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REVIEW ARTICLE

Combination *vs.* single-drug nonprescription analgesics for acute pain management: A narrative review

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Combining nonprescription analgesics with different mechanisms of action has been proposed as a rational strategy to optimize the management of acute pain. This review assessed the efficacy and safety of nonprescription analgesics, including paracetamol (acetaminophen), metamizole and nonsteroidal anti-inflammatory drugs (NSAIDs) used in combination *vs.* monotherapy in acute pain conditions. A literature search identified 25 studies that compared oral paracetamol combined with a nonprescription NSAID (oral or topical) *vs.* either or both components alone in an acute pain condition or in an acute episode or exacerbation of a chronic pain condition. Combination therapy provided superior pain relief *vs.* monotherapy in the dental impaction pain model; potential dose-sparing and opioid-sparing effects were also evident. After endodontic surgery, combination therapy provided greater pain relief *vs.* either component alone following a single dose, but a difference was not apparent with multiple dosing, indicating a faster onset of action with combination therapy. Studies in acute musculoskeletal pain yielded mixed results. Studies in patients with headache included caffeine in addition to paracetamol/NSAIDs and showed that this combination provided faster and more effective pain relief *vs.* paracetamol or an NSAID alone. Across all settings, oral combination therapy with paracetamol/NSAIDs was well tolerated, with adverse event rates similar to or even lower than those observed with monotherapy. Findings of this narrative review support the use of combination therapy with paracetamol and an NSAID in the postsurgical setting but not in acute non–low-back musculoskeletal pain. Fixed-dose oral combinations of caffeine/paracetamol/NSAIDs provide efficacy-related advantages over paracetamol or NSAID monotherapy.

KEYWORDS
acute postoperative pain, analgesia, anti-inflammatory agents, drug combinations, musculoskeletal pain, nonsteroidal, paracetamol

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1 | INTRODUCTION

Acute pain is a common source of suffering with broad clinical and societal impact.[1] It often results from a specific event and is typically caused by direct tissue damage,[2] with pain lasting from a few days to up to 30 days.[1,3] Inadequate management of acute pain may have considerable consequences for patients, including reduced quality of life, impaired physical function, disrupted sleep and increased risk of developing chronic pain.[1,4] The clinical spectrum of acute pain is wide ranging and includes conditions such as headache, acute pharyngitis, musculoskeletal injury (e.g., strains and sprains), postoperative pain and dysmenorrhoea.[1,2] Depending on the type and severity of pain, patients may self-treat their pain or visit a healthcare provider.[1,5] A systematic review and meta-analysis of the prevalence of postoperative pain, based on pooled data from 27 studies, estimated that rates of moderate-to-severe pain ranged from 31% 1 day after discharge to 58% 1–2 weeks postdischarge.[6] Lost work productivity and postsurgical hospital readmission due to inadequately controlled acute pain contribute to a substantial socioeconomic burden.[4,7] Illustrating the ubiquity of acute pain, representative surveys in the USA, Germany, Russia and China found that approximately 1/2 to 2/3 of adults suffered from acute back pain in the preceding 6 months.[5] Treatment options for acute pain include nonpharmacological interventions (e.g., massage therapy, heat, nerve blocks, acupuncture, joint manipulation and transcutaneous electrical nerve stimulation) and prescription and nonprescription medications.[2,8,9] Nonprescription herbal products are also used to treat acute pain[10] but are beyond the scope of this review.

Analgesic options available without a prescription in at least some countries include paracetamol (**acetaminophen**), **metamizole** (dipyrone) and nonsteroidal anti-inflammatory drugs (NSAIDs), available as single- and multiple-entity products, including fixed-dose combinations (FDCs). NSAIDs act primarily by inhibiting cyclooxygenase (COX) enzymes **COX1** (constitutive) and **COX2** (induced by inflammatory stimuli) within inflamed or injured tissue, resulting in inhibition of the biosynthesis of thromboxanes and prostaglandins, depending on their selectivity; COX2 inhibition mediates anti-inflammatory effects of NSAIDs.[11–13] Immune-modulating effects of NSAIDs may also have beneficial impacts on inflammation and pain.[14] Whereas the activity of NSAIDs is predominantly peripheral, paracetamol is mainly a centrally acting agent.[15] In addition to inhibiting prostaglandin synthesis, paracetamol may affect the serotonergic system and other pain pathways.[12,16] Analgesic effects may also be mediated by the central actions of paracetamol metabolite N-acylphenolamine (AM404) as an uptake inhibitor of the endogenous cannabinoid **anandamide** and on **transient receptor potential vanilloid 1** and **cannabinoid 1** receptors.[16,17] Although paracetamol lacks the anti-inflammatory properties of NSAIDs, preclinical studies suggest that AM404 may reduce inflammatory pain.[16] Consequently, paracetamol is widely indicated for the treatment of mild-to-moderate acute pain or in combination with an opioid analgesic for severe acute pain.[18] Metamizole is believed to exert its analgesic effects via inhibition of COX2 and activation of endogenous opioid and cannabinoid pathways.[19] This drug was withdrawn from the market in several countries, including the USA, due to the risk of agranulocytosis, but it continues to be widely used on a prescription or nonprescription basis in several countries.[19,20]

Pain is multifactorial with a range of pathophysiological mechanisms, including nociceptive, neuropathic, inflammatory and ischaemic, all of which contribute to acute pain to some degree.[1] However, the predominant features of most cases of acute somatic pain are tissue damage and inflammation at the site of injury.[1] As a result, in situations where inflammation significantly contributes to pain, such as musculoskeletal injury, dental surgery and osteoarthritis, NSAIDs are often more effective than paracetamol alone due to their anti-inflammatory mechanisms described above.[21]

Despite the availability of different nonprescription analgesics, unmet needs in the management of acute pain remain. Many patients fail to achieve adequate control of acute pain, in part because ceiling effects and safety concerns (i.e., gastrointestinal side effects with NSAIDs; hepatic toxicity/potential for acute liver failure with paracetamol at higher than recommended doses) limit the ability to increase doses of analgesics indefinitely to achieve further pain relief.[2,22,23] Specific patient populations may have increased susceptibility to the adverse effects of NSAIDs (e.g., older patients, those taking concomitant medications such as anticoagulants or selective serotonin reuptake inhibitors that may increase bleeding risk, patients with *Helicobacter pylori* infection or a history of ulcer complications) or paracetamol (e.g., older patients, those with poor nutritional status, chronic liver disease or chronic alcohol use).[2,24–26] Poor adherence to product labels or a clinician's instructions may also contribute to inadequate pain control.[4,27–29]

Combining paracetamol and NSAIDs has been proposed as a rational strategy to optimize the management of acute pain. Given their differing mechanisms of action, it has been hypothesized that combining paracetamol and oral NSAIDs provides additional therapeutic benefit.[12,15] This approach may also have a dose-sparing effect, enabling use of lower dosages of one or both medications, which could minimize the risk of side effects.[15] Combination of paracetamol with a topical NSAID may also represent a rational treatment option for acute, localized pain.[30]

This narrative review summarizes published data on efficacy and safety of non-opioid combination nonprescription analgesics used in an outpatient setting, including FDCs, *vs.* monotherapy for the management of acute pain or acute exacerbations of chronic pain, to inform healthcare provider recommendations. We further identify areas for future research and provide an expert perspective regarding the use of non-opioid combination nonprescription analgesics in the primary care setting.

2 | METHODS

PubMed and Embase literature searches were performed to identify studies published from database inception up to 31 December 2023, in acute pain conditions comparing oral paracetamol in combination with a nonprescription NSAID (oral or topical) *vs.* either or both components

alone. Individual components alone could have been used at the same dose or at a higher dose than in combination therapy. The search strategy was limited to English-language articles. The primary search string was: pain (NSAID OR paracetamol OR acetaminophen OR ibuprofen or diclofenac) (combination OR combined OR addition OR adjunctive) ("over-the-counter" OR "over the counter" OR non-prescription OR nonprescription) (postoperative OR osteoarthritis OR dysmenorrhoea OR headache OR migraine OR musculoskeletal OR "sore throat" OR toothache OR dental OR earache OR vaccination OR immunization OR sprain OR strain OR injury OR back OR arthritis OR arthritic). To ensure that all relevant articles were identified, multiple other searches were conducted in PubMed that included these additional terms: aceclofenac, acetylsalicylic, dexketoprofen, dipyrone, flurbiprofen, ketoprofen, metamizole, naproxen, topical, oral, exacerbation, flare. Some but not all of these searches were limited to clinical trials. The specified list of NSAIDs included in the search terms may not be inclusive of all NSAIDs available without a prescription worldwide, but inclusion of the term NSAID should identify these. Abstracts of records resulting from the searches were screened for relevance, followed by assessment of the full-text articles.

Studies in patients with chronic pain conditions were included only if treatment was in the setting of an acute episode or exacerbation. Studies were excluded in which drugs of interest were administered using a route not available in a nonprescription setting or that were used in a preoperative or operative (nondental) setting or did not compare combination therapy with monotherapy using statistical methods (excepting studies in headache, given the paucity of data in this indication).

3 | RESULTS

3.1 | Evidence from clinical studies

The initial PubMed and Embase literature searches identified 176 and 201 articles, respectively. Additional searches in PubMed identified 786 articles. Of the 1163 articles, 50 were obtained based on abstract review; 25 studies (including 4 studies in headache reported as a pooled analysis[31]) describing use of combination nonprescription analgesics met the search criteria and are summarized below. All medications used in the studies were administered orally. Details of study designs and findings, organized by acute pain condition, are summarized in Table 1. No relevant studies were identified comparing monotherapy with combination therapy for the treatment of dysmenorrhoea, acute pharyngitis or earache.

