Present and Future of Pharmacological Management for Acute Moderate-to-Severe Postoperative, Traumatic, or Musculoskeletal Pain in Europe: A Narrative Review

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ABSTRACT

Acute moderate-to-severe pain is common after surgery, trauma, or musculoskeletal injury, but its management remains suboptimal. Current single-agent treatments are limited by safety concerns, narrow therapeutic windows, and abuse potential, leaving substantial unmet needs. Here, we aimed to review guidelines for the management of acute moderate-to-severe post-surgical, trauma-related, or musculoskeletal pain in adults and discuss existing and potential future analgesics in this setting. We searched PubMed to identify relevant guidelines and existing analgesics for acute pain. To identify compounds in development, we searched ClinicalTrials.gov and the European Union Clinical Trials Register. Guidelines universally recognize the limitations of single-agent analgesics (particularly those with a single mechanism of action [MoA]) and recommend a multimodal approach as an established standard for acute pain. The benefit–risk profiles of traditional treatments, including paracetamol (acetaminophen), nonsteroidal anti-inflammatory drugs, selective cyclooxygenase-2 inhibitors, and opioids, can be improved by combining agents targeting different pain pathways. In multimodal approaches, lower doses of constituent agents can be used to achieve the same or superior analgesic effects relative to the individual agents. In some cases, novel formulations and co-crystal technology offer enhanced physicochemical and pharmacokinetic properties over individual agents. Lastly, initiatives to increase patient awareness and education around pain management may improve treatment satisfaction and quality of life, and hasten recovery. In conclusion, management of acute moderate-to-severe pain remains inadequate. Multimodal analgesics may offer advantages over traditional single-agent treatments (that often have a single MoA) for acute moderate-to-severe post-surgical, trauma-related, or musculoskeletal pain in adults. Multimodal analgesics, combined with patient education initiatives and non-pharmacological measures, when necessary, offer promise in addressing unmet needs in this setting.

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Key Summary Points
Management of acute moderate-to-severe pain in Europe is suboptimal despite the availability of a range of analgesic therapy options.
There is an unmet need for treatments with improved safety, wider therapeutic windows, and reduced abuse potential, with respect to current single-agent/single mode of action treatment options.
Novel multimodal analgesics may address these unmet needs, with the potential for enhanced efficacy at lower doses of constituent agents compared with single-agent analgesics.
Combined with patient education initiatives surrounding pain management, treatment approaches incorporating novel multimodal analgesics and non-pharmacological measures, where appropriate, offer the potential to improve the management of acute moderate-to-severe pain in post-surgical, trauma-related, or musculoskeletal pain in Europe.

INTRODUCTION

Acute pain due to illness, trauma, or musculoskeletal injury affects millions of people each year [1, 2]. Patients often report acute pain of moderate-to-severe intensity after surgery or following discharge from emergency departments [3–6]. Effective pain control facilitates recovery and allows patients to return to activities of daily living faster [7, 8]. Conversely, inadequate treatment has negative consequences for patients, healthcare systems, and society, including increased costs of care and progression to chronic pain [9–12]. Despite this, the management of acute moderate-to-severe pain remains suboptimal across treatment settings [5, 6, 13, 14].

Several factors may underlie suboptimal treatment of acute moderate-to-severe pain. Although a wide range of analgesic drugs are available [2, 5]—many having been in clinical use for decades—their utilization can be limited by safety concerns [15–17]. Analgesics with a single mechanism of action (MoA) have a ceiling effect, and doses needed to achieve analgesia in monotherapy may be associated with dose-limiting toxicities [18]. By contrast, a multimodal approach to treating acute moderate-to-severe pain recognizes its multifaceted nature [7, 18, 19] and may improve outcomes and quality of life while avoiding pain chronification. Furthermore, multimodal analgesia can target multiple inflammatory pathways that have a key role in pain physiology [20], and allow for varied pain management approaches suited to different procedures [21, 22]. Additionally, the pressure to discharge patients soon after surgery, with "day-case" or ambulatory surgeries and procedures having become increasingly popular [23], has led to requirements for noninvasive methods of pain management that can be self-administered.

Here, we aimed to review the management of acute moderate-to-severe pain in the settings of post-surgical (including ambulatory surgery), trauma-related, and musculoskeletal pain, focusing on multimodal analgesia. The review focuses on these three settings, as they share similar unmet needs, and a similar approach to pain management would be followed based on the general principles of the World Health Organization analgesic ladder [24]. We review the guidelines and literature on currently used treatments and those recently available or in development. We provide an overview of the European treatment guideline recommendations, describe key characteristics of non-injectable treatments and novel or in-development multimodal treatments, and discuss how these may address the unmet needs in this setting. As such, this review provides insights into the current management strategies and future directions in moderate-to-severe pain management, to inform clinicians, researchers, and patients.

Search Strategies

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.

