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Postgraduate Medicine

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ipgm20

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To cite this article: Pam Kushner, Bill H. McCarberg, Wendy L. Wright, Walid Aldoori, Peter Gao, Ahsia Iqbal & Richard Petruschke (2024) Ibuprofen/acetaminophen fixed-dose combination as an alternative to opioids in management of common pain types, Postgraduate Medicine, 136:6, 594-602, DOI: 10.1080/00325481.2024.2382671

To link to this article: https://doi.org/10.1080/00325481.2024.2382671

Published online: 27 Jul 2024.

POSTGRADUATE MEDICINE
2024, VOL. 136, NO. 6, 594–602
https://doi.org/10.1080/00325481.2024.2382671

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REVIEW

Ibuprofen/acetaminophen fixed-dose combination as an alternative to opioids in management of common pain types

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ABSTRACT

Opioids are frequently used first line to manage acute pain in a variety of settings; however, the use of nonprescription analgesics for acute pain is recognized by experts as a practical and effective opioid-sparing strategy. Variations in dosages and formulations and a lack of standardization in reporting clinical data hinder the awareness of nonprescription treatments and recommendation of their use before opioids and other prescription options. A fixed-dose combination (FDC) of two common nonprescription analgesics, ibuprofen (IBU) and acetaminophen (APAP), is an appealing alternative to opioids in acute pain settings with a range of potential benefits. This narrative review evaluates the evidence in support of IBU/APAP FDCs containing IBU (≤1200 mg/day) and APAP (≤4000 mg/day), the nonprescription maximum daily doses in Canada and the United States, as alternatives to opioids and as a means to reduce the need for rescue opioid medication in acute pain management. A literature search was performed to identify clinical studies that directly compared IBU/APAP FDCs with opioids or nonopioids and measured the need for opioid rescue therapy in acute pain. Across studies, IBU/APAP FDCs consistently demonstrated pain relief similar to or better than opioid and nonopioid comparators and reliably reduced the use of rescue opioids with fewer adverse events. Based on these data, healthcare clinicians should consider FDC nonprescription analgesics as a potential first-line option for the management of acute pain.

PLAIN LANGUAGE SUMMARY

The growing trend of opioid-sparing treatment demands effective nonopioid pain management solutions. A fixed-dose combination (FDC) of ibuprofen and acetaminophen (IBU/APAP) has shown promise as an alternative to opioids in a range of pain management scenarios, but the available data are limited and can be difficult to compare across studies. In this review, the authors performed a comprehensive evaluation of the clinical studies that assessed the use of IBU/APAP FDCs as a means to prevent or decrease the use of opioids for patients with acute pain. In the included studies, IBU/APAP FDCs consistently and safely provided pain relief that could replace or reduce the need for opioids across a range of procedures. This manuscript can serve as a resource for healthcare clinicians when considering the use of IBU/APAP FDC treatments for acute pain management.

ARTICLE HISTORY
Received 15 May 2024
Accepted 11 July 2024

KEYWORDS
Acetaminophen; acute pain; analgesics; opioid; drug combinations; ibuprofen; multimodal treatment

1. Introduction

The ongoing opioid crisis, fueled in large part by the availability of illegally produced synthetic opioids [1], is in urgent need of strategies to help combat the epidemic of opioid overuse and misuse and to mitigate the rise in opioid-related deaths. Among these efforts is the consideration of alternatives to opioids for pain management, such as nonprescription analgesics, across the range of acute pain conditions and healthcare settings [2,3]. Choosing between nonprescription analgesics can be difficult for healthcare clinicians because these products are available at various dosages and formulations, and not all analgesics are equally effective in every patient or with all pain types [2]; in addition, clinical data and educational resources may be lacking. However, clinical practice guidelines consistently provide recommendations and directions for use of nonsteroidal anti-inflammatory drugs (NSAIDs) as alternatives to opioids and support the use of nonopioid combination treatments instead of, or in addition to, opioids where possible [4–7].

An ibuprofen (IBU) and acetaminophen (APAP) fixed-dose combination (FDC) for pain management represents an area of growing interest and focus and is appealing for several practical reasons. First, the individual components in an IBU/APAP FDC have established efficacy and safety profiles, providing pain relief benefitting from the drugs' complementary mechanisms of action (MOA). In addition to analgesic activity in the central nervous system, IBU inhibits cyclooxygenase (COX) enzymes COX-1 and COX-2, which results in the inhibition of prostaglandin synthesis at the periphery of the pain or injury site and pain relief through analgesic and anti-

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inflammatory effects [8,9]. Although the MOA is not completely delineated, APAP is believed to relieve pain related to an injury by inducing analgesia through direct action in the central nervous system [10,11]. Second, in an FDC formulation, the pharmacokinetics and pharmacodynamics are similar to those of the individual active components; however, an FDC may be preferable as it can administer analgesia through the dual mechanisms of action of the two ingredients to help patients stay ahead of the pain cycle [12]. Third, the FDC formulation provides effective and tolerable analgesia per tablet/dose and follows a fixed frequency of dosing for optimization of analgesia [13,14], often at a lower dose of each component compared with doses administered individually [13]. Tested FDCs include IBU at doses of 75 mg to 800 mg combined with APAP at 500 mg to 1000 mg [14–16]. Fourth, individuals looking for pain relief may start with just one component of an FDC and will add the other component if pain relief is not obtained. Starting with the FDC will eliminate the need to go through a trial-and-error period. Fifth, an FDC in a single pill may be a better option than taking each medication separately; several studies have shown that compared with 'free'-dose combination treatment approaches, FDCs reduce pill burden, support adherence, and lead to improved clinical outcomes [17–21]. Sixth, FDC medications also have lower barriers to use, such as availability as over-the-counter (OTC) medications in some markets [22,23].

