and studied nonopioid analgesics, particularly for pain with an inflammatory component. Their effects are mediated primarily through inhibition of cyclooxygenase enzymes (COX-1 and COX-2), which decreases downstream prostaglandin synthesis [122, 123]. Because prostaglandins help drive inflammation and make pain receptors more sensitive, NSAIDs are useful for inflammatory pain, including postoperative, dental, musculoskeletal, menstrual, arthritis-related, and renal colic pain [122, 123]. By contrast to opioids, NSAIDs do not function through opioid receptor activation and thus do not cause respiratory depression or euphoria. Ultimately, this makes them important components of multimodal and opioid-sparing pain regimens [124].

The rationale for SL NSAID administration is slightly different compared with that of highly lipophilic opioids. For SL NSAIDs, the priority may not be rapid systemic exposure, but rather a practical solution when swallowing or gastrointestinal absorption is unreliable. Sublingual delivery may be useful in patients with nausea, vomiting, dysphagia, perioperative fasting requirements, or poor tolerance of oral medications [125]. However, this route is not necessarily more advantageous for every NSAID. Transmucosal absorption depends on drug-specific properties, including lipophilicity, ionization, molecular size, and formulation design [125]. As a result, SL NSAID delivery is best viewed as formulation-dependent rather than a class-wide advantage.

11.2 Clinical Applications

Ketorolac and piroxicam are the NSAIDs most studied for SL use. Ketorolac is a potent NSAID used for short-term treatment of moderate-to-severe acute pain and is traditionally administered orally, intramuscularly, intravenously, or intranasally [126]. Galán-Herrera et al. compared two 30 mg SL ketorolac tromethamine tablet formulations in healthy adult volunteers with results supporting the feasibility of SL administration of the drug [127]. Piroxicam, a long-acting NSAID, has also been studied as a fast-dissolving SL formulation, particularly in dental, endodontic, oral surgery, and acute renal colic settings [128–132]. Most clinical evidence for SL NSAIDs comes from dental and oral surgery studies. In lower third molar extraction, SL ketorolac 10 mg four times daily and SL piroxicam 20 mg once daily provided similar postoperative pain control, with both groups reporting low pain scores [129]. In another study, piroxicam 20 mg showed broadly similar outcomes when comparing oral and SL administration [128]. More recent randomized data have suggested that a single preoperative dose of SL fast-dissolving piroxicam 20 mg may reduce postoperative pain after endodontic treatment [130]. Evidence outside dental pain is more limited, but SL ketorolac 0.5 mg/kg has shown similar pain reduction to SL tramadol 2 mg/kg in children with suspected fractures or dislocations [133]. Fast-dissolving SL piroxicam has also been studied in acute renal colic, where it was evaluated as a nonparenteral NSAID option for rapid analgesia [131, 132]. Overall, these studies suggest possible use in select acute inflammatory pain settings, although the evidence base remains small.

The main limitation of SL NSAID use is that the literature remains relatively narrow. Most available studies are small, procedure-specific, and concentrated in specific settings [128–131, 133]. There are limited data comparing SL NSAIDs with placebo, parenteral NSAIDs, opioids, or modern multimodal analgesic protocols. In addition, few NSAIDs are commercially available in SL formulations. Although the route is pharmacologically plausible, its broader clinical role remains incompletely defined.

11.3 Safety Considerations

Safety concerns are similar to those of systemic NSAIDs given by other routes. Sublingual administration may bypass part of the gastrointestinal absorption process, but it does not eliminate systemic NSAID toxicity. Important risks include gastrointestinal ulceration or bleeding, renal injury, fluid retention, hypertension, cardiovascular thrombotic events, and hypersensitivity reactions [134]. These risks are especially relevant in older adults and in patients with chronic kidney disease, cardiovascular disease, peptic ulcer disease, anticoagulant use, dehydration, or concurrent nephrotoxic medications [134]. As with other NSAID formulations, SL NSAIDs should be used at the lowest effective dose for the shortest appropriate duration [134].

Overall, SL NSAIDs remain a relatively underdeveloped but potentially useful nonopioid option for acute inflammatory pain. Their most realistic role is likely in short-term settings such as dental pain, postoperative pain, musculoskeletal trauma, and renal colic when oral administration is undesirable, but intravenous or intramuscular therapy is not necessary [128–133]. Future studies should clarify whether optimized SL NSAID formulations offer faster onset, better tolerability, improved patient satisfaction, or meaningful opioid-sparing effects compared with standard oral and parenteral NSAID regimens.

12 Conclusions

This review highlights the evolving role of SL analgesics in modern pain management, emphasizing that their clinical utility is largely determined by drug-specific pharmacokinetics, formulation characteristics, and patient-specific factors. From a clinical perspective, the SL route may be particularly valuable in scenarios where oral administration is not feasible and can provide a noninvasive alternative to parenteral administration in both inpatient and outpatient settings.

Across currently available and emerging opioid and nonopioid therapies, evidence suggests potential utility in a range of pain conditions, including neuropathic, musculoskeletal, inflammatory, cancer-related, mucosal, and procedural pain (Table). However, the strength of evidence varies substantially across agents and disease states, and several applications remain investigational or supported by limited comparative clinical data. Accordingly, the primary goal of this review was to synthesize the pharmacologic principles, pharmacokinetic properties, therapeutic applications, and safety considerations of SL analgesics rather than provide an exhaustive disease-specific review of pain management.