3.2 | Postsurgical setting (extraction of third molars)

Nine studies (8 placebo-controlled and 1 double-dummy but without a placebo group) used the dental impaction pain model (DIPM) to compare the efficacy of combining paracetamol and NSAIDs *vs.* monotherapy, with all but 3 studies specifying that patients should have moderate-to-severe pain.[32–40] This model, which assesses postsurgical pain following extraction of third molars (wisdom teeth), is considered the gold standard for evaluating analgesics for the management of acute pain and can theoretically be applied to other acute pain conditions.[56] Six studies assessed paracetamol (250–1000 mg)/**ibuprofen** (100–400 mg) combinations,[32–37] while 2 studies examined paracetamol (500–1000 mg) in combination with **diclofenac** (50–100 mg),[38,39] and 1 study evaluated the combination of metamizole 1000 mg and ibuprofen 400 mg.[40]

Overall, studies using the DIPM found that combination therapy, with either an FDC or separate capsules/tablets, produced greater pain relief compared with monotherapy. In single-dose studies, combination therapy with paracetamol 500 mg/ibuprofen 250 mg provided significantly greater pain relief *vs.* ibuprofen 250 mg alone ($P < .008$),[37] and the combination of paracetamol 1000 mg/ibuprofen 400 mg provided significantly greater pain relief compared with either component alone (each, $P < .001$).[34] Higher-dose FDC (paracetamol 1000 mg/ibuprofen 400 mg) was more efficacious than lower-dose FDC (paracetamol 500 mg/ibuprofen 200 mg).[34] Similarly, the 3 multiple-dose studies comparing FDCs of paracetamol/ibuprofen with monotherapy using the same doses as in the FDCs found that combination therapy produced significantly greater pain relief than either drug alone.[32,35,36]

Combining paracetamol with ibuprofen can produce a dose-sparing effect. As demonstrated in 3 single-dose studies, paracetamol 500 mg/ibuprofen (200, 250 or 300 mg) provided similar pain relief as ibuprofen 400 mg,[33] and paracetamol 500 mg/ibuprofen 200 mg provided greater pain relief than paracetamol 1000 mg (but not ibuprofen 400 mg).[34] Furthermore, paracetamol 500 mg/ibuprofen 250 mg produced significantly greater pain relief ($P < .001$), faster time to pain relief ($P = .031$) and greater duration of pain relief ($P < .001$) compared with paracetamol 650 mg.[37]

Combination therapy may also reduce the requirement for rescue treatment. Supplemental oxycodone was required by significantly fewer patients receiving multiple doses of paracetamol 975 mg/ibuprofen 292.5 mg *vs.* either component alone ($P \leq .002$).[32] However, in another study there was no significant difference in rescue medication among patients receiving multiple doses of paracetamol 500 mg/ibuprofen 150 mg compared with monotherapy.[36] In 2 studies, 82–93% of patients receiving combination therapy responded *excellent*, *very good* or *good* 8 h after surgery in response to the question, "How do you rate the study medication?" compared with 47–84% for monotherapy.[34,35]

One study investigated whether combining paracetamol 1000 mg with diclofenac 100 mg enhanced the analgesic effect *vs.* either drug alone over 8 h following a single dose.[38] Combination therapy with paracetamol/diclofenac provided significantly greater pain relief compared with either drug alone ($P < .002$) and was also associated with both a significantly lower requirement for rescue medication ($P = .027$) and a significantly longer time to administration of rescue medication ($P < .05$). Additionally, patients rated combination therapy as superior to either agent alone ($P < .05$).

TABLE 1 Clinical trials comparing combination paracetamol (APAP)/NSAID therapy with monotherapy for management of acute pain.

First author date[ref]	Study design	Setting/patient population	Treatment groups (no. randomized)[a]	Summary of efficacy findings	Summary of safety findings
Postsurgical (extraction of third molars, wisdom teeth extraction)					
Daniels 2018[32]	Phase 3, double-blind, randomized, placebo-controlled, parallel-group trial	Patients aged 18–60 years with moderate-to-severe pain after surgical removal of ≥2 impacted third molars	FDC: APAP 975 mg/IBU 292.5 mg ($n = 110$) APAP 975 mg ($n = 111$) IBU 292.5 mg ($n = 112$) Placebo ($n = 75$) Q6h for 48 h	Combination therapy provided significantly greater pain relief than APAP or IBU alone over 48 h (all, $P < .001$) and within the first 6 h (all, $P \leq .001$) Onset of significant pain relief was significantly faster for combination therapy *vs*. APAP or IBU alone (all, $P < .05$) Percentage of patients with ≥50% reduction in pain was significantly greater with combination therapy (87.2%) *vs*. APAP (69.4%) or IBU (76.6%; all, $P < .05$) Supplemental therapy with oxycodone required by significantly fewer patients receiving combination therapy (23.9%) *vs*. APAP (53.2%) or IBU (43.2%; $P \leq .002$)	Rates of AEs lower with combination therapy (37.3%) *vs*. APAP (48.6%), IBU (39.3%) or placebo (50.7%), but there were no significant differences between treatment groups Most common AEs were nausea (APAP/IBU, 25.0%; APAP, 23.1%; IBU, 22.7%; placebo, 30.4%), vomiting (APAP/IBU, 13.9%; APAP, 18.7%; IBU, 9.1%; placebo, 11.6%) and headache (APAP/IBU, 13.9%; APAP, 11.0%; IBU, 13.6%; placebo, 11.6%) No AEs rated as probably or definitely related to study drug
Kellstein 2020[33]	Phase 2, double-blind, randomized, placebo-controlled, parallel-group trial	Patients aged 16–40 years with moderate-to-severe pain after surgical removal of ≥3 impacted third molars	FDC: APAP 500 mg/IBU 200 mg ($n = 90$) FDC: APAP 500 mg/IBU 250 mg ($n = 93$) APAP 500 mg/IBU 300 mg ($n = 89$) IBU 400 mg ($n = 92$) Placebo ($n = 30$) Single dose	Combination treatments provided similar pain relief *vs*. IBU 400 mg Trend observed toward faster onset of analgesia with combination therapy (especially APAP 500 mg + IBU 300 mg) *vs*. IBU 400 mg Time to treatment failure was not significantly different with combination therapies *vs*. IBU 400 mg	No significant differences between treatment groups in rates of AEs Most common AEs were nausea (APAP/IBU 200 mg, 24.4%; APAP/IBU 250 mg, 19.4%; APAP/IBU 300 mg, 18.0%; IBU 400 mg, 23.9%; placebo, 46.7%), vomiting (APAP/IBU 200 mg, 8.9%; APAP/IBU 250 mg, 11.8%), APAP/IBU 300 mg, 5.6%; IBU 400 mg, 15.2%; placebo, 23.3%) and dizziness (APAP/IBU 200 mg, 10.0%; APAP/IBU 250 mg, 6.5%), APAP/IBU 300 mg, 7.9%; IBU 400 mg, 7.6%; placebo, 10.0%) No treatment-related AEs
Mehlisch 2010a[34]	Double-blind, randomized, placebo-controlled, parallel-group, modified factorial study	Patients aged 16–40 years with moderate-to-severe pain after surgical removal of ≥3 impacted third molars	FDC: APAP 500 mg/IBU 200 mg ($n = 33$) FDC: APAP 1000 mg/IBU 400 mg ($n = 67$) APAP 1000 mg ($n = 34$) IBU 400 mg ($n = 69$) Placebo ($n = 31$) Single dose	Significantly greater pain relief with APAP 1000 mg/IBU 400 mg *vs*. APAP 500 mg/IBU 200 mg ($P = .02$) or APAP ($P < .001$) or IBU alone ($P < .001$) Significantly greater pain relief with APAP 500 mg/IBU 200 mg *vs*. APAP alone ($P = .03$) but not IBU alone Percentages of patients rating treatment as *excellent*, *very good* or *good* was 88% for APAP 1000 mg/IBU 400 mg, 82% for APAP 500 mg/IBU 200 mg, 47% for APAP alone and 67% for IBU alone	Similar frequency of treatment-related AEs in all treatment arms (APAP 500 mg/IBU 200 mg, 18.2%; APAP 1000 mg/IBU 400 mg, 14.9%; APAP 1000 mg, 35.3%; IBU 400 mg, 27.5%; placebo, 41.9%) Most common AEs were nausea (combination groups: 21.2–22.4%; APAP, 29.4%; IBU, 26.1%; placebo, 35.5%), vomiting (combination groups: 12.1–13.4%; APAP, 29.4%; IBU, 18.8%; placebo, 25.8%), headache (combination groups: 3.0–7.5%; APAP, 20.6%; IBU,

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TABLE 1 (Continued)