The goals of this narrative review are to evaluate the evidence in support of FDCs containing IBU (≤1200 mg/day) and APAP (≤4000 mg/day), the nonprescription maximum daily doses in Canada and the United States, as effective alternatives to opioids, and to assess their ability to reduce the need for rescue opioid medication in acute pain management.

2. Methods

A search was performed for all published articles up to March 2023 using OVID Medline, EMBASE, and PubMed databases to screen for clinical studies that compared IBU/APAP FDCs with active comparators (i.e. opioids or nonopioids) and/or measured the need for opioid rescue medication in acute pain models. The following search terms were used: (ibuprofen OR Advil) AND (acetaminophen OR paracetamol OR Tylenol) AND (opioids OR narcotics OR rescue). Note that acetaminophen and paracetamol are the same medication. Results were restricted to studies published in English. Studies were included if they were randomized, had orally administered treatments, used active comparators, and the dosing regimen of IBU and APAP in the FDC was within the nonprescription dose range in at least one arm.

For the purposes of this study, the dosing range of IBU and APAP in the FDC included IBU 75 mg to 400 mg per dose and IBU ≤1200 mg per day (nonprescription dose for IBU in the United States and Canada) and APAP 250 mg to 1000 mg per dose and APAP ≤4000 mg/day (nonprescription dose for APAP in the United States and Canada). Studies were categorized into the following two groups based on design: 1) studies assessing opioids as direct comparators to FDC formulations and 2) studies with nonopioid FDC direct comparators, where reduced opioid use was evaluated as an endpoint.

3. Results

3.1. Search results

A total of 1207 unique articles were identified through the database search. After screening, seven randomized clinical trials met the inclusion criteria. Reasons for exclusion were that studies 1) did not use IBU and APAP as an FDC, 2) used a dose of IBU and/or APAP outside the designated range, 3) did not have the appropriate opioid or nonopioid comparator arms, and 4) had other design components that did not align with requirements. Three studies used opioids as direct comparators to IBU/APAP FDC. Of these, two included endpoints of reduced opioid use. Four studies used nonopioid direct comparators to IBU/APAP FDC, and all included endpoints of reduced opioid use.

3.2. Direct opioid comparators

3.2.1. Postoperative acute dental pain

A double-blind, randomized, placebo-controlled single-dose trial evaluated the safety and efficacy of five treatment regimens in patients with postoperative dental pain following third molar extraction: 2 tablets of IBU 200 mg/APAP 500 mg, 1 tablet of IBU 200 mg/APAP 500 mg plus 1 placebo tablet, 2 tablets of IBU 200 mg/codeine 12.8 mg, 2 tablets of APAP 500 mg/codeine 15 mg, or 2 placebo tablets [24]. Among the 678 patients included in efficacy assessments of the sum of pain relief intensity difference over 12 hours ($SPRID_{0–12}$), 1 and 2 tablets of IBU/APAP offered significantly greater pain relief vs 2 tablets of placebo and APAP/codeine ($p < 0.0001$ for 2 tablets IBU/APAP vs 2 tablets placebo and vs 2 tablets APAP/codeine; $p < 0.0001$ for 1 tablet IBU/APAP vs 2 tablets placebo and $p = 0.0001$ for 1 tablet IBU/APAP vs 2 tablets APAP/codeine; Table 1, Figure 1). Two IBU/APAP tablets offered significantly greater pain relief than 2 IBU/codeine tablets ($p = 0.0001$), and 1 IBU/APAP tablet was noninferior to the opioid combination [24].

Two tablets of IBU/APAP resulted in significantly less use of rescue medication (either APAP/hydrocodone or tramadol alone) vs all other treatment arms ($p < 0.04$; Table 2). The median time to use of rescue medication was 597 minutes for 2 tablets of IBU/APAP, 491 minutes for 1 tablet of IBU/APAP, 483 minutes for 2 tablets of IBU/codeine, 347 minutes for 2 tablets of APAP/codeine, and 101 minutes for placebo. Among patients taking 2 tablets of IBU/APAP, 33.3% did not use rescue medication over the 12-hour study period [24].

IBU/APAP resulted in significantly fewer treatment-emergent adverse events (AEs) compared with codeine combinations ($p = 0.0001$ vs 2 tablets of APAP/codeine; $p = 0.0008$ vs 2 tablets of IBU/codeine). A total of 5.8% and 4.8% of patients taking 1 and 2 tablets, respectively, experienced a treatment-related AE. There were no serious AEs or withdrawals due to AEs during the study [24].

3.2.2. Acute extremity pain in the emergency department (ED)

A two-center, double-blind trial enrolled 416 adults undergoing an ED visit for acute extremity pain (pain originating

Table 1. A randomized, five-parallel-group, placebo-controlled trial comparing the safety and efficacy of analgesic combinations including a single-tablet combination of ibuprofen/acetaminophen for postoperative dental pain [24].