Safety considerations remain particularly important for potent opioid formulations, and careful patient selection, dosing, and monitoring are essential. Future research should focus on optimizing formulation technologies to improve bioavailability and reduce interpatient variability, while large, well-designed randomized controlled trials are needed to better define efficacy across different pain conditions and clinical settings (Fig. 1). Comparative studies evaluating SL agents against alternative routes of administration may further clarify their role within multimodal and individualized pain management strategies.

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Declarations

Conflict of interest Sarang S. Koushik, Karina Gritsenko, Dhanesh D. Binda, Isaac S. Daybell, Nathan S. Hill, Jagun Raghavan, Emmanuella Borukh, Bradford B. Smith, Molly Kraus, and Naum Shaparin declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

Authors' contributions Sarang S. Koushik, Karina Gritsenko, Bradford B. Smith, Molly Kraus, and Naum Shaparin were responsible for conception and design and contributed to critical revision of the manuscript for important intellectual content. Dhanesh D. Binda, Isaac S. Daybell, Nathan S. Hill, Jagun Raghavan, and Emmanuella Borukh were responsible for literature review, data synthesis, and drafting the manuscript. All authors have read and approved the final version of the manuscript.

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References

1. Narita M, Imai S, Itou Y, Yajima Y, Suzuki T. Possible involvement of mu1-opioid receptors in the fentanyl- or morphine-induced antinociception at supraspinal and spinal sites. Life Sci. 2002;70(20):2341–54. https://doi.org/10.1016/s0024-3205(01)01550-8.
2. Weinberg DS, Inturrisi CE, Reidenberg B, et al. Sublingual absorption of selected opioid analgesics. Clin Pharmacol Ther. 1988;44(3):335–42. https://doi.org/10.1038/clpt.1988.159.
3. Lötsch J, Walter C, Parnham MJ, Oertel BG, Geisslinger G. Pharmacokinetics of non-intravenous formulations of fentanyl. Clin Pharmacokinet. 2013;52(1):23–36. https://doi.org/10.1007/s40262-012-0016-7.
4. Darwish M, Kirby M, Jiang JG, Tracewell W, Robertson P. Bioequivalence following buccal and sublingual placement of fentanyl buccal tablet 400 microg in healthy subjects. Clin Drug Investig. 2008;28(1):1–7. https://doi.org/10.2165/00044011-200828010-00001.
5. Rauck R, Reynolds L, Geach J, et al. Efficacy and safety of fentanyl sublingual spray for the treatment of breakthrough cancer pain: a randomized, double-blind, placebo-controlled study. Curr Med Res Opin. 2012;28(5):859–70. https://doi.org/10.1185/03007995.2012.683111.
6. Zecca E, Brunelli C, Centurioni F, Manzoni A, Pigni A, Caraceni A. Fentanyl sublingual tablets versus subcutaneous morphine for the management of severe cancer pain episodes in patients receiving opioid treatment: a double-blind, randomized, noninferiority trial. J Clin Oncol. 2017;35(7):759–65. https://doi.org/10.1200/JCO.2016.69.9504.
7. Reisfield GM, Wilson GR. Rational use of sublingual opioids in palliative medicine. J Palliat Med. 2007;10(2):465–75. https://doi.org/10.1089/jpm.2006.0150.
8. Chwieduk CM, McKeage K. Fentanyl sublingual: in breakthrough pain in opioid-tolerant adults with cancer. Drugs. 2010;70(17):2281–8. https://doi.org/10.2165/11200910-000000000-00000.
9. Guastella V, Delorme J, Chenaf C, Authier N. The prevalence of off-label prescribing of transmucosal immediate-release fentanyl