For this narrative review article concerning acute moderate-to-severe post-surgical, trauma-related, or musculoskeletal pain in adults, a nonsystematic literature search was performed to identify English language records during the date range 01/01/2010–15/06/2023. Guidelines for the management of acute pain were identified through a literature search using the PubMed database and the following search string: (guidelines) AND (acute) AND (pain) AND (analgesic OR post-operative pain OR traumatic pain OR musculoskeletal pain). We then conducted an online search using Google advanced search and the following search string: guidelines, pain, acute, management, Europe, emergency, OR post-operative, OR trauma, OR musculoskeletal, OR analgesic, OR care "acute pain"; (excluded terms) – "mild -pain", – "rheumatoid -arthritis", –osteoarthritis, – "ankylosing -spondylitis". For the review of existing analgesic agents in this setting, the following search string was used in PubMed and Google Advanced Search: (NSAIDs [OR non-steroidal anti-inflammatory drugs]/COX-2 inhibitors/opioids) AND (pain) AND (acute) AND (moderate OR severe) AND ((post-surgical) OR (ambulatory) OR (musculoskeletal) OR (trauma-related)) NOT (arthritis, rheumatoid, osteoarthritis). For compounds in development, we searched ClinicalTrials.gov using the terms "acute pain", "moderate", and "severe", and the EU Clinical Trials Register using the following search string with "adult" selected as the age range: "acute pain" AND "moderate" OR "severe" AND ((post-surgical) OR (ambulatory) OR (musculoskeletal) OR (trauma)).

Search results were manually reviewed to identify references for inclusion, based on their relevance to the topic of management of acute moderate-to-severe pain, in the opinion of the authors. In the case of compounds in development, their European Medicines Agency summaries of product characteristics were reviewed to confirm relevance. Additional references could be included from the bibliographies of articles identified in the primary search or based on the knowledge of the authors.

Regional anesthesia techniques—although commonly used in clinical practice during the immediate postoperative period, to reduce both pain and opioid requirements—were considered outside the scope of this review.

TREATMENT GUIDELINES

Several European guidelines provide recommendations for the management of acute moderate-to-severe pain in adults and almost universally recommend a multimodal analgesic approach as an established standard. A summary of key guidelines is provided in Table 1. The European Society for Emergency Medicine developed guidelines for the management of acute pain in an emergency setting [2], recommending a multimodal analgesic approach using agents with different MoAs (including both opioids and non-opioids) if insufficient analgesia is achieved with one class alone. The European Society of Regional Anaesthesia and Pain Therapy's postoperative pain management initiative provides evidence-based recommendations for pain management in the perioperative period on a procedure-specific basis [21], including the recommendation for a multimodal analgesic for cardiac surgery via median sternotomy, based on results of a systematic review [25].

A multimodal analgesic approach is established and recommended clinical practice in the UK [26]. The UK's National Institute for Health and Care Excellence's evidence review for managing acute postoperative pain underpins their guidelines on perioperative care in adults [26]. A recent consensus statement on the preoperative management of patients with chronic moderate-to-severe shoulder pain also emphasized the use of multimodal analgesia to help improve outcomes after surgery [27]. Non-steroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX-2) inhibitors are recommended for short-term management of postoperative acute pain, while oral opioids are recommended for moderate-to-severe pain [26]. The British Society of Physical and Rehabilitation Medicine's musculoskeletal rehabilitation guidance recommends NSAIDs

Table 1 Summary of key recommendations from relevant treatment guidelines for acute moderate-to-severe pain

Guideline	Key recommendations for management of acute pain
European Society for Emergency Medicine (EUSEM) European Pain Initiative (EPI) [2]	Moderate pain: Paracetamol AND NSAID/COX-2 inhibitor (ibuprofen, naproxen, diclofenac, ketorolac, celecoxib) AND metamizole AND opioid (codeine phosphate or tramadol) Severe pain: First line: Opioid (morphine or fentanyl or sufentanil) Second line: Paracetamol (intravenous) AND an opioid (codeine phosphate or tramadol or oxycodone) Third line: Ketamine
European Society of Regional Anaesthesia and Pain Therapy's (ESRA) procedure-specific postoperative pain management (PROSPECT) [99]	Tonsillectomy Pre- and intraoperative: Combination of paracetamol and NSAIDs Postoperative: Combination of paracetamol and NSAIDs Opioids as rescue treatment
National Institute for Health and Care Excellence's (NICE) evidence review for managing acute postoperative pain [26]	Multimodal analgesic approach NSAIDs/COX-2 inhibitors: Oral ibuprofen if no contraindications Opioids for moderate-to-severe pain only
British Society of Physical and Rehabilitation Medicine's (BSRM) musculoskeletal rehabilitation guidance [28]	Foot and lower limb care: Combination of analgesics with an NSAID Acute spinal pain: Analgesics and/or NSAIDs
World Health Organization's (WHO) analgesic ladder[a] [30]	Step 1: Non-opioid ± adjuvants Step 2: Opioid for mild-to-moderate pain (i.e., codeine) ± non-opioid ± adjuvants Step 3: Opioid for moderate-to-severe pain ± non-opioid ± adjuvants
Revision to World Health Organization's (WHO) analgesic ladder [24, 31]	Step 1 (mild pain): Non-opioids (NSAIDs) Step 2 (moderate pain): Weak opioids Step 3 (severe and persistent pain): Strong opioids, or methadone, via oral administration or transdermal patch NSAIDs (± adjuvants) at each step

COX-2 cyclooxygenase-2, *NSAID* nonsteroidal anti-inflammatory drug

Intravenous recommendations have been omitted as these are considered outside the scope of this review

[a]Originally developed to provide guidance on the principles of cancer pain management

in combination with non-specified analgesics for several musculoskeletal conditions, including acute lower back pain, and podiatry [28].

