



HAL
open science

Perioperative Opioid-sparing Strategies: Utility of Conventional NSAIDs in Adults

Luc Martinez, Evan Ekman, Nardine Nakhla

► **To cite this version:**

Luc Martinez, Evan Ekman, Nardine Nakhla. Perioperative Opioid-sparing Strategies: Utility of Conventional NSAIDs in Adults. *Clinical Therapeutics*, 2019, 41, pp.2612 - 2628. 10.1016/j.clinthera.2019.10.002 . hal-03488586

HAL Id: hal-03488586

<https://hal.science/hal-03488586>

Submitted on 21 Jul 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

PERIOPERATIVE OPIOID-SPARING STRATEGIES: THE UTILITY OF CONVENTIONAL NSAIDS IN ADULTS

Authors: Luc Martinez, MD^a; Evan Ekman, MD^b; Nardine Nakhla, PharmD^c

Affiliations: ^aGeneral Medicine for University Paris VI, Paris, France; ^bAiken Professional Association Orthopaedic Surgery, Aiken, North Carolina, USA, and Edward Via College of Osteopathic Medicine, Spartanburg, North Carolina, USA; ^cUniversity of Waterloo School of Pharmacy, Kitchener, Ontario, Canada

Address for correspondence:

Luc Martinez, MD

Former Professor of General Practice at University Paris VI

30, Rue du Stade -17000

La Rochelle, France

Phone: + 33 (0)6 61 59 81 81

luc.martinez@orange.fr

Author Contributions

Luc Martinez: Study design, data analysis/interpretation, critical revision and review of the manuscript, project/data management, approval of final draft for submission

Evan Ekman: Study design, data analysis/interpretation, critical revision and review of the manuscript, project/data management, approval of final draft for submission

Nardine Nakhla: Study design, data analysis/interpretation, critical revision and review of the manuscript, project/data management, approval of final draft for submission

Declaration of Interest Statement

Luc Martinez has served as an advisor or consultant for Amgen Inc., AstraZeneca Pharmaceuticals LP, GlaxoSmithKline, Ipsen, Eli Lilly and Company, Mayoly Spindler, Menarini, Merck, MSD France, MSD Vaccines, Novo Nordisk, Pfizer Inc, Sanofi, Sanofi Pasteur, and Servier.

Evan Ekman has served as a speaker, researcher, or consultant for Bayer, Eli Lilly and Company, Novartis, and Pfizer.

Nardine Nakhla has served as an advisor or consultant for Allergan, Johnson & Johnson, and Pfizer Inc.

Role of Study Sponsors

These studies were sponsored by Pfizer Consumer Healthcare.

Acknowledgments

Medical writing support was provided by John H. Simmons, MD, of Peloton Advantage, LLC, an OPEN Health company, and was funded by Pfizer.

1 **Abbreviation List**

2 AE = adverse event; ASA = American Society of Anesthesiologists; BID = twice daily;
3 COX = cyclooxygenase; GI = gastrointestinal; IM = intramuscular; IV = intravenous; NR
4 = not reported; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio; OTC =
5 over-the-counter; PBO = placebo; PCA = patient-controlled analgesia; PCEA = patient-
6 controlled epidural analgesia; po = orally; PONV = post-operative nausea and vomiting;
7 pr = per rectum; prn = as needed; q6h = every 6 hours; RCT = randomized, controlled
8 trial; TID = 3 times daily; VAS = visual analog scale.

9

10 **Article Promotion Question**

11 In the perioperative setting, how effective are adjunctive NSAIDs in reducing opioid
12 requirements and opioid-related side effects and improving pain relief?

13 **ABSTRACT**

14 **Purpose:** Opioids have long been used to treat acute post-surgical and post-procedural
15 pain; however, opioid-related adverse events (AEs) contribute to poor patient outcomes.
16 In addition, perisurgical exposure to opioids can potentially increase the risk of
17 developing opioid-use disorder. Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce
18 pain and inflammation by a different mechanism than opioid analgesics and may be
19 able to reduce the use of opioid drugs as part of a multimodal analgesia strategy. We
20 conducted this review to assess the effectiveness and safety of adjunctive conventional
21 NSAIDs given systemically in the perioperative setting in terms of opioid-sparing effects
22 observed post-operatively.

23 **Methods:** Clinical trials published since 2000 that assessed the opioid-sparing effects
24 of conventional, non-selective NSAIDs were identified by conducting a literature search
25 using the PubMed search engine. Search terms were identified for the treatment of
26 interest, the timing of the intervention, and the drugs of interest (NSAIDs). Studies that
27 assessed opioid consumption outcomes with systemic NSAID administration were
28 included in the review; studies in which NSAIDs were administered topically or via
29 periarticular injection, local infiltration, or regional block were excluded.

30 **Findings:** Upon full-text review of search results, 32 studies were chosen for inclusion
31 in this literature review. These included studies that assessed diclofenac, ketorolac,
32 ibuprofen, ketoprofen, dexketoprofen, flurbiprofen, lornoxicam, tenoxicam, meloxicam,
33 and piroxicam. In studies where NSAIDs were associated with opioid-sparing effects
34 within the setting of patient-controlled analgesia, opioid use was reduced by 17%–50%
35 with diclofenac, 9%–66% with ketorolac, 22%–46% with ibuprofen, 34%–66% with

36 ketoprofen, 36%–50% with dexketoprofen, 38%–41% with tenoxicam, 36%–54% with
37 lornoxicam, and 50% with flurbiprofen. No opioid-sparing effect was noted with
38 meloxicam (1 study). The majority of studies that reported on pain score changes
39 revealed either pain reductions with NSAIDs versus placebo or similar pain scores
40 between groups, indicating that NSAIDs did not compromise pain control. Although
41 many studies found no difference in the incidence of AEs in NSAID-treated patients
42 compared with controls, several studies noted lower rates of nausea, vomiting,
43 sedation, and pruritus with NSAIDs versus placebo. Conversely, NSAID-related AEs
44 were few overall but included gastrointestinal bleeding, injection site reactions, transient
45 oliguric renal failure, and dizziness. No surgery-related bleeding complications were
46 observed.