First author date[ref]	Study design	Setting/patient population	Treatment groups (no. randomized)[a]	Summary of efficacy findings	Summary of safety findings
					13.0%; placebo, 6.5%) and dizziness (combination groups: 3.0%; APAP, 20.6%; IBU, 8.7%; placebo, 9.7%)
Mehlisch 2010b[35]	Double-blind, randomized, placebo-controlled, parallel-group, factorial study (stage 1 only described, 8 h after surgery)	Patients aged ≥16 years with moderate-to-severe pain after surgical removal of ≥3 impacted third molars	FDC: APAP 250 mg/IBU 100 mg ($n = 71$) FDC: APAP 500 mg/IBU 200 mg ($n = 143$) FDC: APAP 1000 mg/IBU 400 mg ($n = 149$) APAP 500 mg ($n = 76$) APAP 1000 mg ($n = 74$) IBU 200 mg ($n = 75$) IBU 400 mg ($n = 74$) Placebo ($n = 73$) 6 tablets (3 doses) over 8 h	Significantly greater pain relief with APAP 1000 mg/IBU 400 mg *vs.* APAP 1000 mg ($P < .001$) or IBU 400 mg alone ($P = .02$) Significantly greater pain relief with APAP 500 mg/IBU 200 mg *vs.* APAP 500 mg ($P < .001$) or IBU 200 mg alone ($P < .001$) Combination therapy provided faster onset of action and greater duration of action than monotherapy Percentages of patients rating treatment as *excellent*, *very good* or *good* were higher for combination therapy groups (85.9% for APAP 250 mg/IBU 100 mg group, 88.0% for APAP 500 mg/IBU 200 mg group and 93.2% for APAP 1000 mg/IBU 400 mg group) *vs.* monotherapy groups (48.6% for APAP 500 mg, 65.8% for APAP 1000 mg, 74.0% for IBU 200 mg, 83.8% for IBU 400 mg)	Rates of AEs generally lower with combination therapy *vs.* monotherapy or placebo (or similar in some cases *vs.* monotherapy) Treatment-related AEs occurred in 5.4–11.3% of patients in combination therapy groups *vs.* 22.4% with APAP 500 mg, 13.5% with APAP 1000 mg, 16.0% with IBU 200 mg, 10.8% with IBU 400 mg and 19.2% with placebo Most common AEs were facial swelling (combination therapy, 13.4–16.9%; APAP 500 mg, 14.5%; APAP 1000 mg, 10.8%; IBU 200 mg, 13.3%; IBU 400 mg, 21.6%; placebo, 19.2%), nausea (combination therapy, 2.7–5.6%; APAP 500 mg, 18.4%; APAP 1000 mg, 16.2%; IBU 200 mg, 6.7%; IBU 400 mg, 13.5%; placebo, 17.8%), vomiting (combination therapy, 4.0–12.7%; APAP 500 mg, 18.4%; APAP 1000 mg, 10.8%; IBU 200 mg, 10.7%; IBU 400 mg, 8.1%; placebo, 15.1%) and headache (combination therapy, 2.8–4.2%; APAP 500 mg, 10.5%; APAP 1000 mg, 4.1%; IBU 200 mg, 4.0%; IBU 400 mg, 2.7%; placebo, 15.1%)
Merry 2010[36]	Double-blind, randomized, parallel-group trial	Patients aged ≥16 years after surgical removal of ≥1 third molars	FDC: APAP 500 mg/IBU 150 mg ($n = 44$) APAP 500 mg ($n = 47$) IBU 150 mg ($n = 44$) 2 tablets before surgery and then 2 tablets Q6h for up to 48 h after surgery	Significantly greater pain relief with APAP 500 mg/IBU 150 mg *vs.* APAP 500 mg or IBU 150 mg at rest and on activity (all, $P > .01$) Significantly more patients achieved no or mild pain with combination therapy (68.4%) *vs.* APAP (37.5%; $P = .008$) but not IBU (54.3%; $P = .263$) Differences in use of rescue medication were not statistically significant	AEs consistent with known side-effect profiles and no indication of change in AE profile when drugs combined, but numbers too small for meaningful comparisons
Searle 2020[37]	Phase 3 double-blind, randomized, placebo-controlled, parallel-group trial	Patients aged 18–40 years with moderate-to-severe pain after surgical removal of ≥3 third molar teeth (≥2 must be impacted)	FDC: APAP 500 mg/IBU 250 mg ($n = 172$) APAP 650 mg ($n = 165$) IBU 250 mg ($n = 175$)	Significantly greater pain relief with APAP 500 mg/IBU 250 mg *vs.* APAP 650 mg ($P < .001$) or IBU 250 mg ($P < .008$)	Combination therapy well tolerated Incidences of most common AEs were lowest with combination therapy: nausea (APAP/IBU, 9.9%; APAP, 20.0%; IBU,

TABLE 1 (Continued)

First author date[ref]	Study design	Setting/patient population	Treatment groups (no. randomized)[a]	Summary of efficacy findings	Summary of safety findings
			Placebo ($n = 56$) Single dose	Significantly faster time to pain relief with APAP 500 mg/IBU 250 mg *vs.* APAP 650 mg ($P = .031$) or IBU 250 mg ($P = .003$) Duration of pain relief significantly longer with APAP 500 mg/IBU 250 mg *vs.* APAP 650 mg ($P < .001$) but not IBU 250 mg ($P = .069$) Patient Global Evaluation better for combination *vs.* either monotherapy (IBU, $P = .004$; APAP, $P < .001$)	13.7%; placebo, 30.4%), vomiting (APAP/IBU, 4.1%; APAP, 12.1%; IBU, 8.6%; placebo, 19.6%) and dizziness (APAP/IBU, 2.9%; APAP, 7.3%; IBU, 3.4%; placebo, 7.1%)
Breivik 1999[38]	Double-blind, double-dummy, randomized, parallel-group trial	Patients aged 18–40 years with moderate-to-severe pain after surgical removal of impacted third molars	APAP 1000 mg/DIC 100 mg ($n = 24$)[b] APAP 1000 mg ($n = 24$) DIC 100 mg ($n = 24$)[b] Single dose	Combination therapy provided significantly reduced pain intensity than APAP or DIC alone ($P = .001$) Frequency of rescue medication (APAP/codeine) significantly lower ($P = .027$) and time to rescue medication significantly longer with combination therapy *vs.* APAP or DIC alone ($P < .05$) Patients rated combination therapy as superior to APAP or DIC alone	AE rates were very low, with no significant differences between treatment groups in rates of AEs AEs were nausea, drowsiness, sweating and headache in the combination therapy group ($n = 1$ each, all mild), nausea and drowsiness in the APAP group ($n = 1$ each, all mild) and nausea ($n = 1$, mild) and drowsiness ($n = 3$; 1 mild, 2 moderate) in the DIC group
Matthews 1984[39]	Double-blind, randomized, placebo-controlled crossover trial	Patients after surgical removal of bilateral, symmetrical impacted mandibular third molars (age of enrolled patients ranged from 18 to 37 years)	APAP 500 mg/DIC 50 mg ($n = 18$) APAP 500 mg ($n = 21$) DIC 50 mg ($n = 15$) Placebo ($n = 18$) (each patient randomized to 2 treatments) Immediately after surgery and 6 h later	After initial dose and after second dose, combination therapy provided significantly greater pain relief than APAP alone ($P < .05$) but not *vs.* DIC alone ($P = .05$) No patient taking combination therapy required emergency analgesic (mefenamic acid) *vs.* 2 taking DIC, 6 taking APAP and 6 taking placebo	No AEs occurred
Schneider 2022[40]	Double-blind, randomized, placebo-controlled crossover study	Adult patients undergoing sequential bilateral lower third molar extraction with osteotomy	Metamizole 1000 mg/IBU 400 mg (N = 35)[c] Metamizole 1000 mg/Placebo ($n = 14$)[c] IBU 400 mg/Placebo ($n = 16$) All patients received metamizole/IBU for 1 side and metamizole or IBU for other side of mouth 15 min before surgery and at 6 and 12 h after surgery	Cumulative mean pain scores significantly lower for metamizole/IBU *vs.* metamizole for 4–11 h postsurgery ($P \leq .044$) but not at 3 ($P = .063$) or 12 ($P = .080$) h postsurgery Cumulative mean pain scores significantly lower for metamizole/IBU *vs.* IBU for 5–12 h postsurgery ($P \leq .046$) but not at 3 ($P = .071$) and 4 ($P = .063$) h postsurgery Metamizole/IBU provided significantly lower pain scores for up to 6 h postsurgery *vs.* either drug alone (metamizole, $P = .015$; IBU, $P = .022$;	Not reported, other than no patients had bleeding requiring intervention or events resulting in hospitalization

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TABLE 1 (Continued)

First author date[ref]	Study design	Setting/patient population	Treatment groups (no. randomized)[a]	Summary of efficacy findings	Summary of safety findings
				clinically relevant difference) and for up to 12 h postsurgery *vs.* IBU ($P = .005$) Rescue medication use (tramadol) was lower with metamizole/IBU (25%) *vs.* metamizole (46%) or IBU (50%) alone	
Postsurgical (endodontic surgery, root canal)					
Menhinick 2004[41]	Double-blind, randomized, placebo-controlled, parallel-group trial	Patients aged ≥18 years who underwent emergency endodontic treatment for symptomatic maxillary or mandibular tooth with irreversible pulpitis or necrosis; patients had moderate-to-severe pain prior to surgery	FDC: APAP 1000 mg/IBU 600 mg ($n = 18$) IBU 600 mg ($n = 20$) Placebo ($n = 19$) Single dose	Significantly greater pain reduction with APAP/IBU *vs.* IBU alone ($P = .047$)	Gastrointestinal AEs reported by 6% of patients in APAP/IBU group ($n = 1$), 5% in IBU group ($n = 1$) and 21% in placebo group ($n = 4$) Central nervous system AEs reported by 28% of patients in APAP/IBU group ($n = 5$), 30% in IBU group ($n = 6$) and 53% in placebo group ($n = 10$)
Wells 2011[42]	Double-blind, randomized, parallel-group trial	Patients aged ≥18 years who underwent emergency endodontic treatment for symptomatic maxillary or mandibular tooth with pulpal necrosis; patients had moderate-to-severe pain prior to surgery	FDC: APAP 1000 mg/IBU 600 mg ($n = 35$) IBU 600 mg ($n = 36$) Q6h as needed for pain	No statistically significant differences between APAP/IBU and IBU in pain relief over 5 days, number of treatments per day or rescue medication requirement	Safety results not reported
Elzaki 2016[43]	Double-blind, randomized, placebo-controlled, parallel-group, factorial trial	Patients aged ≥18 years who underwent emergency endodontic treatment for symptomatic maxillary or mandibular tooth with irreversible pulpitis; patients had moderate-to-severe pain prior to surgery	APAP 1000 mg/IBU 600 mg ($n = 37$) APAP 1000 mg/DIC 50 mg ($n = 37$)[b] APAP 1000 mg ($n = 37$) Placebo ($n = 37$) Single dose	APAP/IBU showed greatest pain reduction, followed by APAP/DIC and then APAP alone, with significant differences between treatment groups ($P < .005$) After 2 h (but not after 3, 4 or 6–8 h), pain relief was significantly greater with APAP/IBU *vs.* APAP alone ($P < .005$)	Patients reported no AEs
Acute musculoskeletal pain: low back					
Friedman 2020[44]	Double-blind, double-dummy, randomized, parallel-group trial	Patients aged 21–69 years presenting at ED with acute low-back pain	APAP 500–1000 mg/IBU 600 mg QID ($n = 60$) IBU 600 mg QID ($n = 60$) Patients in APAP/IBU group took 500 mg APAP and took a second capsule (1000 mg APAP total) if did not experience adequate relief within 30 min 7 days of treatment	No significant differences between APAP/IBU and IBU alone in pain relief at 48 h or 1 week (based on 95% CI not crossing zero) No significant differences between treatment groups on a number of secondary outcome measures, such as worst pain and number of days until able to return to usual activities	At 48-h follow up, similar proportions of patients reported new AEs that they attributed to study medication (5% of APAP/IBU *vs.* 7% of IBU patients) At 7-day follow up, 9% of APAP/IBU *vs.* 4% of IBU patients reported new AEs that they attributed to study medication AEs that patients attributed to study medication included abdominal pain or diarrhoea, drowsiness and dizziness with APAP/IBU and blurry vision, diarrhoea, dizziness, nausea and drowsiness with IBU