On an international level, the World Health Organization's analgesic ladder in its original form provides guidance on the principles of

cancer pain management [29, 30], and a later proposed extension encompasses guidance for acute pain, including use of multimodal analgesia [31].

Overall, there is synergy between the current guidelines relevant to Europe on the treatment and management of acute moderate-to-severe pain, particularly in the recommendation for multimodal analgesia.

PHARMACOLOGICAL APPROACHES CURRENTLY USED TO TREAT ACUTE MODERATE-TO-SEVERE PAIN IN EUROPE

Nonselective NSAIDs

NSAIDs are generally less effective during the first 10 min after administration than stronger analgesics such as opioids, although they have an equivalent analgesic effect within 20–30 min [14]. The efficacy of NSAIDs for acute mild-to-moderate pain is well established [32–34]; however, there is variation in the extent of pain relief with single, nonselective NSAIDs. The number of patients needed to treat for at least 50% maximum pain relief versus placebo over 4–6 h ranges from 2.0 to 8.3 in postoperative pain, with some of the available data potentially susceptible to publication bias [34].

Nonselective NSAIDs are associated with a risk of serious gastrointestinal toxicity, which varies between agents [16, 35, 36]: low-risk agents include ibuprofen; intermediate-risk agents include indomethacin, diclofenac, ketoprofen, and naproxen; and high-risk agents include piroxicam, azapropazone, and ketorolac [35, 36]. NSAID-related gastrointestinal toxicity appears to be influenced by the dose and duration of therapy [36].

All oral nonselective NSAIDs can also increase the risk of serious cardiovascular events [35, 36] and lead to renal toxicity in up to 5% of patients [37], meaning that they are not suitable in patients with significant kidney disease and impairment [2]. Although NSAIDs are widely used [36, 38], limitations include healthcare

professionals' concerns regarding their benefit–risk profile [39, 40] and lack of evidence for additional benefit in combining different agents [36].

Selective COX-2 Inhibitors

Selective COX-2 inhibitors are anti-inflammatory, analgesic, and antipyretic, while protecting the gastrointestinal mucosa [41]. Single doses of the oral COX-2 inhibitors celecoxib and etoricoxib are efficacious in the treatment of acute postoperative pain [34].

Meta-analyses have demonstrated the improved gastrointestinal safety profile of COX-2 inhibitors, such as celecoxib, versus nonselective NSAIDs [42–45]. However, COX-2 inhibitors are associated with an increased risk of cardiovascular events, depending on the dose and duration of therapy [46]. Celecoxib may have an improved safety profile relative to other COX-2 inhibitors [46]. The risk of cardiovascular toxicity is reportedly no higher for celecoxib than for nonselective NSAIDs when administered at commonly used daily doses of approximately 200 mg [15, 47]. However, celecoxib is not approved for the treatment of acute pain in Europe [2], and rofecoxib and valdecoxib have been withdrawn from the market worldwide due to an increased risk of cardiovascular events and serious skin reactions [48–51].

Opioids

Opioids are highly effective analgesics for acute moderate-to-severe pain and the cornerstone of treatment for severe pain in the emergency trauma [52] and perioperative settings [53]. However, opioids have numerous side effects, particularly in opioid-naive patients, including nausea, vomiting, sedation, respiratory depression, itching, and anaphylactic reactions [2], as well as other safety concerns, including cardiovascular events such as hypotension, orthostasis, syncope, and bradycardia, associated with acute use [54]. Consequently, healthcare staff organization and availability of appropriate medical technology are important considerations for their use [52].

There are some differences in the characteristics of various opioid agents, including those termed "weak" or "strong" opioids. Drugs with at least two MoAs, including those targeting non-reward pathways, such as tramadol, may have a lower potential for misuse than reward-pathway drugs with a single MoA, such as oxycodone or hydrocodone. This is because lower doses of these mixed-mechanism agents may be required to achieve an equivalent analgesic effect compared with drugs that act only on opioid receptors [55]. Although abuse-deterrent opioid formulations have been developed, some have led to safety concerns [56].

Historic and current reluctance to administer opioids is well documented [52, 57–59]. Doses of opioids administered post-surgery are reported to be lower in Europe than in the USA [60]. This seeming reluctance to administer opioids may be understandable in light of the opioid crisis in the USA [61], which may have already started in some European countries (the UK, Ireland, Norway, and Sweden), albeit on a much smaller scale [61–63]. There is now a trend for "weaker" opioids (e.g., tramadol) being administered in Europe as they are thought to have a lower risk of overdose than "stronger" opioids [60, 61].