47 **Implications:** NSAIDs have the potential to play an important role in reducing post-
48 operative opioid requirements. Reducing the amount of opioids used could be expected
49 to reduce opioid-related side effects and contribute to reversing the opioid epidemic.

50

51 **Keywords:** non-steroidal anti-inflammatory drug; opioid; patient-controlled analgesia;
52 opioid-sparing; multimodal analgesia; postsurgical pain

53

54

55 **INTRODUCTION**

56 Opioids have long been used to treat acute post-surgical and post-procedural pain;
57 however, multiple studies have shown that opioid-related adverse events (AEs)
58 contribute to poor patient health outcomes.¹ A recent retrospective review of clinical and
59 administrative data from more than 135,000 patients treated with opioids after in-
60 hospital surgical or endoscopic procedures found that 10.6% of patients had opioid-
61 related AEs and that these AEs were associated with negative outcomes, including
62 increased inpatient mortality, prolonged length of stay, and higher 30-day readmission
63 rates.² In addition, studies using administrative and insurance claims data have found
64 that patients undergoing minor and major surgical procedures who fill opioid
65 prescriptions perioperatively are at an increased risk for subsequent development of
66 chronic opioid-use disorder.^{3,4} When compared with nonsurgical patients, odds ratios
67 (ORs) for the development of opioid-use disorder were highest in those undergoing total
68 knee arthroplasty (OR: 5.10; 95% CI: 4.67, 5.58; $P < 0.001$), open cholecystectomy
69 (OR: 3.60; 95% CI: 2.80, 4.62; $P < 0.001$), simple mastectomy (OR: 2.65; 95% CI: 2.28,
70 3.08; $P < 0.001$), and total hip arthroplasty (OR: 2.52; 95% CI: 2.11, 3.01; $P < 0.001$).³

71

72 Opioid abuse is a widespread condition that presents a serious threat to public health,
73 and in 2015 nearly 6% of the US population aged 15–64 years was estimated to be
74 abusing opioids.⁵ By 2016, opioid-use disorder had become the 7th leading cause of
75 disability-adjusted life-years after being the 11th leading cause in 1990.⁶ In the United
76 States, current estimates of the incidence of addiction in patients treated with chronic

77 opioid therapy range from 20% to 33%.⁷ Between 2014 and 2016, life expectancy in the
78 United States declined, largely due to the opioid crisis among young adults.⁸

79

80 Partly in response to the well-publicized North American epidemic of opioid abuse, there
81 has been increasing interest in multimodal analgesia pain management strategies in an
82 effort to reduce opioid use. Multimodal analgesia involves a process by which different
83 procedures or techniques and/or medications with differing mechanisms of action are
84 used to achieve adequate pain control while minimizing the potential complications of
85 opioid use. Nonsteroidal anti-inflammatory drugs (NSAIDs), which reduce pain and
86 inflammation by blocking the production of prostaglandins via inhibition of
87 cyclooxygenase (COX) enzymes,⁹ are an increasingly common component of
88 multimodal therapy because they have comparable analgesic efficacy to opioid drugs
89 but are not associated with many of the most concerning complications of opioids.¹⁰ As
90 such, NSAIDs may present a viable alternative to opioid analgesia in the perioperative
91 setting.

92

93 This review was conducted to assess the effectiveness and safety of adjunctive
94 conventional NSAIDs given systemically in the perioperative setting. The primary
95 outcome of interest was the opioid-sparing effects of NSAIDs, as measured by
96 reduction in morphine equivalents required post-operatively. Secondary outcomes of
97 interest included effects on pain scores, AE rates (both NSAID-related and opioid-
98 related), and associated morbidities.

99

100 **METHODS**

101 We conducted a literature search of MEDLINE using PubMed to identify clinical trials
102 published since 2000 that evaluated the use of systemic, conventional NSAIDs as part
103 of a perioperative multimodal pain management strategy in adults. The search included
104 keywords for multimodal pain management, NSAIDs, opioid-sparing, and perisurgical
105 settings, and the exact search string used was “(multimodal pain management OR
106 multimodal analgesia OR opioid sparing) AND (NSAIDs OR dexketoprofen OR
107 diclofenac OR dipyron OR metamizole OR ibuprofen OR indomethacin OR ketoprofen
108 OR ketorolac OR lornoxicam OR meloxicam OR naproxen OR oxaprozin OR piroxicam)
109 AND (surgical OR perioperative OR postoperative OR patient controlled analgesia).”
110 The results were limited to clinical trials in adults \geq 18 years of age published from
111 January 1, 2000, through August 31, 2018 published in English.

112

113 Abstracts of the publications identified by the PubMed search were examined for
114 relevance and inclusion in the review. Articles were included in the review if they
115 reported at least 1 outcome of interest, including outcomes related to opioid
116 consumption (dose requirements for patient-controlled analgesia [PCA], dosage of
117 rescue analgesics, or dosage of titrated opioids), pain scores, AE rates, and time to
118 recovery or discharge, as applicable. As this review was focused on the adjunctive use
119 of systemic, conventional NSAIDs, studies that used NSAIDs administered via
120 periarticular injections, local infiltration, or regional blocks were excluded. Given that
121 conventional NSAIDs were the focus of this review, we excluded studies that compared
122 an opioid/placebo versus either a selective COX-2 inhibitor or acetaminophen alone.

123 However, if a study assessed several interventions and included a conventional NSAID
124 (e.g., ibuprofen, celecoxib, and placebo arms), it was included as long as at least 1 of
125 the outcomes of interest was reported for the conventional NSAID. If a determination of
126 inclusion could not be made solely from the abstract, the full text of the publication was
127 reviewed to determine its suitability for this review.