			Primary endpoint	
	Intervention	Comparator	$SPRID_{0-12}$ (95% CI)	*p*-value
Subjects with at least three impacted third molars and experiencing moderate to severe postoperative pain ($N = 678$)	IBU 200 mg/APAP 500 mg	Placebo	2.15 (1.66, 2.64)	< 0.0001
		APAP 1000 mg/codeine 30 mg	0.75 (0.36, 1.13)	0.0001
		IBU 400 mg/codeine 25.6 mg	0.06 (−0.28, 0.40)[a]	0.72
	IBU 400 mg/APAP 1000 mg	Placebo	2.76 (2.27, 3.25)	< 0.0001
		APAP 1000 mg/codeine 30 mg	1.36 (0.97, 1.74)	< 0.0001
		IBU 400 mg/codeine 25.6 mg	0.67 (0.33, 1.02)	0.0001
		IBU 200 mg/APAP 500 mg	0.61 (0.27, 0.95)	0.0005

[a]One tablet of IBU 200 mg/APAP 500 mg was noninferior to 2 tablets of IBU 400 mg/codeine 25.6 mg.
APAP, acetaminophen; CI, confidence interval; IBU, ibuprofen; $SPRID_{0-12}$, sum of pain relief intensity difference over 12 hours.

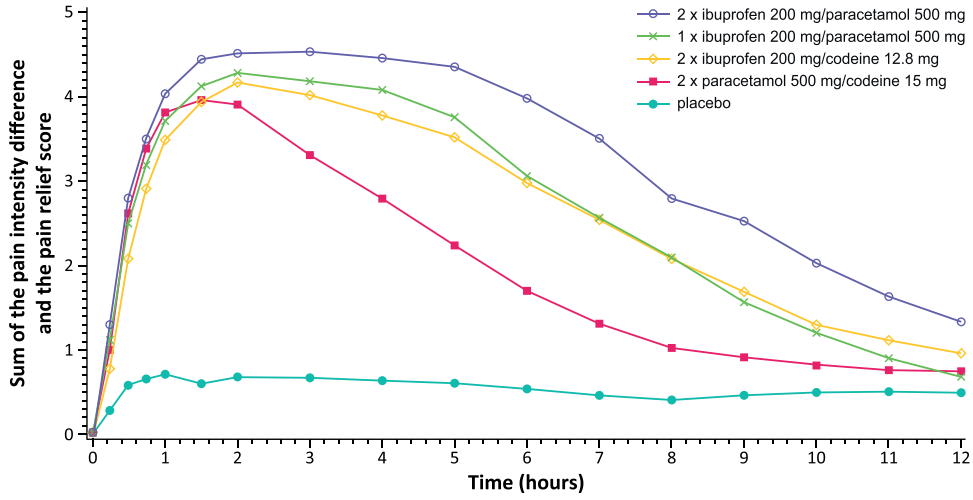

Figure 1. Sum of mean pain relief and intensity difference over 12 hours comparing 1 and 2 IBU/APAP FDC tablets with placebo and two common opioid-containing analgesic combinations after oral surgery [24]. APAP, acetaminophen; FDC, fixed-dose combination; IBU, ibuprofen. Reproduced with permission from Daniels SE, Goulder MA, Aspley S, et al. A randomized, five-parallel-group, placebo-controlled trial comparing the efficacy and tolerability of analgesic combinations including a novel single-tablet combination of ibuprofen/paracetamol for postoperative dental pain. Pain. 2011;152(3):632–642. https://journals.lww.com/pain/Pages/default.aspx.

in the upper extremities [distal to and including the shoulder] and lower extremities [distal to and including the hip]) [25]. Patients were randomly assigned to treatment with either IBU 400 mg/APAP 1000 mg, oxycodone 5 mg/APAP 325 mg, hydrocodone 5 mg/APAP 300 mg, or codeine 30 mg/APAP 300 mg. Patients rated their pain score immediately before receiving treatment and at 1 and 2 hours postdose on the numerical rating scale (NRS; 0 = no pain, 10 = worst possible pain) [25].

Across the four treatment groups, there was no significant difference in pain reduction between any groups at 1 or 2 hours postdose ($p = 0.13$ and $p = 0.053$, respectively) (Table 3). AEs were not assessed [25].

3.2.3. Acute musculoskeletal extremity pain in the ED

A two-center, randomized superiority trial compared oral doses of IBU 400 mg/APAP 1000 mg, IBU 800 mg/APAP 1000 mg, codeine 30 mg/APAP 300 mg, hydrocodone 5 mg/APAP 300 mg, and oxycodone 5 mg/APAP 325 mg in patients with acute musculoskeletal pain in the ED [16]. Adult patients aged 21 to 64 years were enrolled if they presented to the ED with acute (lasting <7 days) musculoskeletal pain in one or more extremities. A total of 600 patients were randomly assigned to one of the five treatment groups, and efficacy was assessed on an 11-point NRS scale before receiving treatment and at 1 and 2 hours postdose [16].

A single dose of IBU 400 mg/APAP 1000 mg provided comparable pain relief (i.e. no significant difference) to opioid combinations at 1 and 2 hours ($p = 0.69$ and $p = 0.85$ for comparison between treatment groups at 1 and 2 hours, respectively; Table 4). The magnitude of difference in NRS scores between treatment groups was not considered to be clinically meaningful at any timepoint throughout the study period. The proportion of patients who received rescue medication (5 mg oral oxycodone at any point during the study) at 1 hour did not differ by treatment (Table 2) [16].