Combination Therapies Incorporating Paracetamol or Nonselective NSAIDs

Combining therapies that target multiple pain pathways can improve benefit–risk profiles, partly because effective analgesia may be achieved with lower doses of individual constituents compared with single-agent doses [19, 57]. In addition to simply administering two or more individual agents concomitantly, as occurs ad hoc in clinical practice, fixed-dose combinations (FDCs) are available. FDCs have been reported to provide greater and faster pain relief than equivalent doses of either agent alone, as seen with paracetamol (acetaminophen) and ibuprofen in patients with moderate-to-severe postoperative dental pain [64, 65]. Other examples of the FDC approach have involved the opioid tramadol combined with either the NSAID dexketoprofen [66] or paracetamol [67]. Of these two combinations, tramadol plus dexketoprofen was superior

at relieving acute moderate-to-severe postoperative pain for patients who underwent surgical removal of an impacted lower third molar in the DAVID study [68].

FDCs involving tramadol require reduced doses of constituent agents, thus potentially providing an opioid-sparing effect [64]. This, in turn, may alleviate opioid-associated toxicities and reduce the potential for misuse. Furthermore, combinations that exclude nonselective NSAIDs may be beneficial when gastrointestinal side effects are of particular concern [64]. FDCs may also provide greater convenience in terms of dosing, as well as reduced pill burden [69], which, in turn, may increase patient adherence. Limitations of combination therapies include an increased chance of drug–drug interactions [69, 70] and the inability to alter any unfavorable characteristics of individual agents by reducing their dose [64, 70].

Summary of Pharmacological Treatments Currently Used in Europe

Although there are several classes of analgesic therapies available, including others not covered here due to space restrictions (e.g., dexamethasone, the anticonvulsants gabapentin and pregabalin, and the local anesthetic/NSAID FDC bupivacaine/meloxicam), each is associated with unmet needs for the treatment of acute moderate-to-severe pain, including toxicities, ceiling effects, administration challenges, and potential for misuse (Table 2). Advances in analgesia in this setting are evolving through the development of both new agents and new approaches to multimodal analgesia.

NOVEL TREATMENTS AND DRUGS IN DEVELOPMENT FOR ACUTE MODERATE-TO-SEVERE PAIN

Several new non-injectable therapies for treating acute moderate-to-severe pain are in development or, in some cases, close to approval or have recently been approved (Table 3). Many are multimodal or have characteristics that might help

Table 2 Summary of key characteristics and unmet needs relating to pharmacological approaches currently used for acute moderate-to-severe pain in Europe

Drug class	Drug names	Key characteristics	Unmet needs in the acute pain treatment landscape
Nonselective NSAIDs	Acemetacin	Analgesic effect starts relatively soon after the first dose is administered [33]	Onset of efficacy is slower than with stronger analgesics (e.g., opioids) [14]
	Fenbufen		
	Ibuprofen (± caffeine)	Widely used for mild-to-moderate pain, but there are concerns with the benefit–risk profile in some patients (those with a high risk of cardiovascular events) [36]	Associated with serious gastrointestinal toxicity [16], particularly in older patients [35, 36]
	Ibuprofen/paracetamol		Increased risk of cardiovascular events [35, 36]
	Indomethacin		Unsuitable for patients with renal insufficiency [36]
	Ketoprofen		
	Mefenamic acid	Efficacy for mild-to-moderate pain is well established [32–34]	Ceiling effect due to benefit–risk ratio and lack of additional benefit from combining NSAIDs [36, 39, 40]
	Meloxicam		
	Naproxen	Most NSAIDs are given orally [100], which is a convenient route of administration for various settings of acute pain management	Limited efficacy in trauma setting, particularly in transport to the emergency department [52]
	Sulindac		
	Tenoxicam		
	Tiaprofenic acid		

Table 2 continued

Drug class	Drug names	Key characteristics	Unmet needs in the acute pain treatment landscape
COX-2 inhibitors	Celecoxib Etoricoxib Nimesulide	Prevent inflammation and exert analgesic and antipyretic effects [41] Some efficacy in the treatment of acute postoperative pain [34] Improved gastrointestinal safety profile compared with nonselective NSAIDs [42–45] Typically administered orally	Increased risk of cardiovascular events, dependent on the dose and duration of therapy; for example, celecoxib 400 or 800 mg/day for 3 years increased the risk of myocardial infarction and stroke by 2.5- and 3.4-fold, respectively, vs. placebo [46] Moderate daily doses of celecoxib (mean 209 ± 37 mg/day) do not appear to be associated with an increased risk of cardiovascular events compared with the nonselective NSAIDs ibuprofen and naproxen [47], despite previously widely held beliefs that naproxen may be associated with better cardiovascular outcomes than other NSAIDs [101] Two COX-2 inhibitors (rofecoxib and valdecoxib) have been removed from the market worldwide, rofecoxib due to a high risk of myocardial infarction and stroke, and valdecoxib owing to serious skin reactions and increased risk of cardiovascular events in those who have undergone bypass surgery [48–51]