128

129 **RESULTS**

130 The original search using PubMed and the pre-specified limits generated a list of 202
131 potentially relevant results. Of these, 148 were excluded upon abstract review and 22
132 were excluded after full text review. Reasons for study exclusion included: 1)
133 conventional NSAID was not the focus of the study (n=130, 76%); 2) reported on the
134 non-systemic (e.g., topical) use of a conventional NSAID (n=19, 11%); 3) outcomes of
135 interest were not reported (n=17, 10%); and 4) identified article was not a clinical study
136 (n=4 (2%). In total, 32 published clinical trials met our inclusion criteria for this analysis.
137 Some of the included studies (n = 8) examined more than 1 NSAID of interest. The
138 breakdown of individual NSAIDs examined in our review is shown in **Figure 1** and
139 included diclofenac (n = 12); ketorolac (n = 7); ibuprofen (n = 5); ketoprofen (n = 4);
140 dexketoprofen (n = 3); lornoxicam (n = 2); tenoxicam (n = 2); meloxicam (n = 1);
141 flurbiprofen (n = 1); and piroxicam (n = 1).

142

143 The majority of the studies included in this review (26/32) administered opioids via PCA,
144 and the opioid-sparing effects of NSAIDs could be captured as a percentage reduction
145 in morphine equivalents required. PCA morphine was most commonly used, although

146 there were some variations, including oxycodone¹¹ and ketobemidone.¹² Also, a single
147 study used meperidine patient-controlled epidural analgesia.¹³ Of the studies not
148 employing PCA, opioid-sparing effects were assessed by measuring patient
149 consumption of oral opioid rescue medication. Hydrocodone/acetaminophen or
150 oxycodone/acetaminophen tablets were used in 2 studies,^{14,15} and in the final 3 studies,
151 intravenous (IV) morphine,¹⁶ IV tramadol,¹⁷ and intramuscular (IM) pethidine¹⁸ were
152 administered until patient-reported pain scores fell below pre-determined thresholds.

153

154 All included trials were conducted in adult populations aged 18 years or older, and 1
155 study was conducted specifically in a geriatric population over 65 years of age.¹⁹ All
156 studies were conducted in the surgical setting, and common surgeries in the trials
157 reviewed included gynecologic surgery/cesarean delivery (n = 15),^{12,13,18,20-26}
158 orthopedic/arthroscopic surgery (n = 10),^{11,14,19,27-33} and spinal surgery (n = 4).³⁴⁻³⁷
159 Findings from individual NSAIDs are presented below.

160

161 **Diclofenac**

162 Diclofenac was the most frequently tested NSAID among the trials in this review; results
163 from these studies are summarized in **Table 1**.^{11,12,14,18-20,23,24,26,31,33,38} The total daily
164 dose of diclofenac administered as a component of multimodal analgesia ranged from a
165 low of 54 mg¹⁴ to a high of 225 mg¹¹ across the 12 studies reviewed. In 9/10 studies
166 evaluating the effects of diclofenac versus placebo in the setting of PCA opioid
167 use,^{11,12,20,23,24,26,31,33,38} diclofenac was associated with a 17% to 50% reduction in opioid
168 use; no difference between diclofenac and placebo was noted in the remaining study of

169 patients 65 years of age and older who underwent open reduction and internal fixation
170 for subcapital femur fracture.¹⁹

171

172 Pain control was assessed versus placebo in each of the 12 trials. In 6 of these, pain
173 scores were significantly lower (i.e., improved) in the diclofenac treatment groups than
174 the placebo groups,^{11,12,18,23,31,38} while 5 studies found no difference in pain scores
175 between treatment groups,^{19,20,24,26,33} i.e., there was no compromise in pain relief with
176 diclofenac added to PCA morphine versus those receiving PCA morphine alone. Pain
177 score changes were not reported in 1 study.¹⁴

178

179 In total, 5 of the trials testing diclofenac versus placebo reported no significant
180 differences in the incidence or nature of AEs in either group.^{12,14,20,24,33} In the 5 trials
181 reporting significant differences in AEs, Alexander et al reported a greater incidence of
182 post-operative nausea and vomiting (PONV) and pruritus in patients receiving placebo
183 versus diclofenac,³¹ Ng et al found significantly higher sedation and nausea scores in
184 the placebo group than in the diclofenac group,²³ Al-Waili et al showed diclofenac-
185 treated patients were less sedated than those in the placebo group,¹⁸ Fayaz found
186 higher rates of PONV with placebo,³⁸ and Silvanto et al found diclofenac was associated
187 with less nausea and more injection site irritation versus placebo.¹¹ Other reported AEs
188 in diclofenac-treated patients included a single case of epigastric pain and melena³⁸ and
189 a bladder perforation.²⁶

190

191 **Ketorolac**

192 Seven studies examined ketorolac at various doses as an opioid-sparing strategy, and
193 results from these studies are summarized in **Table 2**.^{13,16,21,25,31,39,40} Each study
194 evaluated ketorolac treatment against a control group that did not receive the NSAID,
195 and all of these studies reported significant opioid-sparing effects with ketorolac. Opioid-
196 sparing effects were determined versus a background of PCA opioids in 6 of the 7
197 studies,^{13,21,25,31,39,40} and versus morphine titrated to pain level as rescue medication in
198 the remaining study.¹⁶ Ketorolac use was associated with a reduction of PCA opioid use
199 ranging from 9% to 66% in 6 studies^{13,21,25,31,39,40} and a 59% reduction in rescue
200 medication use compared with placebo in the remaining study.¹⁶

201
202 Pain scores were assessed in each of the 7 ketorolac trials reviewed. No statistically
203 significant differences in pain scores between ketorolac-treated patients and control
204 patients were noted in 2 trials.^{13,39} Three studies reported significantly lower pain levels
205 in patients treated with ketorolac at 2 hours and 24 hours after surgery,^{21,25,31} and 1
206 additional study found significant reduction in pain on movement on post-operative day
207 3 only.⁴⁰ In contrast, Cepeda et al found significantly greater pain in the ketorolac group
208 during the first 30 minutes after surgery (a time at which patients had received ketorolac
209 but no morphine) compared with those who received morphine alone, but these
210 differences were not sustained at any point thereafter.¹⁶