TABLE 1 (Continued)

First author date[ref]	Study design	Setting/patient population	Treatment groups (no. randomized)[a]	Summary of efficacy findings	Summary of safety findings
Ostojic 2017[45]	Randomized, open-label, parallel-group trial	Patients aged 18–65 years presenting at tertiary care centres (institutions specializing in treatment of musculoskeletal diseases) with uncomplicated and localized acute low-back pain or an acute exacerbation of chronic low-back pain, moderate-to-severe pain at least 2 days before randomization and aggravation by movement/improvement with rest	FDC: APAP 325 mg/IBU 200 mg TID ($n = 40$) IBU 400 mg TID ($n = 40$) 3 days of treatment	Use of rescue medication (additional APAP) did not differ significantly between treatment groups on days 1–3 ($P = .59$) or days 4–10 ($P = .30$), but the number of additional APAP tablets used from days 4–10 (but not 1–3) was significantly higher with IBU *vs.* APAP/IBU ($P < .001$) Among patients who did not use rescue medication: Pain intensity was significantly lower with APAP/IBU on day 4 ($P = .045$) but not day 10 ($P = .15$) The percentage of patients with *no pain* or *mild pain* was significantly higher with combination therapy on day 10 (84.4 *vs.* 60.7%, $P = .039$) but not on day 4 ($P = .065$) APAP/IBU treatment produced significantly greater improvement than IBU in mobility of the upper lumbar spine at day 10 ($P = .03$) At day 10, APAP/IBU was associated with significantly higher rates *vs.* IBU of patient (90 *vs.* 60%, $P = .001$) and investigator (90 *vs.* 65%, $P = .007$) satisfaction	No significant difference between APAP/IBU and IBU in proportions of patients who were satisfied with acceptability of treatment 1 patient receiving APAP/IBU and 2 receiving IBU reported AEs (all gastrointestinal [i.e., nausea, epigastric pain, heartburn] and considered minor and related to treatment)
Hancock 2007[46]	Double-blind, double-dummy, placebo-controlled, randomized, parallel-group trial	Patients with low-back pain of <6 weeks' duration presenting to a general practitioner (age range not specified)	APAP 1000 mg QID/DIC 50 mg BID ($n = 60$)[b] APAP 1000 mg QID ($n = 60$) ≤4 weeks of treatment (stopped earlier if recovered)	No significant differences between APAP/DIC and APAP monotherapy with respect to days until recovery from pain (log rank $P = .506$, $P = .906$) No significant differences between APAP/DIC and APAP monotherapy in pain, disability, function or global perceived effect at any time point	11 AEs occurred in patients taking APAP/DIC and 11 AEs occurred in patients taking APAP; AEs included gastrointestinal AEs, dizziness and heart palpitations (frequency of individual AEs not specified) 1 patient taking DIC experienced a suspected hypersensitivity reaction and discontinued treatment
Acute musculoskeletal pain: non–low back					
Bondarsky 2013[47]	Double-blind, double-dummy, randomized, parallel-group trial	Adults presenting at ED with acute musculoskeletal injury and pain	APAP 1000 mg/IBU 800 mg ($n = 30$) APAP 1000 mg ($n = 30$) IBU 800 mg ($n = 30$) Single dose	No significant differences between treatment groups in pain scores over the 1-h study period or requirement for rescue medication ($P = .59$)	Low frequency of AEs in all treatment arms (1 patient [3%] in APAP/IBU group reported abdominal pain; no AEs in APAP group; 1 patient [3%] in IBU group reported nausea)

(Continues)

TABLE 1 (Continued)

First author date[ref]	Study design	Setting/patient population	Treatment groups (no. randomized)[a]	Summary of efficacy findings	Summary of safety findings
Hung 2018[48]	Double-blind, double-dummy, randomized, parallel-group trial	Patients aged ≥18 years presenting at an ED with an isolated soft tissue injury	APAP 1000 mg QID/IBU 400 mg TID ($n = 263$) APAP 1000 mg QID ($n = 263$) IBU 400 mg TID ($n = 258$) 3 days of treatment	Both at 2 h and at 3 days, no significant differences between treatment groups in pain relief at rest ($P = .68$) or on activity ($P = .22$) Among those with initial moderate-to-severe pain, no significant differences between treatment groups both at 2 h and 3 days in the proportions of patients with adequate response at rest (2 h, $P = .98$; 3 days, $P = .86$) or on activity (2 h, $P = .83$; 3 days, $P = .57$) No significant differences between treatment groups in satisfaction with analgesic drug treatment ($P = .3$)	Similar frequency of AEs in all treatment arms, including for each category of AEs No episodes of gastrointestinal haemorrhage, shortness of breath or chest pain reported Most common AE during ED phase was sleepiness (APAP/IBU, 2.3%; APAP, 2.3%; IBU, 4.7%), with all other AEs occurring in <2% of each treatment group
Man 2004[49]	Double-blind, double-dummy, randomized, parallel-group feasibility/pilot study	Patients aged ≥16 years presenting at an ED with an isolated soft tissue limb injury	APAP 1000 mg QID/DIC 25 mg TID ($n = 11$)[b] APAP 1000 mg QID ($n = 16$) DIC 25 mg TID ($n = 12$)[b] 3 days of treatment	No clinically or statistically significant difference between treatments in pain relief at rest or with activity over 2 h or over 3 days	Only 1 patient developed an AE (mild allergic reaction to APAP)
Ridderikhof 2018[50]	Double-blind, double-dummy, randomized, parallel-group trial	Patients aged ≥18 years presenting with nonpenetrating minor musculoskeletal trauma of an extremity occurring within 48 h before presentation	APAP 1000 mg QID/DIC 50 mg TID ($n = 182$)[b] APAP 1000 mg QID ($n = 182$) DIC 50 mg TID ($n = 183$)[b] 3 days of treatment	Both in the acute phase (phase 1; 90 min after study drug administration) and phase 2 (up to 3 consecutive days after discharge), pain relief with APAP was noninferior to that with DIC or APAP/DIC both at rest and with movement No significant differences in pain relief between treatment groups No significant differences between treatment groups in requirement for additional analgesia No significant differences between treatment groups in patient satisfaction	Phase 1: minor neurological AEs (e.g., headache, dizziness and tiredness) occurred more frequently in the APAP group (13.2%) *vs.* the DIC (6.6%) or APAP/DIC group (7.1%); the most common AEs were tiredness (APAP/DIC, 5.5%; APAP, 7.1%; DIC, 3.8%), nausea (APAP/DIC, 3.8%; APAP, 4.9%; DIC, 3.8%) and dizziness (APAP/DIC, 1.6%; APAP, 4.4%; DIC, 2.7%) Phase 2: rates of gastrointestinal (APAP/DIC, 19.8%; APAP, 25.8%; DIC, 20.2%) and neurological (APAP/DIC, 15.9%; APAP, 18.1%; DIC, 15.3%) AEs were similar across treatment groups; potentially serious AEs were: chest pain when supine ($n = 1$ in combination group), dyspnoea ($n = 2$ in APAP group and 1 in combination group), dark urine ($n = 2$ APAP group, $n = 1$ combination group), bloody stools ($n = 1$ APAP group; $n = 1$ diclofenac group; $n = 3$ combination group)

TABLE 1 (Continued)