in France. J Pain Symptom Manag. 2022;63(6):980–7. https://doi.org/10.1016/j.jpainsymman.2022.02.016.
10. Cánovas-Martínez L, Carceller-Ruiz JJ, Díaz-Parada P, et al. Efficacy and safety of sublingual fentanyl tablets for the management of breakthrough pain in patients with chronic musculoskeletal pain with neuropathic component: multicenter prospective study. Clin Drug Investig. 2015;35(3):169–77. https://doi.org/10.1007/s40261-015-0268-8.
11. Fihlman M, Karru E, Varpe P, et al. Feasibility of a transmucosal sublingual fentanyl tablet as a procedural pain treatment in colonoscopy patients: a prospective placebo-controlled randomized study. Sci Rep. 2020;10(1):20897. https://doi.org/10.1038/s41598-020-78002-0.
12. Rauck RL, Oh DA, Singla N, et al. Pharmacokinetics and safety of fentanyl sublingual spray and fentanyl citrate intravenous: a multiple ascending dose study in opioid-naïve healthy volunteers. Curr Med Res Opin. 2017;33(11):1921–33. https://doi.org/10.1080/03007995.2017.1371681.
13. ACMT Position Statement. Safety issues regarding prescription fentanyl products. J Med Toxicol. 2016;12(2):211–2. https://doi.org/10.1007/s13181-016-0535-y.
14. Rollman JE, Heyward J, Olson L, Lurie P, Sharfstein J, Alexander GC. Assessment of the FDA risk evaluation and mitigation strategy for transmucosal immediate-release fentanyl products. JAMA. 2019;321(7):676–85. https://doi.org/10.1001/jama.2019.0235.
15. Research C for DE and. Transmucosal immediate-release fentanyl (TIRF) medicines. *FDA*. Published online September 19, 2024. https://www.fda.gov/drugs/information-drug-class/transmucosal-immediate-release-fentanyl-tirf-medicines. Accessed 17 May 2026.
16. Virk MS, Arttamangkul S, Birdsong WT, Williams JT. Buprenorphine is a weak partial agonist that inhibits opioid receptor desensitization. J Neurosci. 2009;29(22):7341–8. https://doi.org/10.1523/JNEUROSCI.3723-08.2009.
17. Dahan A, Yassen A, Bijl H, et al. Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. Br J Anaesth. 2005;94(6):825–34. https://doi.org/10.1093/bja/aei145.
18. Dahan A, Yassen A, Romberg R, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. Br J Anaesth. 2006;96(5):627–32. https://doi.org/10.1093/bja/ael051.
19. Elkader A, Sproule B. Buprenorphine: clinical pharmacokinetics in the treatment of opioid dependence. Clin Pharmacokinet. 2005;44(7):661–80. https://doi.org/10.2165/00003088-200544070-00001.
20. Lim SCB, Schug S, Krishnarajah J. The pharmacokinetics and local tolerability of a novel sublingual formulation of buprenorphine. Pain Med. 2019;20(1):143–52. https://doi.org/10.1093/pm/pnx321.
21. Cote J, Montgomery L. Sublingual buprenorphine as an analgesic in chronic pain: a systematic review. Pain Med. 2014;15(7):1171–8. https://doi.org/10.1111/pme.12386.
22. Mendelson J, Upton RA, Everhart ET, Jacob P, Jones RT. Bioavailability of sublingual buprenorphine. J Clin Pharmacol. 1997;37(1):31–7. https://doi.org/10.1177/009127009703700106.
23. Nair AS, Dudhedia U, Bodas PV, Rangaiah M, Borkar N. Efficacy and safety of sublingual buprenorphine in managing acute postoperative pain - a systematic review. J Anaesthesiol Clin Pharmacol. 2024;40(4):574–81. https://doi.org/10.4103/joacp.joacp_245_23.
24. Grass JA. Sufentanil: clinical use as postoperative analgesic--epidural/intrathecal route. J Pain Symptom Manag. 1992;7(5):271–86. https://doi.org/10.1016/0885-3924(92)90061-l.
25. Fisher DM, Chang P, Wada DR, Dahan A, Palmer PP. Pharmacokinetic properties of a sufentanil sublingual tablet intended to treat acute pain. Anesthesiology. 2018;128(5):943–52. https://doi.org/10.1097/ALN.0000000000002145.