Table 2 continued

Drug class	Drug names	Key characteristics	Unmet needs in the acute pain treatment landscape
Opioids	Buprenorphine Codeine Dihydrocodeine Hydromorphone Oxycodone (± naloxone) Pethidine Sufentanil Tapentadol Tramadol	Highly effective for severe acute pain; cornerstone treatments for severe pain in emergency trauma and perioperative settings [52, 53] Opioids administered parentally have a more rapid onset of efficacy than those given orally, but oral opioids can be as effective at equianalgesic doses [102] "Weak" opioids, e.g., tramadol, have a lower risk of tolerance, dependency, and respiratory depression than classic opioids due to milder action on opioid receptors [103] Orally administered opioids are considered favorable for acute pain owing to titration difficulties associated with transdermal opioids (e.g., fentanyl and buprenorphine patches) and the subsequent risk of overdose in opioid-naive patients [104]	Some evidence suggests that opioids have only similar or reduced efficacy compared with NSAIDs for certain acute pain conditions (surgical dental pain, kidney stones, and lower back pain) [105] Associated with serious cardiovascular events (including hypotension, orthostasis, syncope, and bradycardia), acute dyspeptic syndrome (with nausea and vomiting), and increased risk of respiratory failure [52–54, 106] Specific agents should be avoided in patients with a history of seizures (tramadol) and used with caution in patients with severe renal impairment and in older patients (tramadol and tapentadol) [104] High potential for tolerance and dependence with strong opioids, and a reluctance for healthcare practitioners to administer opioids [52] Ceiling effect as higher doses confer greater risk of longer-term dependence than lower doses [53, 107] Risk of adverse events (e.g., respiratory depression) means patients must be monitored for long periods, especially in trauma setting [52]

Table 2 continued

Drug class	Drug names	Key characteristics	Unmet needs in the acute pain treatment landscape
Combination therapies incorporating paracetamol or nonselective NSAIDs	Paracetamol + NSAIDs **Opioid + paracetamol** Codeine/paracetamol Tramadol/paracetamol Oxycodone/paracetamol **Opioid + NSAID** Ibuprofen/codeine Tramadol/dexketoprofen Tramadol/diclofenac	Combining agents that target different pathways allows lower doses to be used than if the individual drugs were used alone, potentially reducing possible safety and tolerability problems [67] Combinations of agents may be opioid-sparing [64], e.g., tramadol and paracetamol fixed-dose combinations require a lower fixed dose of tramadol than if tramadol is used alone	Combination therapies can lead to an increased risk of drug–drug interactions, which may in turn increase the likelihood of adverse events [64, 69, 70, 108] The individual doses of fixed-dose combination analgesics cannot be adjusted to meet patients' specific needs [64, 70]

COX-2 cyclooxygenase-2, *NSAID* nonsteroidal anti-inflammatory drug

to address current unmet needs in this setting. Multimodal agents include drugs targeting non-reward pathways, such as diclofenac in the case of tramadol/diclofenac FDC [71], dexketoprofen in tramadol/dexketoprofen [68], and celecoxib in co-crystal of tramadol-celecoxib (CTC; see below [72]), and may have a lower potential for misuse than single MoA drugs acting on reward pathways. Furthermore, compared with treatment involving multiple single MoA drugs, multimodal agents in a FDC or co-crystal formulation offer a standardized approach where the pill burden can be lessened and the variability in drug ratios can be reduced.

Here, we review agents in order of development stage and/or approval status.

Co-Crystal of Tramadol-Celecoxib

CTC is a multimodal analgesic co-crystal of racemic tramadol hydrochloride and celecoxib that combines four MoAs targeting central and peripheral analgesic pathways (μ-opioid agonism, norepinephrine and serotonin reuptake inhibition, and COX-2 inhibition; Table 3) [73]. The approved CTC dose (200 mg twice daily) exposes patients to 176 mg/day of tramadol [73] (below the CDC-recommended morphine-milligram equivalent threshold for a relatively low-dose opioid) [74, 75]. The twice-daily oral dose potentially offers improved convenience over the four-times-daily tramadol dose. In contrast to FDCs, CTC's co-crystal technology modifies the physicochemical and pharmacokinetic properties of the constituent analgesics, which can hasten the onset of analgesia relative to either agent alone and potentially reduce the risk of adverse events associated with tramadol [73, 76].

CTC demonstrated superior analgesic efficacy compared with tramadol alone in randomized phase 3 trials of patients with acute moderate-to-severe pain following surgery [73, 76–78]. The efficacy of CTC was coupled with a safety profile that was similar to tramadol 50 mg four times daily and better than tramadol 100 mg four times daily, due to the lower total daily tramadol exposure (176 mg/day vs. 200–400 mg/day), and this would suggest a clinically relevant improved benefit–risk profile [73, 76–78]. CTC

Table 3 Summary of new or in-development treatment options for acute moderate-to-severe pain