First author date[ref]	Study design	Setting/patient population	Treatment groups (no. randomized)[a]	Summary of efficacy findings	Summary of safety findings
Woo 2005[51]	Double-blind, double-dummy, randomized, parallel-group trial	Patients aged ≥16 years presenting at an ED with an isolated painful limb injury	APAP 1000 mg QID/DIC 25 mg TID ($n = 94$)[b] APAP 1000 mg QID ($n = 66$) DIC 25 mg TID ($n = 69$)[b] 3 days of treatment	No clinically or statistically significant difference between treatments in pain relief at rest or with activity over 2 h or over 3 days No significant differences between treatment groups in proportions of patients who required additional analgesia	AEs in first 2 h occurred in <7% of patients (APAP/DIC, 6%; APAP, 6%; DIC, 4%) and were mild or moderate, with low rates of dizziness (APAP/DIC, 1%; APAP, 2%; DIC, 3%) and indigestion (APAP/DIC, 3%; APAP, 2%; DIC, 3%) Over 3 days, AEs occurred in 19% of patients in APAP/DIC group *vs.* 16% in APAP group and 12% in DIC group, with the most common AEs being indigestion (APAP/DIC, 8.7%; APAP, 7.8%; DIC, 6.0%), dizziness (APAP/DIC, 4.3%; APAP, 7.8%; DIC, 3.0%) and abdominal pain (APAP/DIC, 6.5%; APAP, 0.0%; DIC, 3.0%)
Pareek 2009[52]	Randomized, comparative, multicenter, open-label trial	Male and female patients aged 40–70 years with osteoarthritis, who experienced osteoarthritis flare-up in the past 2–5 days	FDC: APAP 500 mg/ACE 100 mg BID ($n = 101$) ACE 100 mg BID ($n = 98$) 10 days of treatment	Significantly greater decrease in pain intensity relative to baseline with FDC *vs.* ACE alone at 0.5 h ($P = .008$), 1 h ($P = .002$), 2 h ($P = .012$) and 4 h ($P = .028$) after first dose $SPID_{0–4\ h}$ significantly better with FDC *vs.* ACE ($P = .005$) Peak pain intensity difference over 4-h treatment period showed FDC was significantly more effective than monotherapy ($P = .014$) The pain intensity difference was significantly more with FDC than ACE during the first 4 days ($P < .05$), but was similar on days 5–10	Incidence of AE similar for FDC (10.9%) and ACE (9.2%) Most common AEs were nausea (5.0% and 3.1%, respectively) and gastritis (3.0% and 2.0%, respectively) All AEs were mild to moderate and possibly related to treatment
Headache					
Diener 2005[53]	Double-blind, randomized, placebo-controlled, parallel-group trial	Patients aged 18–65 years with headaches for ≥12 months and ≥2 headaches within previous 3 months who treat their headaches with nonprescription medications	FDC: APAP 400 mg/ASA 500 mg/CAF 100 mg ($n = 553$) APAP 400 mg/ASA 500 mg ($n = 561$) APAP 1000 mg ($n = 284$) ASA 1000 mg ($n = 296$) Placebo ($n = 146$) Single dose	Over the course of treatment for 2 headaches, APAP/ASA/CAF provided significantly shorter time to 50% pain relief *vs.* APAP/ASA ($P = .0181$), APAP ($P = .0016$) and ASA ($P = .0398$), as well as significantly shorter time needed to reduce pain intensity to 10 mm The median time to 50% pain relief was 1 h, 13 min for APAP/ASA; 1 h, 21 min for APAP; and 1 h, 19 min for ASA (no statistical comparisons)	Global assessment of treatment tolerability by patients and investigators was good or very good in >90% of all patients Rates of any AE were 7.8% in the APAP/ASA group, 5.8% in the APAP group and 9.7% in the ASA group Rates of any drug-related AE were 2.2% in both the APAP/ASA and APAP groups and 3.6% in the ASA group; none were severe

(Continues)

TABLE 1 (Continued)

First author date[ref]	Study design	Setting/patient population	Treatment groups (no. randomized)[a]	Summary of efficacy findings	Summary of safety findings
				The median time to reduce pain intensity to 10 mm was 2 h, 25 min for APAP/ASA; 2 h, 35 min for APAP; and 2 h, 31 min for ASA (no statistical comparisons) APAP/ASA/CAF provided significantly greater pain reduction at 2 h *vs*. APAP/ASA ($P = .0019$), APAP ($P = .0032$) and ASA ($P = .0228$), while improvement in pain intensity was similar for APAP/ASA *vs*. either component alone The proportion of patients who did not experience relevant impairment of usual daily activities at 2 h was significantly greater with APAP/ASA/CAF *vs*. ASA alone ($P = .0446$) and was 49.4% with APAP/ASA, 48.6% with APAP and 48.4% with ASA Patient assessment of efficacy was significantly higher for APAP/ASA/CAF *vs*. APAP/ASA ($P = .0114$), APAP ($P < .0001$) or ASA ($P = .0085$)	Other than abdominal pain (APAP/ASA, 1.1%; APAP, 0.7%; ASA, 2.5%), no AEs occurred in ≥2% of patients in any treatment group
Diener 2014[31]	Pooled analysis of data from 4 double-blind, randomized, placebo-controlled crossover studies	Patients aged 18–65 years with moderate or severe episodic TTH and 4–10 TTHs per month during the last year that usually responded to nonprescription analgesics	FDC: APAP 500 mg/ASA 500 mg/CAF 130 mg ($n = 1400$)[d] APAP 1000 mg ($n = 1400$)[d] Placebo ($n = 702$)[d] Single dose	Proportion of treated headache episodes that were pain-free at 2 h postdose was significantly higher with APAP/ASA/CAF (28.5%) *vs*. APAP (21.0%; $P < .0001$) Pain-free response at 1 h postdose was significantly higher with APAP/ASA/CAF (8.6%) *vs*. APAP (6.1%; $P = .0004$) At 2 h postdose, headache response (reduction from moderate/severe to mild/no pain) was significantly higher with APAP/ASA/CAF *vs*. APAP ($P < .0001$) APAP/ASA/CAF was associated with significantly lower rates of interference with daily activities *vs*. APAP ($P \leq .0005$)	AE rate was higher with APAP/ASA/CAF (17%) *vs*. APAP alone (10%) or placebo (9%) Slightly higher rates were observed with APAP/ASA/CAF *vs*. APAP alone or placebo for stomach upset (APAP/ASA/CAF, 9%; APAP, 5%; placebo, 5%), nervousness (APAP/ASA/CAF, 4%; APAP, 1%; placebo, 1%) and dizziness (APAP/ASA/CAF, 4%; APAP, 2%; placebo, 1%)
Goldstein 2006[54]; *posthoc* analysis, Goldstein 2014[55]	Double-blind, randomized, placebo-controlled, parallel-group trial	Patients aged ≥18 years with migraine and ≥1 attack every 2 months but ≤6 times monthly during past 12 months; untreated attacks were of ≥moderate intensity	FDC: APAP 500 mg/ASA 500 mg/CAF 130 mg ($n = 737$) IBU 400 mg ($n = 734$) Placebo ($n = 243$) Single dose	APAP/ASA/CAF provided significantly greater pain relief *vs*. IBU (2 h, $P < .03$; 3 h, $P < .01$; 4 h, $P < .007$) Median time to meaningful pain relief was significantly shorter with APAP/ASA/CAF *vs*. IBU ($P = .036$)	Overall AE incidence was low but about twice as high for APAP/ASA/CAF (9.7%) *vs*. IBU (5.1%) and placebo (5.5%) No individual AEs occurred in ≥2% of patients in any treatment group

TABLE 1 (Continued)

First author date[ref]	Study design	Setting/patient population	Treatment groups (no. randomized)[a]	Summary of efficacy findings	Summary of safety findings
				Pain-free rates were higher for APAP/ASA/CAF *vs*. IBU at 3 and 4 h postdose ($P < .035$) The proportion of patients with pain intensity reduced to mild/none was significantly higher for APAP/ASA/CAF *vs*. IBU at 2 h postdose ($P < .046$) The proportion of patients free of migraine-associated symptoms (functional disability, nausea, photophobia and phonophobia) was comparable for APAP/ASA/CAF and IBU treatment groups *Posthoc* analysis of patients with severe baseline migraine pain demonstrated similar results, with APAP/ASA/CAF being significantly faster acting and providing greater pain relief *vs*. IBU alone ($P = .026$; $P = .037$)	Rates of digestive system AEs were higher in the APAP/ASA/CAF group (3.4%) *vs*. the IBU (0.9%) and placebo (1.8%) groups as were rates of nervous system AEs (APAP/ASA/CAF, 5.7%; IBU, 2.2%; placebo, 3.6%) In *posthoc* analysis of patients with severe baseline migraine pain, the most common AEs with active treatment (nausea, dizziness) were similar to those observed in overall population and were generally mild, transient and similar in incidence and severity to placebo

[a]Treatment groups with prescription drugs or nonanalgesics and corresponding results were not described.
[b]Oral diclofenac is not available without a prescription in the USA but is available without a prescription in some countries in a 25-mg dose.
[c]Metamizole is not approved in the USA but is available without a prescription in some countries.
[d]Includes patients who took any medication because number of patients randomized was not reported.
ACE, aceclofenac; ASA, acetylsalicylic acid; AE, adverse event; APAP, paracetamol; BID, twice daily; CAF, caffeine; CI, confidence interval; DIC, diclofenac; ED, emergency department; FDC, fixed-dose combination; IBU, ibuprofen; NSAID, nonsteroidal anti-inflammatory medication; QID, 4 times a day; Q6h, every 6 h; $SPID_{0-4\ h}$, sum of pain intensity differences over 4 h between treatments; TID, 3 times a day; TTH, tension-type headache.

A placebo-controlled crossover study compared paracetamol 500 mg/diclofenac 50 mg with either drug alone.[39] Each patient underwent 2 surgical operations, performed within a 6-week period; while 36 patients were enrolled, 8 patients (4 who received paracetamol and 4 who received placebo) withdrew from the trial after the first operation due to intolerable pain and thus did not receive a second treatment. In this study, the combination of paracetamol and diclofenac provided comparable pain relief to diclofenac alone and both treatments produced significantly greater pain relief than paracetamol alone (which did not differ from placebo; $P < .05$). Notably, no patients receiving combination therapy required rescue analgesia (*vs.* 2–6 patients in the other treatment groups).