AEs were generally similar across groups with the exception of nausea and vomiting, which differed significantly across treatment groups ($p = 0.048$). Nausea and vomiting occurred in 4.7% of the overall study population but were more frequent with opioid combinations vs IBU/APAP (6.7% in those treated with an opioid-containing regimen vs 1.7% in those who were not).

3.3. Direct nonopioid comparators

3.3.1. Postoperative acute dental pain

3.3.1.1. Mehlisch 2010. A two-center, double-blind trial assessed five different analgesic regimens and rescue medication use in patients aged 16 to 40 years who were scheduled for removal of three to four impacted molars. Patients were

Table 2. Studies evaluating the effectiveness of IBU/APAP combinations in opioid sparing.

Comparison of the efficacy and tolerability of analgesic combinations including a single-tablet combination of IBU/APAP for postoperative dental pain [24]					
Secondary endpoint: Duration of effect (time to first administration of rescue medication)	IBU 200 mg/APAP 500 mg ($n = 173$)	IBU 400 mg/APAP 1000 mg ($n = 168$)	IBU 400 mg/ codeine 25.6 mg ($n = 169$)	APAP 1000 mg/ codeine 30 mg ($n = 113$)	Placebo ($n = 55$)
Median time (min) to use of rescue medication	491	597	483	347	101
% rescue medication use within 90 minutes, n	4.0% (7)	0% (0)	1.8% (3)	1.8% (2)	23.6% (13)
Comparison of the efficacy of five oral analgesics for treatment of acute musculoskeletal extremity pain in the emergency department [16]					
Secondary outcome: Receipt of rescue medication at 1 and 2 h	IBU 400 mg/APAP 1000 mg	IBU 800 mg/APAP 1000 mg	APAP 300 mg/ codeine 30 mg	APAP 300 mg/ hydrocodone 5 mg	APAP 325 mg/ oxycodone 5 mg
% rescue medication use at 1 h, n	1.7% (2)	2.5% (3)	0% (0)	2.5% (3)	0% (0)
% rescue medication use at 2 h, n	24.2% (29)	24.1% (28)	21.8% (26)	22.9% (27)	23.3% (28)
Comparison of the analgesic efficacy of concurrent IBU/APAP with IBU or APAP alone in the management of moderate-to-severe acute postoperative dental pain in adolescents and adults [26]					
Secondary endpoint: Kaplan-Meier analysis of mean time to use of rescue medication	IBU 400 mg/APAP 1000 mg ($n = 67$)	IBU 200 mg/APAP 500 mg ($n = 33$)	IBU 400 mg ($n = 69$)	APAP 1000 mg ($n = 34$)	Placebo ($n = 31$)
Time (min) to use of rescue medication (n)	376.3 (21)	328.5 (20)	296.2 (47)	261.2 (24)	144.4 (28)
% rescue medication use	31%	61%	68%	71%	90%
Analgesic efficacy of an IBU/APAP FDC in moderate-to-severe postoperative dental pain [27]					
Secondary endpoints	IBU 292.5 mg/APAP 975 mg q6h × 48 h ($n = 110$)	APAP 975 mg q6h × 48 h ($n = 111$)	IBU 292.5 mg q6h × 48 h ($n = 112$)	Placebo ($n = 75$)	
Participants requiring rescue medication, no. (%)	26 (23.9)	59 (53.2)	48 (43.2)	61 (81.3)	
p-value[a]		<0.001	0.002	<0.001	
Median time to the requirement of rescue medication, h	-	20.33		1.75	
p-value[a]		<0.001	<0.014	<0.001	
Mean (SD) consumption of rescue medication, mg	3.7 (9.11)	11.0 (14.92)	7.1 (11.57)	17.9 (18.29)	
p-value[a]		<0.001	0.003	<0.001	
Amount of rescue opioid medication (mg) used among patients in three IBU/APAP treatment groups compared with placebo after oral surgery [15]					
Secondary endpoints	IBU 300 mg/APAP 1000 mg q6h for 24 h ($n = 30$)	IBU 150 mg/APAP 500 mg q6h for 24 h ($n = 34$)	IBU 75 mg/APAP 250 mg q6h for 24 h ($n = 46$)	Placebo ($n = 49$)	
Participants requiring rescue (%)	53.3%	61.8%	56.5%	81.6%	
Pairwise comparison to placebo (p-value)	0.007	0.044	0.008	-	
Median amount of rescue medication, mg (range)	5 (0 to 60)	5 (0 to 80)	5 (0 to 45)	20 (0 to 55)	
Pairwise comparison to placebo (p-value)	0.001	0.003	0.001	-	
Mean time to first rescue dose, hours (SE)	12.70 (1.97)	11.15 (1.86)	12.24 (1.63)	5.36 (1.23)	
Pairwise comparison to placebo (p-value)	0.001	0.004	0.001	-	
24-Hour morphine consumption using patient-controlled analgesia in pairwise comparisons between two IBU/APAP FDCs and either agent alone after total hip arthroplasty [28]					
Primary endpoint: 24-h morphine consumption using patient-controlled analgesia in pairwise comparisons between the four groups	IBU 400 mg/APAP 1000 mg ($n = 136$)	APAP 1000 mg ($n = 142$)	IBU 400 mg ($n = 141$)	IBU 200 mg/ APAP 500 mg ($n = 140$)	
Median 24-h morphine consumption (99.6% CI), mg	20 (0 to 148)	36 (0 to 166)	26 (2 to 139)	28 (2 to 145)	
Compared with IBU 400 mg/APAP 1000 mg, median (99.6% CI), mg	NA	−16 (−24 to − 6.5) $p < 0.001$	−6 (−16 to 2) $p = 0.002$	−8 (−16 to 2) $p = 0.005$	

[a]Compared with IBU 292.5 mg/APAP 975 mg. APAP, acetaminophen; CI, confidence interval; FDC, fixed-dose combination; h, hour; IBU, ibuprofen; min, minute; NA, not applicable; q6h, every 6 hours; SD, standard deviation; SE, standard error.