26. van de Donk T, Ward S, Langford R, Dahan A. Pharmacokinetics and pharmacodynamics of sublingual sufentanil for postoperative pain management. Anaesthesia. 2018;73(2):231–7. https://doi.org/10.1111/anae.14132.
27. Willsie SK, Evashenk MA, Hamel LG, Hwang SS, Chiang YK, Palmer PP. Pharmacokinetic properties of single- and repeated-dose sufentanil sublingual tablets in healthy volunteers. Clin Ther. 2015;37(1):145–55. https://doi.org/10.1016/j.clinthera.2014.11.001.
28. Babazade R, Turan A. Pharmacokinetic and pharmacodynamic evaluation of sublingual sufentanil in the treatment of post-operative pain. Expert Opin Drug Metab Toxicol. 2016;12(2):217–24. https://doi.org/10.1517/17425255.2016.1134487.
29. Sacerdote P, Coluzzi F, Fanelli A. Sublingual sufentanil, a new opportunity for the improvement of postoperative pain management in Italy. Eur Rev Med Pharmacol Sci. 2016;20(7):1411–22.
30. Frampton JE. Sublingual sufentanil: a review in acute postoperative pain. Drugs. 2016;76(6):719–29. https://doi.org/10.1007/s40265-016-0571-6.
31. Deeks ED. Sufentanil 30 µg sublingual tablet: a review in acute pain. Clin Drug Investig. 2019;39(4):411–8. https://doi.org/10.1007/s40261-019-00772-x.
32. REMS Information for DSUVIA | Home. https://www.dsuviarems.com/. Accessed 17 May 2026.
33. Jove M, Griffin DW, Minkowitz HS, Ben-David B, Evashenk MA, Palmer PP. Sufentanil sublingual tablet system for the management of postoperative pain after knee or hip arthroplasty: a randomized, placebo-controlled study. Anesthesiology. 2015;123(2):434–43. https://doi.org/10.1097/ALN.0000000000000746.
34. Pogatzki-Zahn E, Kranke P, Winner J, et al. Real-world use of the sufentanil sublingual tablet system for patient-controlled management of acute postoperative pain: a prospective noninterventional study. Curr Med Res Opin. 2020;36(2):277–84. https://doi.org/10.1080/03007995.2019.1681133.
35. Lomangino I, Berni A, Lloret Madrid A, et al. Sublingual sufentanil in pain management after pulmonary resection: a randomized prospective study. Ann Thorac Surg. 2022;113(6):1867–72. https://doi.org/10.1016/j.athoracsur.2021.06.063.
36. Reardon CE, Kane-Gill SL, Smithburger PL, Dasta JF. Sufentanil sublingual tablet: a new option for acute pain management. Ann Pharmacother. 2019;53(12):1220–6. https://doi.org/10.1177/1060028019863144.
37. Miner JR, Melson TI, Leiman D, et al. Pooled phase III safety analysis of sufentanil sublingual tablets for short-term treatment of moderate-to-severe acute pain. Pain Manag. 2019;9(3):259–71. https://doi.org/10.2217/pmt-2018-0090.
38. Oh SK, Lee IO, Lim BG, et al. Comparison of the analgesic effect of sufentanil versus fentanyl in intravenous patient-controlled analgesia after total laparoscopic hysterectomy: a randomized, double-blind, prospective study. Int J Med Sci. 2019;16(11):1439–46. https://doi.org/10.7150/ijms.34656.
39. Guyette FX, Chaudhary P, Vincent LE, et al. A randomized controlled trial of sublingual sufentanil in early management of pain in trauma. Anesth Analg. 2025;141(1):172–80. https://doi.org/10.1213/ANE.0000000000007384.
40. Inturrisi CE. Clinical pharmacology of opioids for pain. Clin J Pain. 2002;18(4 Suppl):S3-13. https://doi.org/10.1097/00002508-200207001-00002.
41. Listos J, Łupina M, Talarek S, Mazur A, Orzelska-Górka J, Kotlińska J. The mechanisms involved in morphine addiction: an overview. Int J Mol Sci. 2019;20(17):4302. https://doi.org/10.3390/ijms20174302.