211
212 All 7 ketorolac studies in this review reported safety/tolerability results, and 3 found no
213 significant difference in AEs between patients treated with ketorolac compared with

214 other treatments used.^{25,39,40} Of the 4 studies reporting differences in AEs, ketorolac
215 was significantly better tolerated in terms of rates of pruritus,^{16,31} and nausea.^{21,31} In
216 contrast, the final study found significantly more pruritus in the ketorolac-treated group
217 than in the placebo group.¹³

218

219 **Ibuprofen**

220 The opioid-sparing effects of ibuprofen were assessed in 5 placebo-controlled trials, and
221 the results are shown in **Table 3**.^{15,28,30,32,36} The doses tested ranged from 1200 mg/day
222 to 3200 mg/day, and all 5 studies reported positive results for opioid-sparing outcomes.
223 White et al¹⁵ found a statistically significant decrease in the use of opioid-containing
224 rescue medication (hydrocodone/acetaminophen tablets) over 48 and 72 hours post-
225 operatively, and Pinar et al³⁶ reported significant decreases in morphine use with
226 ibuprofen versus placebo at 2, 4, 8, 12, and 48 hours after surgery (all $P < 0.05$).
227 However, neither study quantified the opioid-sparing effect further. In the 3 remaining
228 trials, ibuprofen treatment was associated with significant decreases in the consumption
229 of PCA morphine ranging from 22% to 46% compared with placebo-treated
230 patients.^{28,30,32} A single study tested 2 doses of ibuprofen, 1600 mg/day and 3200
231 mg/day, and found a significant morphine-sparing effect (22% reduction) in patients
232 receiving the higher dose from hours 1–24 after surgery ($P = 0.030$), while the lower
233 dose was not significantly different from placebo.³²

234

235 Each of the 5 studies^{15,28,30,32,36} found ibuprofen was associated with significantly lower
236 pain scores than placebo, and 3 of the studies^{28,30,36} reported no differences in the AEs

237 reported by patients in the ibuprofen and placebo groups. A study using a relatively low
238 prescription dose of ibuprofen (1200 mg/day; also the maximum daily over-the-counter
239 [OTC] dose allowed) in patients following ambulatory surgery found significantly less
240 post-operative constipation in patients receiving ibuprofen versus placebo,¹⁵ while the
241 study by Southworth et al found significant decreases in pyrexia, nausea, and
242 gastrointestinal (GI) AEs in patients receiving either 1600 mg/day or 3200 mg/day
243 ibuprofen compared with placebo.³² However, the higher ibuprofen dose was also
244 associated with an increase in the incidence of dizziness in that study.

245

246 **Ketoprofen and Dexketoprofen**

247 The racemic NSAID ketoprofen and its *S*(+)-enantiomer, dexketoprofen,⁴¹ were
248 assessed in 6 total trials^{11,17,27,29,35,42} (1 study reported on both agents²⁷), and the results
249 are summarized in **Table 4**. Ketoprofen was given at a dose of 100 mg in 4
250 trials,^{11,17,27,42} while dexketoprofen was administered at 50 mg in 2 studies^{27,29} and 25
251 mg in the final study.³⁵

252

253 All trials testing ketoprofen reported that it was associated with opioid-sparing effects.
254 Patients who received ketoprofen and PCA opioids after abdominal or orthopedic
255 surgery used 36% to 55% less morphine^{27,42} and 34% to 66% less oxycodone¹¹ than
256 placebo-treated control patients. In the remaining study, ketoprofen-treated patients
257 used 18% less tramadol and metamizole rescue medication for post-surgical pain than
258 controls.¹⁷ All studies testing dexketoprofen, likewise, found significant reductions in the
259 consumption of PCA morphine by post-surgical patients compared with those receiving

260 placebo. The reductions in morphine use associated with dexketoprofen ranged from
261 36% to 50%.^{27,29,35}

262

263 Ketoprofen was associated with significantly lower pain scores in 3 of the 4
264 studies,^{11,17,27} whereas no difference in pain scores between patients in the treatment
265 and control groups was observed by Rao and colleagues.⁴² In 2 studies evaluating
266 patients after orthopedic surgery, pain levels were significantly lower in dexketoprofen-
267 treated patients compared with those receiving placebo.^{27,29} However, Kesimci et al
268 found no difference in post-surgical pain levels in patients who received oral
269 dexketoprofen or placebo after laminectomy.³⁵

270

271 Of the 5 ketoprofen/dexketoprofen trials that reported safety outcomes, 3 noted
272 numerical reductions in PONV in active versus control groups,^{17,27,42} but the difference
273 for PONV was not significant in any study. A significantly increased incidence of
274 irritation at the infusion site with ketoprofen versus placebo was noted in 1 study.¹¹ One
275 patient taking ketoprofen developed transient oliguric renal failure.⁴² Additionally, Hanna
276 et al reported a single ketoprofen-treated patient and 2 dexketoprofen-treated patients
277 with GI bleeding.²⁷

278

279 **Other NSAIDs**

280 In addition to the more commonly tested NSAIDs discussed above, there were several
281 drugs that were examined in 2 or fewer trials, including flurbiprofen, lornoxicam,

282 tenoxicam, meloxicam, and piroxicam; results for these analgesics are detailed in **Table**

283 **5**.^{22,24,29,34,37,43}

284

285 One study tested pre- and post-surgical administration of flurbiprofen in patients

286 undergoing spinal surgery and found that pre-surgical flurbiprofen (1 mg/kg) significantly

287 reduced PCA morphine consumption versus placebo over the 24-hour study period and

288 significantly reduced pain compared with either the post-surgical or placebo groups from

289 0–6 hours after surgery.³⁷

290

291 Two studies tested tenoxicam, including one that used a dose of 40 mg in patients

292 undergoing spinal surgery³⁴ and one that studied tenoxicam 20 mg in women

293 undergoing Cesarean delivery.²² De Decker et al reported a 41% reduction in PCA

294 morphine use and significantly lower pain scores with tenoxicam 40 mg compared with

295 controls,³⁴ and Yeh et al found a similar 38% reduction in morphine use and significantly