Table 3. Effect of a single dose of oral opioid and nonopioid analgesics on acute extremity pain in the emergency department [25].

	Intervention	Comparator	Primary endpoint: NRS pain score decline 2 h postdose (99.2% CI)	p-value
Patients aged 21–64 years with moderate to severe acute extremity pain and presenting to the ED ($N = 416$)	IBU 400 mg/APAP 1000 mg	Oxycodone 5 mg/APAP 325 mg	−0.1 (−1.0 to 0.8)	NS
		Hydrocodone 5 mg/APAP 300 mg	0.8 (−0.2 to 1.7)	NS
		Codeine 30 mg/APAP 300 mg	0.4 (−0.6 to 1.3)	NS

APAP, acetaminophen; CI, confidence interval; ED, emergency department; h, hour; IBU, ibuprofen; NRS, numerical rating scale; NS, not significant.

randomly assigned to treatment with a single oral dose of IBU 400 mg/APAP 1000 mg, IBU 200 mg/APAP 500 mg, IBU 400 mg alone, APAP 1000 mg alone, or placebo [26]. The sum of pain relief and pain intensity difference from baseline (0 hour) to 8 hours after dosing ($SPRID_8$) was determined, and opioid use was assessed by a Kaplan–Meier analysis of time to use of rescue medication. If rescue medication was required within the first 4 hours, patients were given tramadol 100 mg; after the first 4 hours, patients were given APAP 500 mg/hydrocodone 5 mg or APAP 500 mg/tramadol 100 mg [26].

Among the 234 enrolled patients, those treated with IBU 400 mg/APAP 1000 mg had significantly better mean $SPRID_8$ vs IBU alone ($p < 0.001$), APAP alone ($p < 0.001$), and IBU 200 mg/APAP 500 mg ($p = 0.02$). Patients receiving combination IBU/APAP

Table 4. A randomized trial comparing the efficacy of five oral analgesics for treatment of acute musculoskeletal extremity pain in the emergency department [16].

	Primary endpoint	IBU 400 mg/ APAP 1000 mg	IBU 800 mg/ APAP 1000 mg	Codeine 30 mg/ APAP 300 mg	Hydrocodone 5 mg/ APAP 300 mg	Oxycodone 5 mg/ APAP 325 mg	*p*-value
Patients aged 21–64 years with acute musculoskeletal extremity pain and presenting to the ED ($N = 600$)	Mean decrease in NRS pain score from baseline to 1 h (95% CI)	3.0 (2.6 to 3.5)	3.0 (2.5 to 3.5)	3.4 (2.9 to 3.9)	3.1 (2.7 to 3.5)	3.3 (2.8 to 3.7)	0.69
	Mean decrease in NRS pain score from baseline to 2 h (95% CI)	4.3 (3.9 to 4.8)	4.6 (4.1 to 5.1)	4.4 (3.9 to 4.9)	4.5 (4.1 to 5.0)	4.7 (4.2 to 5.2)	0.85

APAP, acetaminophen; CI, confidence interval; ED, emergency department; h, hour; IBU, ibuprofen; NRS, numerical rating scale.

treatment were less likely to require opioid-containing rescue medication; across interventions, the IBU 400 mg/APAP 1000 mg treatment group had the lowest requirement for rescue medication use (Table 2). Most patients (90%) receiving placebo required rescue medication, while rescue medication was required in 31% of patients taking IBU 400 mg/APAP 1000 mg and 61% taking IBU 200 mg/APAP 500 mg. Patients in the IBU 400 mg/APAP 1000 mg group had a mean time to use of rescue medication of 376.3 minutes, compared with 328.5 minutes, 296.2 minutes, 261.2 minutes, and 144.4 minutes in the IBU 200 mg/APAP 500 mg, IBU 400 mg, APAP 1000 mg, and placebo groups, respectively [26].

AEs were mild, similar across treatments, and consistent with those expected after surgical extraction of impacted molars. In all groups, the most frequent AEs were nausea (26.1% [61/234]), vomiting (18.8% [44/234]), headache (10.3% [24/234]), and dizziness (8.1% [19/234]) [26].

3.3.1.2. Daniels 2018. A phase 3, multicenter, double-blind trial assessed four different analgesic regimens and rescue medication use in adults (18 to 60 years) undergoing surgical removal of at least two impacted third molars under local or general anesthesia [27]. Patients were randomly assigned to treatment with 3 tablets of IBU 97.5 mg/APAP 325 mg (FDC: 292.5/975), APAP 325 mg, IBU 97.5 mg, or placebo. Patients were treated every 6 hours for 48 hours. Rescue medication (oxycodone 5–10 mg every 4–6 hours as needed) was permitted; participants were advised to wait at least 90 minutes after receiving the study drug before taking any rescue medication, and the study drug was still administered per protocol if rescue medications were used. The time-adjusted sum of pain intensity differences from baseline over a 48-hour period ($SPID_{48}$) was determined, and the time to first dose of rescue medication and cumulative consumption of rescue medication were assessed [27].