42. Mazák K, Noszál B, Hosztafi S. Advances in the physicochemical profiling of opioid compounds of therapeutic interest. ChemistryOpen. 2019;8(7):879–87. https://doi.org/10.1002/open.201900115.
43. Roy SD, Flynn GL. Solubility behavior of narcotic analgesics in aqueous media: solubilities and dissociation constants of morphine, fentanyl, and sufentanil. Pharm Res. 1989;6(2):147–51. https://doi.org/10.1023/a:1015932610010.
44. Davis T, Miser AW, Loprinzi CL, et al. Comparative morphine pharmacokinetics following sublingual, intramuscular, and oral administration in patients with cancer. Hosp J. 1993;9(1):85–90. https://doi.org/10.1080/0742-969x.1993.11882756.
45. Dyal BW, Powell-Roach KL, Robison J, Campbell B, Yoon SL, Wilkie DJ. Sublingual versus swallowed morphine: a comparison. Cancer Nurs. 2021;44(1):E13–22. https://doi.org/10.1097/NCC.0000000000000784.
46. Hydromorphone: Uses, Interactions, Mechanism of Action | DrugBank. https://go.drugbank.com/drugs/DB00327. Accessed 17 May 2026.
47. Kestenbaum MG, Vilches AO, Messersmith S, et al. Alternative routes to oral opioid administration in palliative care: a review and clinical summary. Pain Med. 2014;15(7):1129–53. https://doi.org/10.1111/pme.12464.
48. Sarhill N, Walsh D, Nelson KA. Hydromorphone: pharmacology and clinical applications in cancer patients. Support Care Cancer. 2001;9(2):84–96. https://doi.org/10.1007/s005200000183.
49. Liu L, Xu M, Wang J, Hu Y, Huang Z. Research progress of hydromorphone in clinical application. Physiol Res. 2025;74(1):41–8. https://doi.org/10.33549/physiolres.935354.
50. Haumann J, Geurts JW, van Kuijk SMJ, Kremer B, Joosten EA, van den Beuken-van Everdingen MHJ. Methadone is superior to fentanyl in treating neuropathic pain in patients with head-and-neck cancer. Eur J Cancer. 2016;65:121–9. https://doi.org/10.1016/j.ejca.2016.06.025.
51. Deng M, Chen SR, Pan HL. Presynaptic NMDA receptors control nociceptive transmission at the spinal cord level in neuropathic pain. Cell Mol Life Sci. 2019;76(10):1889–99. https://doi.org/10.1007/s00018-019-03047-y.
52. Fredheim OMS, Moksnes K, Borchgrevink PC, Kaasa S, Dale O. Clinical pharmacology of methadone for pain. Acta Anaesthesiol Scand. 2008;52(7):879–89. https://doi.org/10.1111/j.1399-6576.2008.01597.x.
53. Cruciani RA, Sekine R, Homel P, et al. Measurement of QTc in patients receiving chronic methadone therapy. J Pain Symptom Manag. 2005;29(4):385–91. https://doi.org/10.1016/j.jpainsymman.2004.06.012.
54. Fonseca F, Marti-Almor J, Pastor A, et al. Prevalence of long QTc interval in methadone maintenance patients. Drug Alcohol Depend. 2009;99(1–3):327–32. https://doi.org/10.1016/j.drugalcdep.2008.06.018.
55. Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MCP. QTc interval screening in methadone treatment. Ann Intern Med. 2009;150(6):387–95. https://doi.org/10.7326/0003-4819-150-6-200903170-00103.
56. Hagen NA, Moulin DE, Brasher PM, et al. A formal feasibility study of sublingual methadone for breakthrough cancer pain. Palliat Med. 2010;24(7):696–706. https://doi.org/10.1177/0269216310375999.
57. Spaner D. Effectiveness of the buccal mucosa route for methadone administration at the end of life. J Palliat Med. 2014;17(11):1262–5. https://doi.org/10.1089/jpm.2013.0522.
58. Gupta A, Duckles B, Giordano J. Use of sublingual methadone for treating pain of chemotherapy-induced oral mucositis. J Opioid Manag. 2010;6(1):67–9. https://doi.org/10.5055/jom.2010.0007.