Drug name	Drug type/MoA	Onset and duration of action	Pain intensity reduction/analgesic efficacy	Safety and tolerability	Ease of use	Development status
CTC (co-crystal of tramadol-celecoxib)	Racemic tramadol hydrochloride (a μ-opioid receptor agonist and an SNRI) and celecoxib (selective COX-2 inhibitor); CTC therefore exhibits four MoAs, targeting both central and peripheral analgesic pathways [73, 109]	Faster onset of analgesia compared with tramadol [77] Synchronized absorption and optimized bioavailability of tramadol and celecoxib (pharmacokinetic profiles of tramadol and celecoxib in CTC are modified by co-crystallization vs. single-entity reference products; celecoxib's absorption was faster while tramadol's absorption was slower, and tramadol's C_{max} was lower than when administered alone or concomitantly with celecoxib) [72, 109–112]	CTC 200 mg BID had superior efficacy to tramadol (50 mg QID) or celecoxib (100 mg BID) following bunionectomy with osteotomy ($n = 637$) [77] CTC 200 mg BID provided superior relief, vs. tramadol alone (100 mg QID), from moderate-to-severe pain up to 72 h after elective third molar extraction requiring bone removal [78] CTC 200 mg BID was non-inferior to tramadol (100 mg QID) following abdominal hysterectomy ($n = 1136$) [76] Lower rates of rescue medication use and lower cumulative/total opioid exposure with respect to comparators [76–78]	Safety profile consistent with that of the individual components, and no additive effects noted [73] CTC provides analgesia at lower daily or cumulative doses of tramadol; this tramadol-sparing effect results in the observation of fewer opioid-related adverse events vs. tramadol alone [73] Reduced levels of respiratory depression and lower potential for abuse or dependence with tramadol than with potent opioids [103, 113]; lower rate of gastrointestinal toxicity with celecoxib than with other NSAIDs, e.g., ibuprofen or naproxen [47]	Oral dosing every 12 h [79]	FDA-approved in 2021; phase 3 trials complete [73, 76–78] Approved in Spain for the short-term symptomatic treatment of acute moderate-to-severe somatic pain in adults [79]

Table 3 continued

Drug name	Drug type/MoA	Onset and duration of action	Pain intensity reduction/analgesic efficacy	Safety and tolerability	Ease of use	Development status
CL-108 (hydrocodone, paracetamol, promethazine)	Hydrocodone (7.5 mg): full opioid receptor agonist with relative selectivity for the μ-opioid receptor and no ceiling effect for analgesia [81]; paracetamol (325 mg): antinociceptive and antipyretic [114]; promethazine (12.5 mg): antiemetic [80, 81]	Not available	Significantly more effective analgesia than with ibuprofen over 24- and 48-h treatment periods following bunionectomy (n = 149) (based on patient pain intensity ratings) [80]. Reduction in pain intensity ≥ 30% in 51% of patients treated with CL-108 (20%) vs. placebo following surgical extraction of impacted molar teeth (n = 466) [81]	Adverse effects of hydrocodone include nausea and vomiting, CNS effects, and respiratory depression. Frequency of these adverse events correlates with plasma concentrations of the opioid [81]. CL-108 had superior prophylactic antiemetic efficacy compared with equivalent doses of conventional hydrocodone and paracetamol (~ 39% reduction in risk of moderate-to-severe nausea vs. hydrocodone/paracetamol) and no increase in moderate/severe drowsiness or dizziness compared with hydrocodone/paracetamol [81]	Oral dosing, self-dosed every 4–6 h as required for pain (maximum of six doses every 24 h [81])	Has been under development in the USA (brand name Hydexor™) for the relief of moderate-to-severe pain while preventing or reducing opioid-induced nausea and vomiting. To date, the FDA has rejected applications for approval due to concerns over prospectively identifying patients at risk of opioid-induced nausea and vomiting, and a lack of specific safety data in older patients, who have the highest risk of respiratory depression [82]

Table 3 continued

Drug name	Drug type/MoA	Onset and duration of action	Pain intensity reduction/analgesic efficacy	Safety and tolerability	Ease of use	Development status
Uniflash® paracetamol	Antinociceptive and antipyretic [85]	Rapid absorption through the oral mucosa and passage into the bloodstream (thus avoiding a hepatic first-pass effect) [85]	Not available	Reduced hepatic first-pass metabolism allows for a lower dose of paracetamol to be administered, limiting potential adverse events [85]	Single-dose oromucosal solution (125 mg; liquid stick-pack, pre-measured, ready-to-use). Can be taken without water [85]	Phase 3 trial (NCT04640376) of analgesic efficacy of a single dose of Uniflash paracetamol vs. 500 mg and 1000 mg of oral paracetamol for acute pain following tooth extraction (n = 407) was completed in November 2022, pending results
Nefopam hydrochloride and paracetamol FDC	Nefopam hydrochloride: non-opioid analgesic; paracetamol: antinociceptive and antipyretic [114, 115]	Not available	Not available	Not available	Oral FDC	Phase 3 trial (NCT04622735) in patients with acute moderate-to-severe pain following molar tooth extraction (n = 321) was completed in October 2022, pending results

Table 3 continued

Drug name	Drug type/MoA	Onset and duration of action	Pain intensity reduction/analgesic efficacy	Safety and tolerability	Ease of use	Development status
APSCTC	Not available	Not available	Not available	Not available	Oral dosing	Phase 3 trial (NCT04647435) in patients with acute pain following surgery for molar extraction is planned with ketorolac and tramadol as comparators