A significantly greater analgesic effect was observed for patients treated with IBU/APAP (292.5 mg/975 mg) vs equivalent doses of APAP alone, IBU alone, or placebo (all $p < 0.001$). IBU/APAP exhibited greater efficacy vs the three comparators for time to onset of meaningful pain relief, maximum visual analog scale (VAS) pain scores, percentage of patients requiring rescue medication, time to first dose of rescue medication, and amount of rescue medication [27].

Patients in the IBU/APAP group had a lower requirement for opioid rescue medication than patients in the other groups (23.9% vs 81.3%, 53.2%, and 43.2% in patients receiving placebo, APAP 325 mg, and IBU 97.5 mg, respectively; $p \leq 0.002$) (Table 2). The mean total dose of rescue medication in the IBU/APAP group was 3.7 mg, significantly less than that of the other treatment groups (11 mg APAP 325 mg, $p < 0.001$; 7.1 mg IBU 97.5 mg, $p = 0.009$; 17.9 mg placebo, $p < 0.001$) [27].

The most common AE reported was nausea (25% of all AEs). The highest proportion of patients reporting AEs was in the placebo group (50.7%), and the lowest proportion was in the IBU/APAP group (37.3%). There were no significant differences in the rate of AEs across treatment groups ($p = 0.15$) [27].

3.3.1.3. Atkinson 2015. A multicenter, double-blind trial evaluated four different analgesic treatments in patients aged between 16 and 60 years to treat pain associated with extraction of two to four impacted third molar teeth and assess rescue medication use [15]. A total of 159 enrolled patients were randomly assigned to treatment with IBU 300 mg/APAP 1000 mg, IBU 150 mg/APAP 500 mg, IBU 75 mg/APAP 250 mg, or placebo. Rescue medication (immediate-release oxycodone) was permitted upon patient request. The time-adjusted summed pain intensity difference (SPID) up to 24 hours after the first dose was determined, and the amount of rescue medication used, time to rescue medication, and percentage of participants requiring rescue medication were assessed [15].

The overall effect of IBU/APAP on SPID was significant vs placebo ($p = 0.002$). In pairwise comparisons, all doses of IBU/APAP provided significant pain relief vs placebo ($p = 0.004$ for IBU 300 mg/APAP 1000 mg, $p = 0.002$ for IBU 150 mg/APAP 500 mg, $p = 0.002$ for IBU 75 mg/APAP 250 mg) [15].

A total of 81% of participants in the placebo group required rescue medication compared with 56%, 62%, and 53% of participants in the IBU 75 mg/APAP 250 mg, IBU 150 mg/APAP 500 mg, and IBU 300 mg/APAP 1000 mg groups, respectively ($p = 0.025$ vs placebo) (Table 2). All IBU/APAP doses had longer time to rescue medication use (mean: 12.7 hours in the IBU 300 mg/APAP 1000 mg group, 11.15 hours with IBU 150 mg/APAP 500 mg, 12.24 hours with IBU 75 mg/APAP 250 mg, and 5.36 hours with placebo; $p < 0.001$ vs placebo). The IBU/APAP groups also required significantly lower amounts of rescue medication (median: 5 mg with IBU 300 mg/APAP 1000 mg, 5 mg with IBU 150 mg/APAP 500 mg, 5 mg with IBU 75 mg/APAP 250 mg, and 20 mg with placebo; $p < 0.001$ vs placebo) compared with placebo [15].

AEs were reported by 50.0% of patients in the IBU 300 mg/APAP 1000 mg group, 41.2% of patients in the IBU 150 mg/

APAP 500 mg group, 37.0% of patients in the IBU 75 mg/APAP 250 mg group, and 40.8% of patients in the placebo group. Most AEs were of mild or moderate severity and were considered to be not related or unlikely to be related to the study medication. The most common AEs were gastrointestinal issues including nausea, vomiting, and stomach discomfort [15].

3.3.2. Nondental postsurgery acute pain

A multicenter, randomized, blinded trial assessed the impact of four different analgesic regimens on postoperative opioid consumption in patients undergoing planned primary total hip arthroplasty [28], A total of 559 patients were randomly assigned to treatment with IBU 400 mg/APAP 1000 mg, IBU 200 mg/APAP 500 mg, IBU 400 mg/placebo, or APAP 1000 mg/placebo. Patients received a combination of the trial medication (APAP, IBU, and placebo) based on assignment, with one dose comprising three capsules. Total postoperative morphine consumption using patient-controlled analgesia in the first 24 hours after treatment and the proportion of patients with one or more modified serious AEs within 90 days of surgery were measured [28].

Both doses of IBU/APAP reduced morphine consumption compared with APAP 1000 mg/placebo in the first 24 hours after surgery: the median 24-hour morphine consumption was 20 mg in the IBU 400 mg/APAP 1000 mg group, 28 mg for IBU 200 mg/APAP 500 mg, 26 mg for IBU 400 mg/placebo, and 36 mg for APAP 1000 mg/placebo (Table 2; Figure 2). The median difference in morphine consumption between the IBU 400 mg/APAP 1000 mg group vs APAP 1000 mg/placebo was 16 mg ($p < 0.001$); for the APAP 1000 mg/placebo group vs IBU 200 mg/APAP 500 mg it was 8 mg ($p = 0.001$); and for the IBU 400 mg/APAP 1000 mg group vs IBU 400 mg/placebo it was 6 mg ($p = 0.002$). The IBU/APAP combination was considered not clinically better than IBU alone [28].