59. Peltoniemi MA, Hagelberg NM, Olkkola KT, Saari TI. Ketamine: a review of clinical pharmacokinetics and pharmacodynamics in anesthesia and pain therapy. Clin Pharmacokinet. 2016;55(9):1059–77. https://doi.org/10.1007/s40262-016-0383-6.
60. Orser BA, Pennefather PS, MacDonald JF. Multiple mechanisms of ketamine blockade of N-methyl-D-aspartate receptors. Anesthesiology. 1997;86(4):903–17. https://doi.org/10.1097/00000542-199704000-00021.
61. Sinner B, Graf BM. Ketamine. Handb Exp Pharmacol. 2008;182:313–33. https://doi.org/10.1007/978-3-540-74806-9_15.
62. Rolan P, Lim S, Sunderland V, Liu Y, Molnar V. The absolute bioavailability of racemic ketamine from a novel sublingual formulation. Br J Clin Pharmacol. 2014;77(6):1011–6. https://doi.org/10.1111/bcp.12264.
63. Peltoniemi MA, Saari TI, Hagelberg NM, et al. Exposure to oral S-ketamine is unaffected by itraconazole but greatly increased by ticlopidine. Clin Pharmacol Ther. 2011;90(2):296–302. https://doi.org/10.1038/clpt.2011.140.
64. Noppers I, Olofsen E, Niesters M, et al. Effect of rifampicin on S-ketamine and S-norketamine plasma concentrations in healthy volunteers after intravenous S-ketamine administration. Anesthesiology. 2011;114(6):1435–45. https://doi.org/10.1097/ALN.0b013e318218a881.
65. Maudlin B, Gibson SB, Aggarwal A. Long-term safety and efficacy of sublingual ketamine troches/lozenges in chronic non-malignant pain management. Intern Med J. 2022;52(9):1538–43. https://doi.org/10.1111/imj.15404.
66. Johnson D, Feng L, Johnson C. Retrospective review of the efficacy for sublingual ketamine in the treatment of chronic low back pain defined by a cause and central functional pain symptom focused clinical model. Disabil Rehabil. 2024;46(10):2117–24. https://doi.org/10.1080/09638288.2023.2218652.
67. Zekry O, Gibson SB, Aggarwal A. Subanesthetic, subcutaneous ketamine infusion therapy in the treatment of chronic nonmalignant pain. J Pain Palliat Care Pharmacother. 2016;30(2):91–8. https://doi.org/10.3109/15360288.2016.1161690.
68. Lee YC, Zhao E, Lee KKH, et al. Sublingual ketamine as breakthrough analgesia in patients with advanced cancer-a feasibility randomised controlled repeated cross-over trial. J Pain Palliat Care Pharmacother. 2025;39(4):454–67. https://doi.org/10.1080/15360288.2025.2531008.
69. Chong CC, Schug SA. Efficacy and tolerability of oral compared with sublingual ketamine lozenges as rescue analgesics in adults for acute pain: the OSKet trial. Clin Drug Investig. 2021;41(9):817–23. https://doi.org/10.1007/s40261-021-01066-x.
70. Feder A, Costi S, Rutter SB, et al. A randomized controlled trial of repeated ketamine administration for chronic posttraumatic stress disorder. Am J Psychiatry. 2021;178(2):193–202. https://doi.org/10.1176/appi.ajp.2020.20050596.
71. Hietamies TM, McInnes LA, Klise AJ, et al. The effects of ketamine on symptoms of depression and anxiety in real-world care settings: a retrospective controlled analysis. J Affect Disord. 2023;335:484–92. https://doi.org/10.1016/j.jad.2023.04.141.
72. Brinck EC, Tiippana E, Heesen M, et al. Perioperative intravenous ketamine for acute postoperative pain in adults. Cochrane Database Syst Rev. 2018;12(12):CD012033. https://doi.org/10.1002/14651858.CD012033.pub4.
73. Ketamine: A Review of an Established Yet Often Underappreciated Medication. Anesthesia Patient Safety Foundation. https://www.apsf.org/article/ketamine-a-review-of-an-established-yet-often-underappreciated-medication/. Accessed 17 May 2026.
74. Schwenk ES, Viscusi ER, Buvanendran A, et al. Consensus guidelines on the use of intravenous ketamine infusions for