The combination of metamizole 1000 mg/ibuprofen 400 mg was compared with either drug alone in a randomized, double-blind, placebo-controlled crossover study.[40] Adults undergoing sequential bilateral lower third molar extraction with osteotomy received metamizole 1000 mg/ibuprofen 400 mg for surgery on 1 side of the mouth and either metamizole 1000 mg/placebo or ibuprofen 400 mg/placebo for surgery on the other side, with treatment groups and order of treatment randomized. Combination therapy resulted in significantly lower mean pain scores over 6 h *vs.* metamizole or ibuprofen alone ($P = .015$ and $P = .022$, respectively) and over 12 h *vs.* ibuprofen ($P = .005$). A potential opioid-sparing effect was evident, as fewer patients receiving combination therapy (25%) required rescue therapy with tramadol compared with those receiving metamizole (46%) or ibuprofen (50%).

3.3 | Postsurgical setting (endodontic surgery)

Three studies (2 placebo-controlled) in postsurgical pain following endodontic surgery examined combination therapy with paracetamol 1000 mg/ibuprofen 600 mg (single dose or every 6 h as needed for pain)[41–43]; 1 study additionally assessed combination therapy with paracetamol 1000 mg/diclofenac 50 mg (single dose).[43] Patients in these studies were required to have moderate-to-severe pain before surgery.

Results of the 2 single-dose studies[41,43] suggest that combination therapy with paracetamol 1000 mg/ibuprofen 600 mg provides greater reductions in postendodontic pain compared with either component alone or with paracetamol 1000 mg/diclofenac 50 mg. In contrast, a study comparing an FDC of paracetamol 1000 mg/ibuprofen 600 mg with ibuprofen 600 mg, taken every 6 h as needed, observed no statistically significant differences between treatment groups with respect to pain relief over 5 days, number of treatments per day or rescue medication requirement.[42]

The above studies only compared combination therapy *vs.* individual components at the same doses, thus not allowing for assessment of potential dose-sparing effects.[41–43] It should be considered that postendodontic pain differs from the DIPM in that patients undergoing root canal surgery initially presented with moderate-to-severe pain before the endodontic procedure.[41–43]

3.4 | Acute musculoskeletal pain (low back)

Two studies (1 double-dummy but without a placebo group) evaluated combination therapy with paracetamol and ibuprofen. The first study evaluated patients presenting to the emergency department (ED) with acute nontraumatic low-back pain (LBP),[44] while the second evaluated patients with acute LBP or an acute exacerbation of chronic LBP presenting to a tertiary care center with moderate-to-severe pain.[45] The former study found no significant differences in pain relief between patients treated over 7 days with paracetamol 500–1000 mg/ibuprofen 600 mg *vs.* ibuprofen 600 mg, as well as on a number of secondary outcome measures, including worst pain and number of days until the patient was able to return to usual activities.[44] In the latter study, the number of patients requiring rescue paracetamol did not differ significantly between paracetamol 325 mg/ibuprofen 200 mg or ibuprofen 400 mg 3 times daily (TID) for 3 consecutive days from days 1–3 or days 4–10; however, the number of additional paracetamol tablets used from days 4–10 was significantly higher among patients receiving monotherapy ($P < .001$).[45] Among patients who did not require rescue paracetamol, pain intensity was significantly lower with paracetamol/ibuprofen than with ibuprofen on day 4 ($P = .045$) but not day 10 ($P = .015$), indicating a faster analgesic effect with combination therapy. At day 10, combination therapy was also associated with a significantly greater proportion of patients reporting *no pain* or *mild pain vs.* monotherapy (84.4 *vs.* 60.7%; $P = .039$) as well as with significantly greater improvement in mobility of the upper lumbar spine ($P = .03$) and higher rates of patient and investigator satisfaction ($P = .001$ and $P = .007$, respectively). These findings suggest greater efficacy of combination therapy as well as a dose-sparing effect, since the dose of ibuprofen was lower with combination treatment.

In a separate randomized, double-blind, double-dummy trial, patients with acute LBP presenting to a general practitioner received recommended standard care of paracetamol 1000 mg 4 times daily (QID) and lifestyle advice in addition to diclofenac 50 mg, spinal manipulative therapy, diclofenac/spinal manipulative therapy or placebo (i.e., paracetamol monotherapy).[46] Patients continued treatment until their pain recovered, for up to 4 weeks. Average pain at baseline was of moderate intensity. No significant differences between paracetamol/diclofenac and paracetamol monotherapy were observed with respect to days until recovery from pain or in secondary outcomes of pain relief, disability/function or global perceived effect at any time point.

3.5 | Acute musculoskeletal pain (non-LBP)

Studies of combination therapy with paracetamol and NSAIDs in acute musculoskeletal non-LBP included patients presenting to the ED with a variety of soft tissue injuries (e.g., strains/sprains, contusions, cuts, crush injuries).[47–51] While the severity level of pain was not specified in these studies, enrolled patients had on average mild-to-moderate pain at baseline.[47–51] All 5 studies had a double-dummy design but no placebo group. A sixth open-label study described the

efficacy of aceclofenac plus paracetamol *vs*. aceclofenac alone in patients with osteoarthritis flares.[52]

Two studies compared combination therapy with paracetamol and ibuprofen (single dose: paracetamol 1000 mg/ibuprofen 800 mg; multiple dose: paracetamol 1000 mg/ibuprofen 400 mg) with 1 or both individual components.[47,48] In these studies, combination therapy did not provide any advantages with respect to pain relief over monotherapy with paracetamol or ibuprofen.[47,48] In the multiple-dose study, the subset of patients with initial moderate-to-severe pain found no significant differences between paracetamol/ibuprofen, paracetamol alone and ibuprofen alone, both at 2 h and at 3 days, in the proportions of patients with an adequate analgesia response (visual analogue scale <30 mm) at rest or on activity.[48] Patient satisfaction with analgesic treatment was comparable among patients receiving multiple doses of paracetamol/ibuprofen *vs*. each individual component.[48]

Similar to findings with paracetamol/ibuprofen, studies comparing 3 days of combination therapy with paracetamol 1000 mg QID/diclofenac 50 mg TID (1 study)[50] or paracetamol 1000 mg QID/diclofenac 25 mg TID (2 studies, including a feasibility/pilot study and the corresponding larger study)[49,51] *vs*. the individual components, in adults presenting to an ED with musculoskeletal pain did not demonstrate significant differences between treatment groups in pain relief or need for additional analgesia. Patient satisfaction with pain treatment did not differ significantly between paracetamol 1000 mg QID/diclofenac 50 mg TID and its individual components.[50]

A study comparing a fixed-dose combination of aceclofenac 100 mg/paracetamol 500 mg twice daily with aceclofenac 100 mg twice daily alone demonstrated improved efficacy with the combination in patients with osteoarthritis flare-up for the past 2–5 days.[52] In this randomized, comparative, multicentre, open-label study, the FDC was associated with a significant improvement in the sum of pain intensity differences over 4 h following the first dose ($P = .005$). The pain intensity difference was also significantly greater for the combination than aceclofenac alone during the first 4 days of treatment ($P < .05$), but there was no difference on days 5–10.

3.6 | Headache

All 4 studies in patients with headache that evaluated combination therapy with paracetamol and an NSAID were placebo controlled and also included caffeine.[31,53,54] No formal comparative studies were identified that assessed combination therapy with paracetamol/NSAID (without caffeine) *vs*. either component alone.

One study compared a single dose of paracetamol 400 mg/acetylsalicylic acid 500 mg/caffeine 100 mg with paracetamol 400 mg/acetylsalicylic acid 500 mg, paracetamol 1000 mg or acetylsalicylic acid 1000 mg.[53] Most patients in this study had a usual headache pain intensity of moderate or severe. Although differences between the paracetamol/acetylsalicylic acid, paracetamol and acetylsalicylic acid groups were not compared using statistical methods, median times to pain relief, improvements in pain intensity and proportions of patients without relevant impairment in usual daily activities all favoured combination therapy or were comparable between these 3 treatment groups, suggesting a dose-sparing effect with combination therapy. Results of a pooled analysis of 4 crossover trials comparing an FDC of paracetamol 500 mg/acetylsalicylic acid 500 mg/caffeine 130 mg with paracetamol 1000 mg in patients with moderate or severe episodic tension-type headache[31] and a study comparing the same FDC with ibuprofen 400 mg in patients with migraine[54] suggest that combination therapy provides significantly greater total pain relief ($P < .007$ after 4 h) and faster time to onset of meaningful pain relief ($P = .036$) compared with monotherapy, although the proportion of patients free of migraine-associated symptoms was comparable between the combination therapy and ibuprofen groups. A *posthoc* analysis of the latter study found that results in patients with severe baseline pain were comparable to those in the overall study population, with combination therapy being significantly faster acting ($P = .026$) and more effective ($P = .037$) *vs*. ibuprofen in this subpopulation.[55]

3.7 | Safety

Combination therapy with paracetamol/ibuprofen was well tolerated in the management of dental and musculoskeletal pain, with AE rates comparable to or lower than those observed with monotherapy or, in some cases, placebo. The most common AEs across studies were neurological (headache, dizziness) and gastrointestinal (nausea, vomiting). In some studies,[34,37] substantially higher rates of specific AEs (i.e., nausea, vomiting, headache and dizziness) were observed with monotherapy *vs*. combination therapy. Safety findings were not reported for the combination of metamizole/ibuprofen beyond noting that patients did not experience bleeding requiring intervention or any events resulting in hospitalization.