The IBU/APAP FDCs were well tolerated, and AEs were similar across treatment groups. In the first 24 hours, AEs occurred in 15% of patients in the IBU 400 mg/APAP 1000 mg group, 14% in the IBU 200 mg/APAP 500 mg group, 16% in the IBU 400 mg/placebo group, and 16% in the APAP 1000 mg/placebo group. The most frequent AEs were gastrointestinal [28]. This may be due to the opioid rescue medications, which are known for causing gastrointestinal side effects.

4. Discussion

In randomized clinical trials, IBU/APAP FDCs consistently demonstrated pain relief similar to or better than opioids [16,24,25] and reduced the use of rescue opioid medications [15,24,26–28]. The FDCs were well tolerated, with fewer AEs reported in patients treated with IBU/APAP compared with opioids [15,16,24,26–28]. These studies, several of which only enrolled subjects with moderate-to-severe pain [15,24,25,27], demonstrated that nonprescription FDCs are effective across different acute pain settings and suggest that FDCs can be a viable alternative to opioids in common types of acute pain. This treatment option represents an easy-to-implement OTC approach with the potential to have a positive impact on reducing opioid use in pain management.

Studies of separately administered IBU and APAP lend further support to the efficacy of the FDC in providing analgesia as good as or better than opioids in a variety of clinical conditions. Non-FDC IBU/APAP treatments provided effective pain relief after planned and emergency C-section (studied doses included intravenous [IV] APAP 750 mg + IV IBU 400, 600, and 800 mg; oral APAP 975 mg; oral IBU 600 mg; and oral or IV APAP 1 g every 8 hours + oral IBU 600 mg every 6 hours) and resulted in less use of postsurgical and rescue opioids [29–31]. In carpal tunnel release surgery (studied doses included oral IBU 600 mg and oral APAP 325 mg), patients had equivalent pain control and overall satisfaction with pain management vs those treated with APAP/hydrocodone [32]. Patients treated with non-FDC IBU/APAP in otologic surgery (studied doses included IBU 400 mg + APAP 500 mg) had similar pain control and pain levels as those treated with APAP/codeine, regardless of the type of otologic surgery [33]. Together with the data from the FDC studies presented herein, this body of evidence provides a strong argument for the use of IBU/APAP combination treatments as an effective opioid-sparing strategy for the management of acute pain.

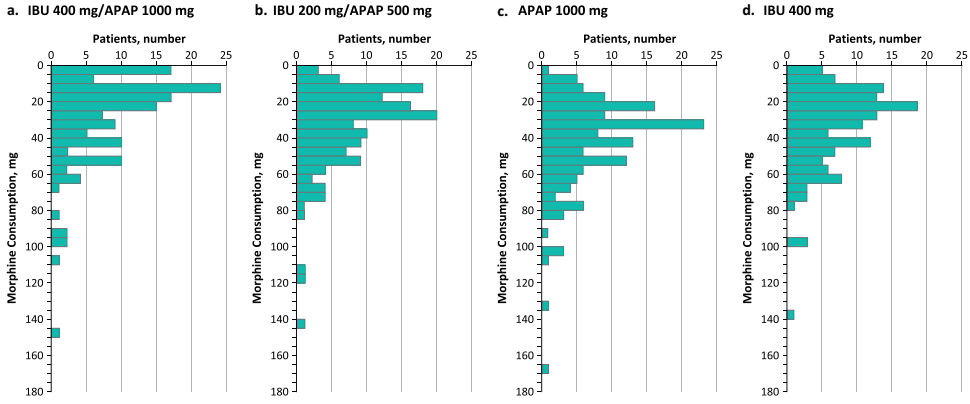

Figure 2. Effect of combination of ibuprofen and acetaminophen vs either alone on patient-controlled morphine consumption in the first 24 hours after total hip arthroplasty [28]. APAP, acetaminophen; IBU, ibuprofen. Adapted with permission from JAMA. 2019. 321(6):562–571. Copyright©2019 American Medical Association. All rights reserved.

FDC therapies present unique risk/benefit profiles based on the simultaneous administration of two drugs that may have different MOAs and, therefore, different efficacy and AE profiles. While two drugs do have the potential to carry an expanded AE profile and level of risk when compared with a single medication, FDCs of IBU/APAP allow effective treatment at lower doses than those used for either treatment when administered alone. Based on the clinical study data, this feature allows for lower maximum daily exposure to either active ingredient and mitigates the risk for expanded AEs with the combination [13,14]. The complementary MOAs of IBU (NSAID) and APAP allow the combination to not only reduce pain sensations but also treat the cause or source of the pain. In contrast, opioids treat symptoms associated with pain, but do not treat the cause. When assessed against oral opioids, IBU/APAP non-FDCs have comparable or better efficacy, benefits, and safety [34]. FDCs have efficacy, benefits, safety, and risks comparable to or better than other commonly used analgesics; in a Cochrane review of OTC oral analgesics for acute pain, among the 21 different treatments assessed (single and combination products), IBU/APAP combinations had the lowest (best) number needed to treat [35]. Another Cochrane review of oral analgesics for acute postoperative pain in adults found a single dose of FDCs to be highly effective based on number needed to treat and compared with single ingredient analgesic products [36]. In a meta-analysis of studies of patients undergoing surgical tooth extraction, IBU/APAP was one of the most effective combinations for pain relief [37].