Table 3 continued

Drug name	Drug type/MoA	Onset and duration of action	Pain intensity reduction/analgesic efficacy	Safety and tolerability	Ease of use	Development status
JNJ-10450232 (NTM-006)	Antinociceptive and antipyretic [88]	Relatively slower onset of action with JNJ-10450232 1000 mg than with paracetamol 1000 mg in postoperative dental pain [88] Duration of action of JNJ-10450232 was sustained up to 24 h (superior to paracetamol ≥ 7 h after administration) [88]	Comparable efficacy of JNJ-10450232 1000 mg and paracetamol over 6 h in moderate-to-severe pain, and superior efficacy of JNJ-10450232 1000 mg over 12 and 24 h [88]	No severe hepatotoxicity in preclinical models [87] First-in-human studies observed no dose-limiting toxicities with single (50–6000 mg) or multiple (250–2500 mg BID) doses for 8 days [86] Most frequently reported adverse events after multiple doses were mild, reversible macular rash and generalized erythema [86] In a Phase 2 trial, there were no clinically important differences between JNJ-10450232, paracetamol, and placebo. Increased bilirubin level, potentially due to UGT1A1 inhibition and ingestion of blood during oral surgery, was reported in ≥ 5% of patients across treatment groups [88]	Oral dosing	Phase 2 trial (NCT02209181) of postoperative dental pain (n = 269) was completed in April 2015 [88]

Table 3 continued

Drug name	Drug type/MoA	Onset and duration of action	Pain intensity reduction/analgesic efficacy	Safety and tolerability	Ease of use	Development status
MR-107A-01	Non-opioid analgesic	Not available	MR-107A-01 10 mg or 15 mg QD or BID showed significant superiority over placebo in reducing pain intensity and ability to provide total pain relief (NCT04571515) Requirement for rescue medication significantly reduced with MR-107A-01 vs. placebo (NCT04571515)	Most commonly reported non-serious adverse events with MR-107A-01 vs. placebo were nausea (0–13% vs. 9.5%), headache (0–14% vs. 5%), and dizziness (0–9% vs. 0%) (NCT04571515)	Oral dosing	Phase 2 trial (NCT04571515) of pain post-dental surgery is complete (n = 114)
HR18042 (imrecoxib/tramadol)	Tramadol: opioid analgesic and an SNRI; imrecoxib: moderately selective COX-2 inhibitor [2, 116]	Not available	Not available	Not available	Multimodal tablet	In phase 2 development in China for the treatment of acute moderate-to-severe pain following surgery for tooth extraction (NCT04812860; NCT05470075)

Table 3 continued

Drug name	Drug type/MoA	Onset and duration of action	Pain intensity reduction/analgesic efficacy	Safety and tolerability	Ease of use	Development status
NTC-510 (buprenorphine–naloxone nanoparticle [NanoBUP™])	Buprenorphine: opioid analgesic; naloxone: opioid receptor antagonist [89]	Not available	Phase 1 studies have reported 60–70% relative bioavailability with NanoBUP compared with sublingual formulations [89]	Not available	Oral nanoparticle delivery system with an immediate-delivery capsule, which aims to mimic an immediate-release drug profile	Phase 1 studies were completed in 2009/2010 [89]. Phase 2 trial (NCT02161354) of pain following surgical extraction of molar teeth was terminated in 2017 (safety and efficacy did not warrant further dose escalation)

BID twice daily, C_{max} maximum plasma concentration, *CNS* central nervous system, *COX-2* cyclooxygenase-2, *FDA* US Food and Drug Administration, *FDC* fixed-dose combination, *MoA* mechanism of action, *NSAID* nonsteroidal anti-inflammatory drug, *QD* once daily, *QID* four times daily, *SNRI* serotonin/norepinephrine reuptake inhibitor

was approved by the US Food and Drug Administration in October 2021 (marketed under the brand name Seglentis®) and authorized in Spain in September 2023 for the management of acute moderate-to-severe somatic pain in adults [79].

CL-108 (Hydrocodone, Paracetamol, Promethazine)

CL-108 is a multimodal, first-in-class, single-tablet combination of the opioid hydrocodone (7.5 mg), paracetamol (325 mg), and rapid-release, low-dose antiemetic promethazine (12.5 mg) [80, 81]. CL-108 exerts an analgesic effect on acute postoperative pain [80, 81] and has superior prophylactic antiemetic efficacy compared with equivalent doses of conventional hydrocodone and paracetamol [81]. CL-108 has been under development in the USA (brand name Hydexor™) for the relief of moderate-to-severe pain while preventing or reducing opioid-induced nausea and vomiting, but approval has not been granted to date [82].

Uniflash® Paracetamol

This novel formulation of paracetamol comprises a single-dose solution that passes quickly into the bloodstream, thus mitigating metabolism-related reduction in efficacy and allowing administration of a lower dose [83–85]. Results are pending from a double-blind phase 3 trial of Uniflash paracetamol for acute pain following tooth extraction (NCT04640376; completed in November 2022).

Nefopam Hydrochloride and Paracetamol FDC

This non-opioid FDC consists of the rapid-acting oral analgesic nefopam (30 mg) and paracetamol (500 mg). The FDC was compared to the individual agents (single and multiple doses) in a randomized, double-blind, phase 3 trial of 321 patients with acute moderate-to-severe pain following molar extraction (NCT04622735; completed in October 2022 and pending results).

APSCTC

A phase 3 trial is planned to evaluate oral APSCTC compared with ketorolac or tramadol every 6 h for 3 days for the treatment of pain following surgery for molar extraction in approximately 396 patients (NCT04647435; estimated completion date: November 2024).