In endodontic surgery, 1 study comparing paracetamol 1000 mg/ibuprofen 600 mg, paracetamol 1000 mg/diclofenac 50 mg, paracetamol 1000 mg and placebo reported that no adverse events (AEs) occurred,[43] and the other found that combination therapy with paracetamol 1000 mg/ibuprofen 600 mg and monotherapy with ibuprofen 600 mg were associated with comparable rates of gastrointestinal and central nervous system AEs that were considerably lower than those observed with placebo.[41]

Combination therapy with paracetamol/acetylsalicylic acid/caffeine was well tolerated, although AE rates were generally higher with combination therapy *vs*. paracetamol or ibuprofen alone.[31,54] Rates of AEs and treatment-related AEs were slightly higher with acetylsalicylic acid 1000 mg (but not paracetamol 1000 mg) compared with paracetamol 400 mg/acetylsalicylic acid 500 mg.[53]

Similar results were seen with the combination of paracetamol/diclofenac in LBP.[46,49–51] AEs included gastrointestinal AEs, dizziness and heart palpitations. In one study, a patient taking diclofenac discontinued treatment following a suspected hypersensitivity reaction.[46] Another study found that minor neurological AEs were more

frequent with paracetamol 1000 mg QID alone *vs*. diclofenac 50 mg TID alone or combination therapy.[50] This study also described a small number of potentially serious AEs that occurred during the 3-day treatment period.

4 | DISCUSSION

The data suggest that combination nonprescription products are more effective than monotherapy for managing postoperative pain and, to some extent, headache, although differences in analgesia between combination therapy and monotherapy were not consistently demonstrated in acute LBP and non-LBP musculoskeletal pain. Interpretation of the findings of the musculoskeletal pain studies is limited by the open-label design, by the absence of paracetamol-only and placebo study arms, and by the inclusion of patients with exacerbation of chronic LBP and osteoarthritis. Overall, it is difficult to ascertain the clinical significance of any differences in pain relief between combination therapy and monotherapy in this setting. The minimum clinically important difference for endpoints in acute pain studies has been shown to be highly variable between studies, being influenced by baseline pain and study design.[57] While the DIPM is considered the gold standard in the evaluation of analgesics for acute inflammatory pain,[56] the lack of consistent efficacy with combination therapy *vs*. monotherapy in acute musculoskeletal pain challenges the generalizability of the model to pain conditions that may involve other (e.g., neuropathic) components.

Recent years have seen a trend toward restricted use of opioids due to safety concerns such as constipation, respiratory depression and opioid-use disorder.[2,58–60] The American Academy of Family Physicians (AAFP) and the American College of Physicians (ACP) recommend against the use of opioids for management of acute pain from non–lower-back musculoskeletal injuries.[3,8] Results of 4 studies in the postsurgical setting after third molar extraction suggest a lower requirement for rescue therapy with opioids in patients receiving combination therapy *vs*. monotherapy,[32,38–40] although studies in settings of endodontic surgery and musculoskeletal pain that assessed rescue therapy use did not observe such a difference (Table 1).

Different levels of neuroinflammation might explain the marked differences between findings in postoperative pain models and in musculoskeletal pain. Additionally, patients in studies using the DIPM had moderate-to-severe pain per inclusion requirements, whereas patients in studies of non–low-back musculoskeletal pain had, on average, mild-to-moderate pain. The lack of superiority of combination therapy over monotherapy in acute non-LBP is, in our opinion, unlikely to be due to a ceiling effect because: (i) a subset analysis of patients with initial moderate-to-severe pain found no differences between paracetamol 1000 mg/ibuprofen 400 mg combination therapy and individual components in the proportions of patients with an adequate analgesia response at rest or on activity[48]; and (ii) examination of mean pain scores suggests that patients on average continued to experience at least mild pain with monotherapy despite improvement.[47–51]

Oral combination therapy with paracetamol/NSAIDs was well tolerated in all acute pain settings in which it was evaluated, with AE rates typically being similar to or even lower than those observed with monotherapy. Higher rates of gastrointestinal and neurological AEs overall and in the placebo group were reported in postsurgical settings relative to nonsurgical acute pain settings (i.e., musculoskeletal pain, headache), suggesting that these AEs may have been attributable to the procedure, anaesthesia, concomitantly prescribed medications (e.g., antibiotics) or pain itself. Lower rates of gastrointestinal and neurological AEs observed with combination therapy *vs*. placebo and, in some studies, *vs*. monotherapy in postsurgical studies may be related to better pain control with combination therapy, although further analyses would be needed to explore the relationship between alleviation of pain symptoms and individual AEs. Although AE rates for combination analgesics may be the same as or lower than reported with monotherapy, because the individual components have different AE profiles it remains necessary to monitor and manage patients accordingly.

Consistent with the findings in this review, a pooled analysis of phase 1–3 clinical trials of a single dose or short course of FDC of paracetamol (500 mg) and ibuprofen (200–300 mg)[61] and an integrated safety analysis from phase 2 and 3 repeated-dose studies of an FDC of paracetamol 325 mg/ibuprofen 97.5 mg (3 tablets per dose every 6 h, or paracetamol 500 mg/ibuprofen 150 mg, 2 tablets per dose every 6 h)[62] concluded that combination therapy was well tolerated, with a safety profile similar to its individual components and with no overall increase in AEs. Safety data suggest that combining paracetamol with an NSAID does not increase the risk of side effects and may decrease it, especially if this strategy allows for use of lower drug doses.

Findings of the current narrative review are consistent with those previously reported in systematic reviews and meta-analyses, which is expected considering the overlap of relevant studies. An overview of Cochrane reviews on nonprescription oral analgesics for acute postoperative pain found that the number needed to treat to achieve a 50% reduction in pain was lower for paracetamol 500 mg/ibuprofen 200 mg (1.6) or paracetamol 1000 mg/ibuprofen 400 mg (1.5) relative to the individual components (paracetamol 500 mg, 3.5; paracetamol 975–1000 mg, 3.6; ibuprofen 200 mg, 2.9; ibuprofen 400 mg, 2.5).[63] Rates of AEs were lower with paracetamol/ibuprofen relative to placebo. Similarly, a systematic review and network meta-analysis of randomized clinical trials of treatment of acute postoperative pain due to dental extraction determined that benefits relative to placebo across a range of pain relief measures were, with little exception, numerically greater with paracetamol 500–1000 mg/ibuprofen 200–400 mg compared with the individual components[64]; the 95% confidence intervals overlapped between combination therapy and ibuprofen but not between combination therapy and paracetamol, although the meta-analysis was not designed to compare treatments with each other.

In contrast to reviews in postoperative pain, a systematic review and network meta-analysis of randomized trials of treatments for acute non-LBP concluded that topical NSAIDs, followed by oral NSAIDs, oral paracetamol and then paracetamol plus diclofenac, offered the most favourable benefit–harm ratio.[65] Paracetamol plus

diclofenac did not appear to be more effective than an oral or topical NSAID alone based on odds ratios and associated confidence intervals.

Recommendations of professional organizations and expert consensus panels are generally consistent with the findings of clinical studies and systematic reviews (Table 2). Several sets of guidelines recommend paracetamol and/or NSAIDs as part of multimodal analgesia for management of acute postoperative pain.[66–69] However, current guidelines do not specifically recommend combining paracetamol with oral NSAIDs for the management of acute musculoskeletal pain.[3,8] An Expert Panel Consensus from China recommends topical or oral NSAID monotherapy for management of musculoskeletal pain but, based on data from studies in osteoarthritis (a chronic pain condition), suggests that oral paracetamol may be used as rescue therapy as needed when using a topical NSAID.[70] A review of scientific evidence by the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine suggests that NSAIDs and paracetamol, either alone or in combination, are effective for the treatment of episodic tension-type headache and pharyngitis.[68] Combination therapy with paracetamol and NSAIDs was not specified in relation to other headache/migraine types and pain conditions, including dysmenorrhoea, covered in the review.

4.1 | Gaps in knowledge

The literature searches performed for this narrative review identified several gaps in knowledge. All studies assessed symptoms with scales

TABLE 2 Recommendations regarding combined use of nonprescription analgesics for treatment of acute pain.

Organization (country or region)	General recommendation	Postoperative pain	Musculoskeletal pain	Headache/ migraine	Other
AAFP/ACP (USA),[3,8a]			Combining APAP with oral NSAIDs not recommended		
APS/ASRAPM/ ASA (USA),[66a]		APAP and/or NSAIDs as part of multimodal analgesia for management of pain in children and adults without contraindications			
American Dental Association (USA),[67a]		NSAIDs alone or in combination with APAP for postoperative pain management following surgical tooth extraction(s) NSAIDs alone or in combination with APAP are more effective in reducing postoperative pain following tooth extraction(s) than opioids			
ANZCA/FPM (Australia),[68b]	Combination of APAP and NSAIDs (in particular ibuprofen) provides superior analgesia *vs.* either drug alone	Multimodal analgesia (combining analgesics with different mechanisms of action) improves pain control and reduces opioid use Combined APAP and NSAIDs superior to either drug alone after dental extraction		Episodic tension-type headache: APAP, NSAIDs or combination	Acute pharyngitis: APAP, NSAIDs or combination is effective
NICE (UK),[69a]		Combination of analgesics from different classes			
Expert Panel Consensus (China),[70c]			Topical or oral NSAID monotherapy recommended, but oral APAP suggested as rescue therapy if needed when using topical NSAID[d]		

[a]Evidence-based guidelines.
[b]Summary report of clinical evidence.
[c]Consensus statement.
[d]Based on evidence in patients with osteoarthritis.
For results described as statistically significant, $P \leq .05$.
AAFP, American Academy of Family Physicians; ACP, American College of Physicians; ANZCA, Australian and New Zealand College of Anaesthetists; APAP, paracetamol; APS, American Pain Society; ASA, American Society of Anesthesiologists; ASRAPM, American Society of Regional Anaesthesia and Pain Medicine; FPM, Faculty of Pain Medicine; NICE, National Institute for Health and Care Excellence; NSAID, nonsteroidal anti-inflammatory drug.

that are not necessarily specific and sensitive to capture the effects of combination therapy, which may involve multiple mechanisms of action. The studies did not examine effects of treatment on the inflammatory response or on tissue damage and repair processes. The contribution of NSAIDs to outcomes unrelated to pain, such as their interaction with the immune system, may also have a relevant impact.[14] In studies of musculoskeletal pain, timing of the intervention relative to the insult was frequently overlooked. In addition, there have been limited efforts in the preclinical space to explore these interactions in a more mechanistic manner.[71,72] These limitations make assessment of the therapeutic value of combinations of different medications challenging.