Clinical practice guidelines provide insight into the positioning of the IBU/APAP combination for pain management. The 2024 American Dental Association (ADA) guidelines for dental pain support the use of combination IBU/APAP as an alternative to opioids for pain management [38]. Recommendations for moderate-to-severe pain include IBU 400 to 600 mg with APAP 500 mg every 6 hours for 24 hours, then IBU 400 mg/APAP 500 mg every 6 hours as needed. For severe pain, recommendations include IBU 400 to 600 mg with APAP 650 mg with hydrocodone 10 mg every 6 hours for the first 24 to 48 hours, then IBU 400 to 600 mg with APAP 500 mg every 6 hours as needed [4]. The 2016 Clinical Practice Guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists strongly recommends that clinicians offer multimodal analgesia, or the use of a variety of analgesic medications and techniques combined with nonpharmacological interventions, for the treatment of postoperative pain in children and adults, including the recommendation of APAP and NSAIDs in patients without contraindications [5]. Based on the guidelines, including the most recent Centers for Disease Control and Prevention guidelines [6], and the data presented in the current study, healthcare clinicians may wish to consider clinical scenarios that traditionally rely on opioids for pain management, but for which IBU/APAP might instead be a rational choice [6,39]. The guidelines are also clear on vigilance required in the use of nonopioid analgesic medications. For example, NSAIDs taken over a prolonged period of time may have gastrointestinal, cardiovascular, and renal effects [6], and patients combining analgesic medications may not be aware of the adverse effects of each medication [5]. Patient education is critical to avoiding these potential dangers.

This study benefits from several strengths stemming from the search strategy and the design of the included studies. Only studies with approved nonprescription IBU/APAP dosing were included, making the conclusions directly transferable to practice. All included studies were randomized, included active comparators, and some assessed multiple dose levels. The studies were consistent in their findings related to the efficacy of IBU/APAP FDCs compared with opioids and opioid-sparing potential, as well as good tolerability, which suggests a strong accord across clinical experiences. The IBU/APAP FDCs worked across a range of pain models and against different comparators, highlighting the value of this combination approach.

However, the studies included in this review have several limitations. Across all studies, there was a lack of long-term data, with some of the studies examining acute pain relief within just 1 or 2 hours. This gap in data highlights a potential avenue for future research (including assessments at >48 hours). The studies used a variety of pain models, IBU/APAP FDCs, and different comparators, which makes it difficult to use the study outcomes to provide broad guidance on the use of IBU/APAP FDCs. Some studies did not include a placebo arm, and the studies directly comparing IBU/APAP FDC with opioids were all single-dose studies. Some studies were also conducted in less-controlled settings, for example, the ED. Included studies also provided limited data in patient populations of interest, such as patients over the age of 64 years and patients with multiple comorbidities. These limitations further underscore the need for more data describing FDC formulations for informing acute pain management decisions.

5. Conclusions

The studies reviewed in this report support the use of IBU/APAP FDCs as effective, well-tolerated, and convenient alternatives to opioids in common acute pain conditions with the potential for an opioid-sparing effect. Implementation of FDC IBU/APAP for acute pain management represents a public health strategy to combat the opioid epidemic. The use of FDC IBU/APAP cannot and is not intended to completely supersede the use of opioids; opioid use remains appropriate for some clinical scenarios, especially as rescue medications in some postsurgical models and in oncology (i.e. late-stage). Providing evidence-based analgesic alternatives that are both safe and effective, such as FDC IBU/APAP, may improve opioid prescribing practices and patient safety. IBU/APAP FDCs are a potential first-line pain therapy for the management of acute pain based on their proven efficacy, generally good tolerability, and potential to help ease the burden of the opioid epidemic.

Acknowledgments

Medical writing assistance was provided by Jenna Bassett, PhD, of Peloton Advantage, LLC, an OPEN Health company, and was funded by Haleon (formerly GSK Consumer Healthcare).

Funding

This study and manuscript were funded by Haleon (formerly GSK Consumer Healthcare). The funder contributed to and collaborated with the authors on the study design, data collection and analysis, decision to publish, and preparation of the manuscript.

Author contributions

Conceptualization: All authors (Pam Kushner, Bill H. McCarberg; Wendy L. Wright; Walid Aldoori; Peter Gao; Ahsia Iqbal; Richard Petruschke). Methodology: All authors (Pam Kushner, Bill H. McCarberg; Wendy L. Wright; Walid Aldoori; Peter Gao; Ahsia Iqbal; Richard Petruschke). Investigation: Walid Aldoori; Peter Gao; Ahsia Iqbal; Richard Petruschke. Writing – Review & Editing: All authors (Pam Kushner, Bill H. McCarberg; Wendy L. Wright; Walid Aldoori; Peter Gao; Ahsia Iqbal; Richard Petruschke). Visualization: All authors (Pam Kushner, Bill H McCarberg; Wendy L. Wright; Walid Aldoori; Peter Gao; Ahsia Iqbal; Richard Petruschke)

Supervision: Richard Petruschke. Project administration: Richard Petruschke. Funding acquisition: Richard Petruschke

Declaration of financial/other relationships

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Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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