JNJ-10450232

JNJ-10450232 (NTM-006) is an oral formulation that is structurally similar to paracetamol and provides comparable analgesia [86, 87]. No dose-limiting toxicities were observed in a double-blind, placebo-controlled trial in healthy male volunteers, with mostly mild adverse events reported [86]. Efficacy has been demonstrated in a phase 2 trial of postoperative dental pain (NCT02209181) [88].

MR-107A-01

MR-107A-01 is an orally administered non-opioid analgesic under development for acute moderate-to-severe post-surgical dental pain. In a phase 2 trial (NCT04571515), different dose schedules of MR-107A-01 were superior to placebo in reducing pain intensity and providing total pain relief.

HR18042 (Imrecoxib/Tramadol)

HR18042 is a multimodal tablet consisting of tramadol and the moderately selective COX-2 inhibitor imrecoxib to provide synergistic analgesia while reducing opioid-related toxicity. The drug is in phase 2 development in China for acute moderate-to-severe pain following surgery for tooth extraction (NCT04812860; NCT05470075).

NTC-510 (Buprenorphine/Naloxone Nanoparticle)

NTC-510 (NanoBUP™) uses a nanoparticle delivery system with an immediate-delivery

capsule that aims to mimic an immediate-release drug profile. Phase 1 trials have been completed [89], but a phase 2 trial (NCT02161354) was terminated in 2017.

Summary of Novel Treatments and Drugs in Development for Acute Moderate-to-Severe Pain

The novel agents discussed here show promise in the management of acute moderate-to-severe pain, particularly with respect to increasing efficacy while balancing toxicities, which is the practitioner's primary concern. Thus, there is cause for optimism for improved patient care with respect to some of the more traditional analgesic treatment approaches used to date in Europe. However, with some exceptions (e.g., the recently approved CTC), many of these newer agents are still in the early stages of development, leaving many limitations and unmet needs related to current treatments unaddressed.

Future Directions

Current single-agent treatments are limited by several factors, including safety issues [15–17]; thus, their therapeutic indices are restricted by dose-limiting toxicities [18]. In addition, the use and avoidance of analgesics are driven by practitioner and patient preferences, as evidenced by the caution surrounding opioids [52, 57–59]. Patients with mild-to-moderate pain typically receive paracetamol and NSAIDs, while the more potent opioids are a mainstay for severe pain in the pre-hospital and emergency department settings [2]. There is a need to balance the desire to avoid an opioid crisis in Europe on the scale of that in the USA [60, 61, 90] with the provision of effective analgesia for individual patients. Multimodal agents that combine drugs with different MoAs to address the multifaceted nature of pain are a key focus. The multimodal approach offers the potential for enhanced efficacy at lower doses of constituent analgesics to limit adverse events and reduce delays in recovery and the potential for abuse [7]. Furthermore, the development of single pills containing multiple agents could alleviate the burden on patients taking multiple pills and reduce variability in drug ratios and combinations.

In addition to the development of novel multimodal analgesics, initiatives and resources are required to support optimal prescribing of analgesics. A good example is the Pain Alleviation Toolkit from the American Society of Anesthesiologists and American Academy of Orthopaedic Surgeons, which comprises a series of modules to help clinicians and patients understand the available approaches to pain management [91]. Other initiatives include a US multi-society organizational consensus process resulting in seven common guiding principles for the management of acute perioperative pain [92].

Involving patients in decision-making is crucial to optimize the management of acute pain. There is evidence to indicate that many patients with acute musculoskeletal pain prefer not to receive an opioid (or any analgesics) [93], which suggests that patient education and creating realistic expectations regarding pain are key areas for development [94]. In addition, non-pharmacological techniques are being increasingly used in combination with pharmaceutical agents in a multimodal approach to pain management, and can help alleviate patient fear, distress, and anxiety [2].

Alternative assessments to determine the efficacy of acute pain medication include measures of symptoms and functioning, such as the Multidimensional Symptom Index [95], and patient-reported outcomes that are more personalized, e.g., the "desire to receive more pain treatment" [96]. Others account for pain at rest and during activity, as well as patients' ability to self-manage pain, such as the core outcome sets defined for perioperative acute pain management [97]. These measures will ultimately provide a better indication of an individual's need for pain relief.

The above approaches may help to address the ongoing need to reduce opioid exposure after discharge from hospital, although further work is needed to increase awareness of the potential dangers of opioid misuse and provide a consensus on appropriate opioid-related pain management and care [98].

CONCLUSIONS

Despite the range of treatments available to date in Europe, the management of acute moderate-to-severe pain remains inadequate across treatment settings [9, 14]. Management may be improved with novel analgesics that have better benefit–risk profiles than existing treatments, including with respect to efficacy, tolerability, and abuse potential. There is a need for orally administered analgesics with an improved therapeutic window and rapid effects in the pre-hospital and hospital emergency settings. It is hoped that the development and availability of novel, multimodal analgesics, alongside initiatives such as those outlined above, will help to address the many unmet needs in the current management of acute moderate-to-severe post-surgical, trauma-related, or musculoskeletal pain.

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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. Eugene R. Viscusi reports consulting fees from ESTEVE Pharmaceuticals, Heron Therapeutics, Merck, Orion Pharma, Salix Pharmaceuticals, and Vertex Pharmaceuticals. Francisco Epelde, Luis Javier Roca Ruiz, and Eva Trillo-Calvo 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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