Only 2 studies (both in the DIPM) reported data on differences in duration of analgesia with combination therapy *vs.* monotherapy, both of which demonstrated an advantage of combination therapy,[35,37] although the duration of analgesia was significantly longer for paracetamol 500 mg/ibuprofen 250 mg *vs.* paracetamol 650 mg but not *vs.* ibuprofen 250 mg in 1 study.[37] Further studies are needed to explore the effects of combination therapy *vs.* monotherapy on duration of analgesia in different acute pain settings.

Studies in the settings of endodontic pain and acute non-LBP did not investigate possible dose-sparing effects of oral combination therapy, as combinations of paracetamol and an NSAID were not compared with individual components used at higher doses. Additional studies on the potential benefits of combination nonprescription therapy on musculoskeletal pain from acute injury (e.g., specific types of injury or more mild injury that is unlikely to result in ED presentation) are warranted. While the studies on acute musculoskeletal pain did not specify sports injury as an exclusion criterion, it was unclear whether these studies included any patients with sports injury; evaluating the potential benefits of combination therapy in sports injury would be of interest.

All 6 studies in headache evaluated treatment combinations that included caffeine, and one study with a paracetamol/NSAID treatment group[53] did not compare this combination with the individual components using statistical tests. Studies are also needed to assess the potential benefits of combination therapy with paracetamol and NSAIDs in other acute pain conditions, such as dysmenorrhoea, earache and acute pharyngitis.

No studies were identified that evaluated the combination of oral paracetamol with a topical NSAID (e.g., diclofenac or methyl salicylate) for acute musculoskeletal pain. A model-based meta-analysis examined findings from studies of systemic paracetamol in combination with systemic diclofenac in acute pain to infer the potential opioid-sparing effect of systemic paracetamol plus topical diclofenac.[30] This analysis included 11 randomized controlled trials (10 in postoperative pain, 1 in musculoskeletal pain), 4 of which were included in the current review,[38,39,43,51] and 7 of which were not included because they involved rectal and/or intravenous routes of administration or use of treatments in a preoperative or operative (nondental) setting. Extrapolation from systemic to topical diclofenac was based on findings that topical diclofenac provides at least equivalent pain relief in osteoarthritis as oral NSAIDs.[73] Results of the model-based meta-analysis indicated greater pain reduction and an opioid-sparing effect with combination therapy *vs.* paracetamol or diclofenac monotherapy, with a more pronounced opioid-sparing effect *vs.* paracetamol (~32%).[30] The findings of the analysis also highlight a need for trials of paracetamol and topical NSAIDs in the setting of acute musculoskeletal pain.

4.2 | Insights and recommendations

Healthcare providers, which may include primary care physicians/general practitioners, physician assistants, nurse practitioners and community pharmacists, play a key role in the management of acute pain. Patients commonly present to their healthcare providers seeking treatment for acute pain conditions.[1] Regular contact with patients affords opportunities to assess how patients are self-treating acute pain and to provide recommendations regarding treatment approaches and safe use of nonprescription medications.

The effectiveness of analgesic treatments is variable among patients, which suggests the need for personalized management of pain.[74] Accordingly, pharmacotherapy for acute pain should be tailored for each patient,[2,74] taking into account the type or cause of pain as well as the patient's responsiveness to different analgesics and their combinations, preferences, lifestyle and comorbidities as they relate to an increased risk for AEs of medications with short-term treatment. A focus on sparing opioid use should remain a priority to minimize the potential for opioid use disorder.[60,74] Educating patients about the appropriate use of nonprescription medications is important. Patients often self-treat their acute pain[5,75] and may be unaware of potential toxicity at high cumulative doses. In particular, caution is warranted regarding the risk of unintended liver injury from exceeding the recommended intake of paracetamol (4 g/day or lower if certain risk factors are present, such as severe alcohol use disorder or advanced hepatic disease),[2,22] especially if the patient is taking other nonprescription preparations that contain paracetamol.[60] Ensuring that patients are aware that the same analgesic medication may be marketed under its generic name and various brand names may also help prevent inadvertent overdose. Patients should also be advised to limit the use of nonprescription analgesics without healthcare provider guidance to a few days. Recommending use of a combination analgesic may help to reduce potential risks while delivering at least equivalent analgesic effectiveness.

The potential effect of NSAIDs on tissue recovery from musculoskeletal injury is an important consideration if paracetamol were to be used in combination with a topical NSAID to treat acute musculoskeletal pain. A systematic review and meta-analysis of the effects of NSAIDs on recovery from acute musculoskeletal injury found that treatment with NSAIDs appears to have a small-to-moderate benefit in reducing pain, loss of muscle strength and blood creatine kinase levels (a marker of muscle damage) and concluded that short-term treatment with nonprescription NSAIDs is warranted in this setting.[76]

Topical NSAIDs are an effective option for treatment of acute musculoskeletal pain because they provide good tolerability with a minimal risk of systemic AEs.[77] Additionally, topical NSAIDs are among the most effective treatments for acute non–low-back musculoskeletal pain and are the only intervention shown to improve all pain-related outcomes.[8] Combination therapy has so far failed to demonstrate better clinical efficacy compared with topical NSAID treatment alone. However, use of oral paracetamol in combination with a topical NSAID appears to be limited to treatment of the mild-to-moderate chronic pain of osteoarthritis when paracetamol alone is insufficient, given its safety relative to oral paracetamol plus an oral NSAID, and is beyond the scope of this review; even in this indication, clinical studies are lacking.[78]

Although this was not a systematic review, an effort was made to identify and include all relevant studies. We used two databases and several search strings and are confident that all relevant peer-reviewed articles were identified. However, bias inherent to search terms/strategy and study selection, and heterogeneity in the designs and sample sizes of the included studies, may compromise the generalizability of findings and ability to draw uniform conclusions.

5 | CONCLUSION

Patients commonly treat acute pain with nonprescription medications, either after consulting with a healthcare provider or on their own. Combining oral paracetamol with an NSAID (topical or oral) may provide greater pain relief than treatment with either drug alone due to differing mechanisms of action and may allow lower drug doses than would be required with monotherapy to achieve the same level of pain control.

While there is a strong pharmacological basis for the potential benefit of combination therapy with an analgesic and anti-inflammatory drug, pain relief in acute pain is often assessed empirically with pain scales. Regardless of comparable symptom improvement following monotherapy or combination therapy, individual patient-level data describing the time course of inflammatory markers of response, as well as objective measures of tissue function and repair, are lacking or not collected systematically in clinical studies. Incorporating measurements of biomarkers, including inflammatory biomarkers (cytokines, growth factors, prostaglandins and other immune mediators) and neurotransmitter biomarkers (substance P, glutamate, γ-aminobutyric acid), into future clinical trial designs may provide objective data on the effectiveness of analgesics.[13,71,79,80] However, interpretation of biomarker data requires further understanding of drug exposure. Similarly, implementation of other novel objective measures, including presence of genetic mutations and polymorphisms, autonomic nervous system monitoring, biopotentials, neuroimaging and composite algorithms, may also help to address the shortcomings of existing trial design.[79] To date, there has been very limited effort in establishing how differences in pharmacokinetics (i.e., drug exposure), both at the local and systemic level, contribute to the overall analgesic response. Integrated evaluation of the effect of interindividual differences in pharmacokinetics and pharmacodynamics is therefore an essential step during the clinical development of novel drug combinations for the treatment of pain. Similar gaps appear to exist in consensus guidelines, which rely on existing evidence but do not endorse efforts to further mechanistic understanding. Additional research is warranted to further explore the benefits of combination therapy with paracetamol and NSAIDs compared with its individual components in different acute pain conditions.

5.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22.[81–83]

AUTHOR CONTRIBUTIONS

Conceptualization: all authors. Methodology: all authors. Formal analysis: all authors. Investigation: all authors. Data curation: all authors. Writing—original draft: all authors. Writing—review and editing: all authors. Visualization: all authors. Supervision: V.S.S. Project administration: V.S.S. Funding acquisition: V.S.S.

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CONFLICT OF INTEREST STATEMENT

A.M. has consulted for Haleon and GSK Consumer Healthcare before Haleon was spun off as an independent global company and currently serves on the Haleon Global Pain Faculty Advisory Board and the Haleon Naturals Advisory Board. B.M. has received honoraria for consultancy over the past 3 years from GSK, Haleon, Sanofi and Krka and has served as a speaker for Krka, GSK, Haleon and Viatris. V.S.S. is an employee of Haleon. M.C. is a member of the Global Pain Advisory Board, Haleon (October 23), and has received honoraria for lectures delivered at educational events organized by Viatris Malaysia. O.D.P. is an employee of GSK and holds GSK and Haleon shares. P.K. is a former employee of Haleon.

DATA AVAILABILITY STATEMENT

The data that support the findings of this review are publicly available, as referenced.

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