296 lower pain from uterine cramping following Cesarean delivery with tenoxicam 20 mg,²²

297 but only among primiparous women. In the study by De Decker and coworkers,

298 tenoxicam was administered either IV or IM. Patients who received tenoxicam IV had

299 significantly fewer urinary retention events requiring catheterization than placebo-

300 treated patients. This study also included a piroxicam arm (40 mg) but no opioid-sparing

301 effects were observed with piroxicam.³⁴

302

303 The opioid-sparing effects of lornoxicam were also assessed in 2 placebo-controlled

304 trials that administered a dose of 8 mg to post-operative patients and used PCA to

305 measure morphine consumption.^{29,43} These studies reported that morphine
306 consumption was 36%²⁹ and 54%⁴³ lower in lornoxicam-treated patients; lornoxicam
307 provided a significant reduction in pain scores in 1 study.²⁹ There were no differences in
308 AEs between the lornoxicam-only and placebo groups in the one study where this
309 outcome was reported.⁴³

310

311 The NSAID meloxicam was tested in 1 trial using a dose of 15 mg that assessed opioid
312 use with PCA morphine.²⁴ Meloxicam treatment was not associated with decreased
313 morphine consumption or decreased pain levels compared with placebo-treated
314 patients.²⁴

315

316 **DISCUSSION**

317 In this review, we examined 32 studies conducted since the turn of the century
318 investigating the utility of NSAIDs as a component of multimodal analgesia in post-
319 surgical patients in terms of opioid-sparing effects, pain control, and AEs. The studies
320 reviewed show that NSAIDs are consistently associated with reductions in opioid
321 requirements for the treatment of post-operative pain; the only exceptions were
322 meloxicam and piroxicam, although only 1 trial assessing each agent was found for this
323 review. While some studies of perioperative multimodal analgesia evaluated more than
324 1 NSAID product, they are too few to draw any firm conclusions. Although ketoprofen
325 and dexketoprofen provided similar rates of opioid sparing, dexketoprofen provided
326 significant pain control for 24 hours versus placebo, while ketoprofen did so for the first
327 6 hours only.²⁷ Intravenous ibuprofen was opioid sparing,^{28,30,32,36} as was oral ibuprofen

328 at a dose of 1200 mg/day.¹⁵ If OTC-strength analgesics are able to provide consistently
329 effective post-operative pain relief, this could provide substantial healthcare cost
330 savings by shifting these costs to the patient. In general, studies show that a reduction
331 in opioid use was accomplished without a compromise in pain control (vs opioid alone)
332 and in addition to a reduction of opioid-related side effects such as nausea, vomiting,
333 sedation, and pruritus.

334

335 Across the studies reviewed, NSAIDs were well tolerated components of multimodal
336 analgesia. The rates of AEs reported in patients receiving NSAIDs were generally
337 similar to those reported by patients receiving placebo, and there were fewer AEs
338 associated with NSAID use than with conventional morphine analgesia. For instance,
339 several studies in this review reported a lower incidence of PONV when NSAIDs were
340 used with PCA opioids, a finding that is likely related to a diminished opioid requirement
341 in patients using NSAIDs. Recently, Zhao-Fleming and colleagues reviewed potential
342 complications associated with perioperative NSAID use.⁴⁴ They found the strongest
343 level of evidence for delayed healing of non-union bone fractures and recommended
344 judicious use of NSAIDs in the perioperative period in this context. For other potential
345 complications reviewed (e.g., anastomotic leak, negative effects on wound healing or
346 wound infections, and post-operative bleeding), more research is required. NSAID-
347 associated AEs reported in these studies (Tables 1–5) included injection site irritation
348 (ketoprofen, n = 12; diclofenac, n = 6, placebo, n = 0; $P < 0.01$ for each active treatment
349 vs placebo),¹¹ dizziness (ibuprofen 800 mg, n = 12 vs placebo, n = 2; $P = 0.011$),³² GI
350 bleeding (diclofenac³⁸ and ketoprofen²⁷ [1 incident each], and dexketoprofen²⁷ [2

351 incidents]), bladder perforation (diclofenac [1 incident]),²⁶ and transient oliguric renal
352 failure (ketoprofen [1 incident]).⁴² Interestingly, although there is a theoretical risk of
353 bleeding associated with NSAIDs due to their mechanism of action,⁹ none of the trials
354 reviewed herein found that NSAIDs were associated with increased post-operative
355 bleeding.

356

357 There are several limitations that must be considered when interpreting the findings of
358 this review. Foremost among them is the variability in terms of study design among the
359 studies cited here. These include the timing of NSAID administration (e.g., pre-
360 operatively vs post-operatively), dosing regimens used, routes of administration, follow-
361 up times, outcome assessments) used among the various trials. In addition, opioid
362 consumption outcomes were measured in several different ways, including reductions in
363 PCA, rescue, or titrated analgesia requirements, and these differences make
364 comparisons among agents difficult. Finally, the included studies may be skewed
365 toward findings of positive efficacy since articles reporting a positive result are broadly
366 over-represented in the scientific literature.⁴⁵

367

368 **CONCLUSIONS**

369 NSAIDs have the potential to play an important role in reducing post-operative opioid
370 requirements. Reducing the amount of opioids used perioperatively could be expected
371 to reduce opioid-related side effects and may contribute to reversing the opioid
372 epidemic by decreasing the risk of development of opioid-use disorder. As the use of

373 NSAIDs as part of a multimodal analgesic strategy becomes more commonplace, more
374 data on the advantages and disadvantages will become apparent to inform such use.
375