acute pain management from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med. 2018;43(5):456–66. https://doi.org/10.1097/AAP.0000000000000806.
75. Bell RF. Ketamine for chronic noncancer pain: concerns regarding toxicity. Curr Opin Support Palliat Care. 2012;6(2):183–7. https://doi.org/10.1097/SPC.0b013e328352812c.
76. Aviram J, Samuelly-Leichtag G. Efficacy of cannabis-based medicines for pain management: a systematic review and meta-analysis of randomized controlled trials. Pain Physician. 2017;20(6):E755–96.
77. Blebea NM, Pricopie AI, Vlad RA, Hancu G. Phytocannabinoids: exploring pharmacological profiles and their impact on therapeutical use. Int J Mol Sci. 2024;25(8):4204. https://doi.org/10.3390/ijms25084204.
78. Pagano C, Navarra G, Coppola L, Avilia G, Bifulco M, Laezza C. Cannabinoids: therapeutic use in clinical practice. Int J Mol Sci. 2022;23(6):3344. https://doi.org/10.3390/ijms23063344.
79. Martinez Naya N, Kelly J, Corna G, Golino M, Abbate A, Toldo S. Molecular and cellular mechanisms of action of cannabidiol. Molecules. 2023;28(16):5980. https://doi.org/10.3390/molecules28165980.
80. McPartland JM, Duncan M, Di Marzo V, Pertwee RG. Are cannabidiol and Δ(9) -tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review. Br J Pharmacol. 2015;172(3):737–53. https://doi.org/10.1111/bph.12944.
81. Castillo-Arellano J, Canseco-Alba A, Cutler SJ, León F. The polypharmacological effects of cannabidiol. Molecules. 2023;28(7):3271. https://doi.org/10.3390/molecules28073271.
82. Mlost J, Bryk M, Starowicz K. Cannabidiol for pain treatment: focus on pharmacology and mechanism of action. Int J Mol Sci. 2020;21(22):8870. https://doi.org/10.3390/ijms21228870.
83. Howlett AC, Abood ME. CB1 and CB2 receptor pharmacology. Adv Pharmacol. 2017;80:169–206. https://doi.org/10.1016/bs.apha.2017.03.007.
84. Mamballn A. The cannabinoids mechanism of action: an overview. 2023;6(Suppl. 2):109-113.
85. Hua T, Li X, Wu L, et al. Activation and signaling mechanism revealed by cannabinoid receptor-Gi complex structures. Cell. 2020;180(4):655-665.e18. https://doi.org/10.1016/j.cell.2020.01.008.
86. Kopustinskiene DM, Masteikova R, Lazauskas R, Bernatoniene J. *Cannabis sativa* L. bioactive compounds and their protective role in oxidative stress and inflammation. Antioxidants (Basel). 2022;11(4):660. https://doi.org/10.3390/antiox11040660.
87. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. Br J Pharmacol. 2008;153(2):199–215. https://doi.org/10.1038/sj.bjp.0707442.
88. de Almeida DL, Devi LA. Diversity of molecular targets and signaling pathways for CBD. Pharmacol Res Perspect. 2020;8(6):e00682. https://doi.org/10.1002/prp2.682.
89. Laprairie RB, Bagher AM, Kelly MEM, Denovan-Wright EM. Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. Br J Pharmacol. 2015;172(20):4790–805. https://doi.org/10.1111/bph.13250.
90. Hosseini A, McLachlan AJ, Lickliter JD. A phase I trial of the safety, tolerability and pharmacokinetics of cannabidiol administered as single-dose oil solution and single and multiple doses of a sublingual wafer in healthy volunteers. Br J Clin Pharmacol. 2021;87(4):2070–7. https://doi.org/10.1111/bcp.14617.
91. Lacerda M, Carona A, Castanheira S, Falcão A, Bicker J, Fortuna A. Pharmacokinetics of non-psychotropic phytocannabinoids. Pharmaceutics. 2025;17(2):236. https://doi.org/10.3390/pharmaceutics17020236.
92. Yau GTY, Tai W, Arnold JC, Chan HK, Kwok PCL. Cannabidiol for the treatment of brain disorders: therapeutic potential and routes of administration. Pharm Res. 2023;40(5):1087–114. https://doi.org/10.1007/s11095-023-03469-1.
93. Tarlovski S, Bar Kadmon A, Goldberg E, Segal D, Gavish D, Stepensky D. Comparative pharmacokinetic assessment of innovative sublingual, rectal and vaporizer cannabis products versus approved cannabis products in healthy volunteers. Cannabis Cannabinoid Res. 2025;10(2):e289–98. https://doi.org/10.1089/can.2023.0229.
94. Johnson DA, Funnell MP, Heaney LM, et al. Cannabidiol oil ingested as sublingual drops or within gelatin capsules shows similar pharmacokinetic profiles in healthy males. Cannabis Cannabinoid Res. 2024;9(5):e1423–32. https://doi.org/10.1089/can.2023.0117.
95. O'Sullivan SE, Jensen SS, Kolli AR, Nikolajsen GN, Bruun HZ, Hoeng J. Strategies to improve cannabidiol bioavailability and drug delivery. Pharmaceuticals (Basel). 2024;17(2):244. https://doi.org/10.3390/ph17020244.
96. PRIME PubMed | Pharmacokinetics of Sativex® in Dogs: Towards a Potential Cannabinoid-Based Therapy for Canine Disorders. https://www.unboundmedicine.com/medline/citation/32054131/Pharmacokinetics_of_Sativex®_in_Dogs:_Towards_a_Potential_Cannabinoid_Based_Therapy_for_Canine_Disorders_. Accessed 17 May 2026.
97. Mannila J, Järvinen T, Järvinen K, Jarho P. Precipitation complexation method produces cannabidiol/beta-cyclodextrin inclusion complex suitable for sublingual administration of cannabidiol. J Pharm Sci. 2007;96(2):312–9. https://doi.org/10.1002/jps.20766.
98. Mannila J, Järvinen T, Järvinen K, Tarvainen M, Jarho P. Effects of RM-beta-CD on sublingual bioavailability of Delta9-tetrahydrocannabinol in rabbits. Eur J Pharm Sci. 2005;26(1):71–7. https://doi.org/10.1016/j.ejps.2005.04.020.
99. Mannila J, Järvinen T, Järvinen K, Tervonen J, Jarho P. Sublingual administration of Delta9-tetrahydrocannabinol/beta-cyclodextrin complex increases the bioavailability of Delta9-tetrahydrocannabinol in rabbits. Life Sci. 2006;78(17):1911–4. https://doi.org/10.1016/j.lfs.2005.08.025.
100. McDonagh MS, Morasco BJ, Wagner J, et al. Cannabis-based products for chronic pain : a systematic review. Ann Intern Med. 2022;175(8):1143–53. https://doi.org/10.7326/M21-4520.
101. Johnson BW, Strand NH, Raynak JC, et al. Cannabinoids in chronic pain management: a review of the history, efficacy, applications, and risks. Biomedicines. 2025;13(3):530. https://doi.org/10.3390/biomedicines13030530.
102. Kawka M, Erridge S, Holvey C, et al. Clinical outcome data of first cohort of chronic pain patients treated with cannabis-based sublingual oils in the United Kingdom: analysis from the UK Medical Cannabis Registry. J Clin Pharmacol. 2021;61(12):1545–54. https://doi.org/10.1002/jcph.1961.
103. Tait J, Erridge S, Holvey C, et al. Clinical outcome data of chronic pain patients treated with cannabis-based oils and dried flower from the UK Medical Cannabis Registry. Expert Rev Neurother. 2023;23(4):413–23. https://doi.org/10.1080/14737175.2023.2195551.
104. Überall MA. A review of scientific evidence for THC:CBD oromucosal spray (Nabiximols) in the management of chronic pain. J Pain Res. 2020;13:399–410. https://doi.org/10.2147/JPR.S240011.
105. Ueberall MA, Essner U, Mueller-Schwefe GH. Effectiveness and tolerability of THC:CBD oromucosal spray as add-on measure in patients with severe chronic pain: analysis of 12-week open-label