376 **REFERENCES**

- 377 1. National Academies of Sciences E, Medicine,. *Pain Management and the Opioid*
378 *Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription*
379 *Opioid Use*. Washington, DC: National Academies Press; 2017.
- 380 2. Shafi S, Collinsworth AW, Copeland LA, et al. Association of opioid-related
381 adverse drug events with clinical and cost outcomes among surgical patients in a
382 large integrated health care delivery system. *JAMA Surg*. 2018;153(8):757-763.
- 383 3. Sun EC, Darnall BD, Baker LC, Mackey S. Incidence of and risk factors for
384 chronic opioid use among opioid-naive patients in the postoperative period.
385 *JAMA Intern Med*. 2016;176(9):1286-1293.
- 386 4. Brummett CM, Waljee JF, Goesling J, et al. New persistent opioid use after minor
387 and major surgical procedures in US adults. *JAMA Surg*. 2017;152(6):e170504.
- 388 5. Theisen K, Jacobs B, Macleod L, Davies B. The United States opioid epidemic: A
389 review of the surgeon's contribution to it and health policy initiatives. *BJU Int*.
390 2018;122(5):754-759.
- 391 6. Mokdad AH, Ballestros K, Echko M, et al. The state of US health, 1990-2016:
392 Burden of diseases, injuries, and risk factors among US states. *JAMA*.
393 2018;319(14):1444-1472.
- 394 7. Kaye AD, Jones MR, Kaye AM, et al. Prescription opioid abuse in chronic pain:
395 An updated review of opioid abuse predictors and strategies to curb opioid
396 abuse: Part 1. *Pain Physician*. 2017;20(2s):S93-s109.
- 397 8. Ho JY, Hendi AS. Recent trends in life expectancy across high income countries:
398 retrospective observational study. *BMJ*. 2018;362:k2562.

- 399 9. Rainsford KD. Ibuprofen: pharmacology, efficacy and safety.
400 *Inflammopharmacology*. 2009;17(6):275-342.
- 401 10. Joshi GP, White PF. Management of acute and postoperative pain. *Curr Opin*
402 *Anaesthesiol*. 2001;14(4):417-421.
- 403 11. Silvanto M, Lappi M, Rosenberg PH. Comparison of the opioid-sparing efficacy of
404 diclofenac and ketoprofen for 3 days after knee arthroplasty. *Acta Anaesthesiol*
405 *Scand*. 2002;46(3):322-328.
- 406 12. Olofsson CI, Legeby MH, Nygard EB, Ostman KM. Diclofenac in the treatment
407 of pain after caesarean delivery. An opioid-saving strategy. *Eur J Obstet Gynecol*
408 *Reprod Biol*. 2000;88(2):143-146.
- 409 13. Pavy TJ, Paech MJ, Evans SF. The effect of intravenous ketorolac on opioid
410 requirement and pain after cesarean delivery. *Anesth Analg*. 2001;92(4):1010-
411 1014.
- 412 14. Argoff C, McCarberg B, Gudin J, Nalamachu S, Young C. SoluMatrix(R)
413 diclofenac: Sustained opioid-sparing effects in a phase 3 study in patients with
414 postoperative pain. *Pain Med*. 2016;17(10):1933-1941.
- 415 15. White PF, Tang J, Wender RH, et al. The effects of oral ibuprofen and celecoxib
416 in preventing pain, improving recovery outcomes and patient satisfaction after
417 ambulatory surgery. *Anesth Analg*. 2011;112(2):323-329.
- 418 16. Cepeda MS, Carr DB, Miranda N, Diaz A, Silva C, Morales O. Comparison of
419 morphine, ketorolac, and their combination for postoperative pain: results from a
420 large, randomized, double-blind trial. *Anesthesiology*. 2005;103(6):1225-1232.

- 421 17. Oberhofer D, Skok J, Neseek-Adam V. Intravenous ketoprofen in postoperative
422 pain treatment after major abdominal surgery. *World J Surg.* 2005;29(4):446-449.
- 423 18. Al-Waili NS. Efficacy and safety of repeated postoperative administration of
424 intramuscular diclofenac sodium in the treatment of post-cesarean section pain: a
425 double-blind study. *Arch Med Res.* 2001;32(2):148-154.
- 426 19. Fredman B, Zohar E, Tarabykin A, Shapiro A, Jedeikin R. Continuous
427 intravenous diclofenac does not induce opioid-sparing or improve analgesia in
428 geriatric patients undergoing major orthopedic surgery. *J Clin Anesth.*
429 2000;12(7):531-536.
- 430 20. Thaweekul Y, Suwannarurk K, Maireang K, Poomtavorn Y. Effect of
431 intramuscular diclofenac after explore laparotomy for gynecologic surgery: a
432 randomized double-blinded placebo controlled trial. *J Med Assoc Thai.* 2011;94
433 Suppl 7:S52-56.
- 434 21. Sousa AM, Rosado GM, Neto Jde S, Guimaraes GM, Ashmawi HA. Magnesium
435 sulfate improves postoperative analgesia in laparoscopic gynecologic surgeries:
436 a double-blind randomized controlled trial. *J Clin Anesth.* 2016;34:379-384.
- 437 22. Yeh YC, Chen SY, Lin CJ, Yeh HM, Sun WZ. Differential analgesic effect of
438 tenoxicam on post-cesarean uterine cramping pain between primiparous and
439 multiparous women. *J Formos Med Assoc.* 2005;104(9):647-651.
- 440 23. Ng A, Parker J, Toogood L, Cotton BR, Smith G. Does the opioid-sparing effect
441 of rectal diclofenac following total abdominal hysterectomy benefit the patient? *Br*
442 *J Anaesth.* 2002;88(5):714-716.

- 443 24. Anwari JS, Anjum S, Al-Khunain S. Placebo controlled comparison of the opioid
444 sparing effect of meloxicam and diclofenac after abdominal hysterectomy. *Saudi*
445 *Med J.* 2008;29(3):379-383.
- 446 25. Lu CH, Liu JY, Lee MS, et al. Preoperative cotreatment with dextromethorphan
447 and ketorolac provides an enhancement of pain relief after laparoscopic-assisted
448 vaginal hysterectomy. *Clin J Pain.* 2006;22(9):799-804.
- 449 26. Costello MF, Abbott J, Katz S, Vancaillie T, Wilson S. A prospective, randomized,
450 double-blind, placebo-controlled trial of multimodal intraoperative analgesia for
451 laparoscopic excision of endometriosis. *Fertil Steril.* 2010;94(2):436-443.
- 452 27. Hanna MH, Elliott KM, Stuart-Taylor ME, Roberts DR, Buggy D, Arthurs GJ.
453 Comparative study of analgesic efficacy and morphine-sparing effect of
454 intramuscular dexketoprofen trometamol with ketoprofen or placebo after major
455 orthopaedic surgery. *Br J Clin Pharmacol.* 2003;55(2):126-133.
- 456 28. Singla N, Rock A, Pavliv L. A multi-center, randomized, double-blind placebo-
457 controlled trial of intravenous-ibuprofen (IV-ibuprofen) for treatment of pain in
458 post-operative orthopedic adult patients. *Pain Med.* 2010;11(8):1284-1293.
- 459 29. Sivrikoz N, Koltka K, Guresti E, Buget M, Senturk M, Ozyalcin S. Perioperative
460 dexketoprofen or lornoxicam administration for pain management after major
461 orthopedic surgery: a randomized, controlled study. *Agri.* 2014;26(1):23-28.
- 462 30. Gago Martinez A, Escontrela Rodriguez B, Planas Roca A, Martinez Ruiz A.
463 Intravenous ibuprofen for treatment of post-operative pain: A multicenter, double
464 blind, placebo-controlled, randomized clinical trial. *PLoS One.*
465 2016;11(5):e0154004.

- 466 31. Alexander R, El-Moalem HE, Gan TJ. Comparison of the morphine-sparing
467 effects of diclofenac sodium and ketorolac tromethamine after major orthopedic
468 surgery. *J Clin Anesth.* 2002;14(3):187-192.
- 469 32. Southworth S, Peters J, Rock A, Pavliv L. A multicenter, randomized, double-
470 blind, placebo-controlled trial of intravenous ibuprofen 400 and 800 mg every 6
471 hours in the management of postoperative pain. *Clin Ther.* 2009;31(9):1922-
472 1935.
- 473 33. Gombotz H, Lochner R, Sigl R, Blasl J, Herzer G, Trimmel H. Opiate sparing
474 effect of fixed combination of diclophenac and orphenadrine after unilateral total
475 hip arthroplasty: A double-blind, randomized, placebo-controlled, multi-centre
476 clinical trial. *Wien Med Wochenschr.* 2010;160(19-20):526-534.
- 477 34. De Decker K, Vercauteren M, Hoffmann V, Lasters B, Adriaensen H. Piroxicam
478 versus tenoxicam in spine surgery: a placebo controlled study. *Acta Anaesthesiol*
479 *Belg.* 2001;52(3):265-269.
- 480 35. Kesimci E, Gumus T, Izdes S, Sen P, Kanbak O. Comparison of efficacy of
481 dexketoprofen versus paracetamol on postoperative pain and morphine
482 consumption in laminectomy patients. *Agri.* 2011;23(4):153-159.
- 483 36. Pinar HU, Karaca O, Karakoc F, Dogan R. Effects of addition of preoperative
484 intravenous ibuprofen to pregabalin on postoperative pain in posterior lumbar
485 interbody fusion surgery. *Pain Res Manag.* 2017;2017:1030491.
- 486 37. Yamashita K, Fukusaki M, Ando Y, et al. Preoperative administration of
487 intravenous flurbiprofen axetil reduces postoperative pain for spinal fusion
488 surgery. *J Anesth.* 2006;20(2):92-95.

- 489 38. Fayaz MK, Abel RJ, Pugh SC, Hall JE, Djaiani G, Mecklenburgh JS. Opioid-
490 sparing effects of diclofenac and paracetamol lead to improved outcomes after
491 cardiac surgery. *J Cardiothorac Vasc Anesth*. 2004;18(6):742-747.
- 492 39. Chen JY, Wu GJ, Mok MS, et al. Effect of adding ketorolac to intravenous
493 morphine patient-controlled analgesia on bowel function in colorectal surgery
494 patients--a prospective, randomized, double-blind study. *Acta Anaesthesiol*
495 *Scand*. 2005;49(4):546-551.
- 496 40. Chen JY, Ko TL, Wen YR, et al. Opioid-sparing effects of ketorolac and its
497 correlation with the recovery of postoperative bowel function in colorectal surgery
498 patients: a prospective randomized double-blinded study. *Clin J Pain*.
499 2009;25(6):485-489.
- 500 41. Moore RA, Barden J. Systematic review of dexketoprofen in acute and chronic
501 pain. *BMC Clin Pharmacol*. 2008;8:11.
- 502 42. Rao AS, Cardoso M, Inbasegaran K. Morphine-sparing effect of ketoprofen after
503 abdominal surgery. *Anaesth Intensive Care*. 2000;28(1):22-26.
- 504 43. Kotsovolis G, Karakoulas K, Grosomanidis V, Tziris N. Comparison between the
505 combination of gabapentin, ketamine, lornoxicam, and local ropivacaine and
506 each of these drugs alone for pain after laparoscopic cholecystectomy: a
507 randomized trial. *Pain Pract*. 2015;15(4):355-363.
- 508 44. Zhao-Fleming H, Hand A, Zhang K, et al. Effect of non-steroidal anti-
509 inflammatory drugs on post-surgical complications against the backdrop of the
510 opioid crisis. *Burns Trauma*. 2018;6:25.