real-world data provided by the German Pain e-Registry. J Pain Res. 2019;12:1577–604. https://doi.org/10.2147/JPR.S192174.
106. Portenoy RK, Ganae-Motan ED, Allende S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain. 2012;13(5):438–49. https://doi.org/10.1016/j.jpain.2012.01.003.
107. Lichtman AH, Lux EA, McQuade R, et al. Results of a double-blind, randomized, placebo-controlled study of nabiximols oromucosal spray as an adjunctive therapy in advanced cancer patients with chronic uncontrolled pain. J Pain Symptom Manag. 2018;55(2):179-188.e1. https://doi.org/10.1016/j.jpainsymman.2017.09.001.
108. Robinson D, Ritter S, Yassin M. Comparing sublingual and inhaled cannabis therapies for low back pain: an observational open-label study. Rambam Maimonides Med J. 2022;13(4):e0026. https://doi.org/10.5041/RMMJ.10485.
109. Botea MO, Andereggen L, Urman RD, Luedi MM, Romero CS. Cannabinoids for acute pain management: approaches and rationale. Curr Pain Headache Rep. 2024;28(7):681–9. https://doi.org/10.1007/s11916-024-01252-4.
110. González Cárdenas VH, Valdivieso Díaz M, Mateus Almeciga CF, et al. Cannabinoids for acute postoperative pain management: a systematic review and meta-analysis of clinical trials. Eur J Pain. 2025;29(3):e4790. https://doi.org/10.1002/ejp.4790.
111. Stevens AJ, Higgins MD. A systematic review of the analgesic efficacy of cannabinoid medications in the management of acute pain. Acta Anaesthesiol Scand. 2017;61(3):268–80. https://doi.org/10.1111/aas.12851.
112. Abdallah FW, Hussain N, Weaver T, Brull R. Analgesic efficacy of cannabinoids for acute pain management after surgery: a systematic review and meta-analysis. Reg Anesth Pain Med. 2020;45(7):509–19. https://doi.org/10.1136/rapm-2020-101340.
113. Sun Y, Yao Y, Li Y, Deng W. Dexmedetomidine for opioid-sparing postoperative analgesia: a systematic review and meta-analysis. BMC Anesthesiol. 2026;26:103. https://doi.org/10.1186/s12871-025-03606-w.
114. Rao S, Rajan N. Dexmedetomidine as an adjunct for regional anesthetic nerve blocks. Curr Pain Headache Rep. 2021;25(2):8. https://doi.org/10.1007/s11916-020-00926-z.
115. Amna S, Øhlenschlaeger T, Saedder EA, Sigaard JV, Bergmann TK. Review of clinical pharmacokinetics and pharmacodynamics of clonidine as an adjunct to opioids in palliative care. Basic Clin Pharmacol Toxicol. 2024;134(4):485–97. https://doi.org/10.1111/bcpt.13979.
116. Cunningham FE, Baughman VL, Peters J, Laurito CE. Comparative pharmacokinetics of oral versus sublingual clonidine. J Clin Anesth. 1994;6(5):430–3. https://doi.org/10.1016/s0952-8180(05)80018-2.
117. U.S. Food and Drug Administration. IGALMI (dexmedetomidine) sublingual film [prescribing information]. Published online April 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215390s000lbl.pdf. Accessed 18 Jan 2026.
118. Webster L, Freyer A, Rodzvilla J, Mack R, Reeves R. An evaluation of the impact of opioid use on the analgesic effects of REC1100 in chronic low back patients. J Pain. 2011;12(4):P46. https://doi.org/10.1016/j.jpain.2011.02.185.
119. Preskorn SH, Zeller S, Citrome L, et al. Effect of sublingual dexmedetomidine vs placebo on acute agitation associated with bipolar disorder: a randomized clinical trial. JAMA. 2022;327(8):727–36. https://doi.org/10.1001/jama.2022.0799.
120. Weerink MAS, Struys MMRF, Hannivoort LN, Barends CRM, Absalom AR, Colin P. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. Clin Pharmacokinet. 2017;56(8):893–913. https://doi.org/10.1007/s40262-017-0507-7.
121. Coralic Z, Allai M, Hwang C, Michaels B, Takamoto P. Severe hypotension following sublingual dexmedetomidine administration in an elderly patient. Am J Health Syst Pharm. 2025. https://doi.org/10.1093/ajhp/zxaf335.
122. Vane JR, Botting RM. Mechanism of action of nonsteroidal anti-inflammatory drugs. Am J Med. 1998;104(3A):2S-8S. https://doi.org/10.1016/s0002-9343(97)00203-9. (**discussion 21S-22S**).
123. Cashman JN. The mechanisms of action of NSAIDs in analgesia. Drugs. 1996;52(Suppl 5):13–23. https://doi.org/10.2165/00003495-199600525-00004.
124. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain. 2016;17(2):131–57. https://doi.org/10.1016/j.jpain.2015.12.008.
125. Hua S. Advances in nanoparticulate drug delivery approaches for sublingual and buccal administration. Front Pharmacol. 2019;10:1328. https://doi.org/10.3389/fphar.2019.01328.
126. DailyMed - KETOROLAC TROMETHAMINE tablet, film coated. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=688f5dec-a6db-43c6-a1f8-5df99d08d395. Accessed 21 May 2026.
127. Galán-Herrera JF, Poo JL, Maya-Barrios JA, et al. Bioavailability of two sublingual formulations of ketorolac tromethamine 30 mg: a randomized, open-label, single-dose, two-period crossover comparison in healthy Mexican adult volunteers. Clin Ther. 2008;30(9):1667–74. https://doi.org/10.1016/j.clinthera.2008.09.011.
128. Trindade PaK, Giglio FPM, Colombini-Ishikiriama BL, et al. Comparison of oral versus sublingual piroxicam during postoperative pain management after lower third molar extraction. Int J Oral Maxillofac Surg. 2011;40(3):292–7. https://doi.org/10.1016/j.ijom.2010.10.026.
129. Trindade PAK, Giglio FPM, Colombini-Ishikiriama BL, et al. Sublingual ketorolac and sublingual piroxicam are equally effective for postoperative pain, trismus, and swelling management in lower third molar removal. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;114(1):27–34. https://doi.org/10.1016/j.tripleo.2011.05.027.
130. Mohamed AF, El-Asfouri HA, Amin SAW. Effect of sublingual fast-dissolving piroxicam premedication on postoperative pain experience in mandibular molars with non-vital pulp: a randomized double-blind controlled trial. Head Face Med. 2024;20(1):52. https://doi.org/10.1186/s13005-024-00453-x.
131. Altay B, Horasanli K, Sarica K, Tanriverdi O, Kendirci M, Miroglu C. Double-blind, placebo-controlled, randomized clinical trial of sublingual or intramuscular piroxicam in the treatment of renal colic. A comparative study. Urol Int. 2007;79(1):73–5. https://doi.org/10.1159/000102918.
132. Supervía A, Pedro-Botet J, Nogués X, et al. Piroxicam fast-dissolving dosage form vs diclofenac sodium in the treatment of acute renal colic: a double-blind controlled trial. Br J Urol. 1998;81(1):27–30.
133. Neri E, Maestro A, Minen F, et al. Sublingual ketorolac versus sublingual tramadol for moderate to severe post-traumatic bone pain in children: a double-blind, randomised, controlled trial. Arch Dis Child. 2013;98(9):721–4. https://doi.org/10.1136/archdischild-2012-303527.
134. Medication Guide for Non-Steroidal Anti-Inflammatory Drugs. FDA-approved medication guide. Published online 2010. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020938s020,021530s008MedGuide.pdf