- 511 45. Fanelli D. Negative results are disappearing from most disciplines and countries.
512 *Scientometrics*. 2012;90:891-904.
513

Number of Studies by NSAID

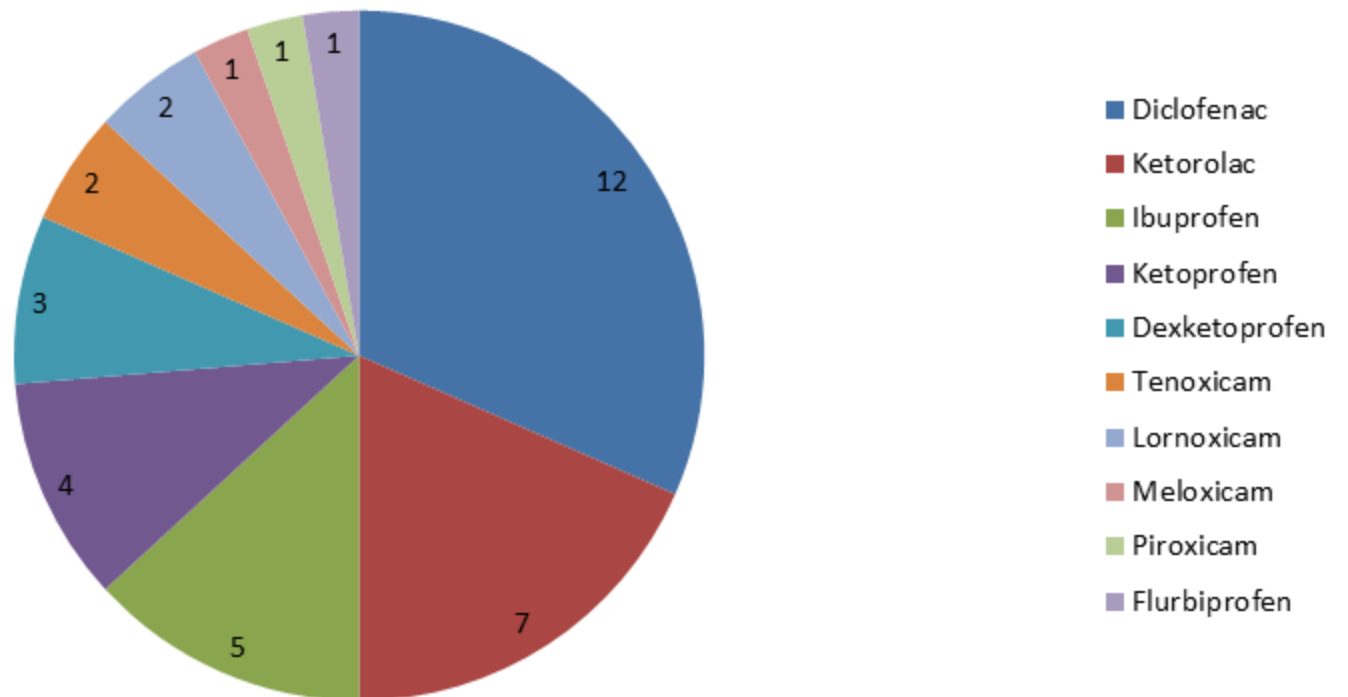


Table 1. Opioid-Sparing Studies of Diclofenac

Reference; Condition	Study Design/ Population	Intervention Arm(s) (n)	Control Arm (n)	Background Analgesia	Opioid Use Reduction	Pain Scores	Adverse Events
Al-Waili NDS, 2001; Cesarean delivery ¹⁸	RCT in female subjects aged 18–40 years	Diclofenac 75 mg IM (n = 60) post-op and prn after 12 hours from last injection up to 2 injections/day	PBO (n = 60)	Pethidine 100 mg IM as rescue medication	In total, diclofenac group used 2800 mg of pethidine vs 22,700 mg in PBO group ($P <$ 0.05) over 48 h; represents an 88% reduction over this time period	Pain scores were significantly reduced with diclofenac vs PBO	Patients in PBO group reported significantly more sedation than diclofenac group ($P <$ 0.05)
Alexander R et al, 2002; Major orthopedic surgery ³¹	RCT in ASA physical status I or II patients aged 18 to 80 years scheduled for prosthetic hip or knee replacement	Single dose diclofenac 75 mg IV (n = 36) or ketorolac 60 mg IV (n = 31) before induction of anesthesia	PBO (n = 32)	PCA morphine 1 mg bolus, 5-minute lockout (max in 4 h: 30 mg); morphine 2 mg (rescue)	Diclofenac 24-h morphine use 30% lower than PBO group ($P <$ 0.01)	Compared with PBO, diclofenac group mean VAS pain scores 22% lower ($P =$ 0.018); verbal pain scores 21% lower ($P =$ 0.047)	PONV more frequent in PBO group ($P <$ 0.05); pruritus more common in PBO group ($P <$.01)
Anwari JS et al, 2008; Abdominal hysterectomy ²⁴	RCT in ASA physical status I or II females aged 25–60 years	Single dose diclofenac 100 mg pr (n = 24) or meloxicam 15 mg pr (n = 23)	PBO (n = 23)	PCA morphine 1.5 mg bolus, 10-minute lockout, basal infusion of 1 mg/h	Diclofenac group 24-h morphine use 17% lower than PBO group ($P <$ 0.05)	No statistically significant difference between groups	No statistically significant difference between groups in sedation or PONV
Argoff C et al, 2016; Bunionectomy ¹⁴	RCT in males and females aged 18–65 years experiencing moderate to severe pain following bunionectomy surgery	Diclofenac 18 mg TID (n = 109); diclofenac 35 mg TID (n = 107); celecoxib 400 mg loading dose + 200 mg BID (n = 106); up to 48 hours	PBO (n = 106)	Rescue medication: hydrocodone/acetamin ophen or oxycodone/acetaminop hen tablets	Mean rescue medication use was significantly less in diclofenac 18 mg group (2.3 tablets) and diclofenac 35 mg group (2.0 tablets) vs PBO group (3.7 tablets; $P <$ 0.001 for both comparisons)	NR	No statistically significant difference between groups reported
Costello MF et al, 2010; Laparoscopic excision of endometriosis ²⁶	Prospective RCT in women aged 18–45 years	Diclofenac 100 mg pr BID until discharge + 0.75% ropivacaine to port sites, excision sites, and topically intraoperatively (n = 30)	PBO (n = 36)	PCA morphine 1 mL bolus, 5-minute lockout	The amount of opioids used by the treatment group through 5 days post-op were 45% lower than control group ($P =$ 0.017)	No statistically significant difference between groups	A bladder perforation in 1 treatment-group patient was only AE reported during trial
Fayaz MK et al, 2004; Cardiac surgery ³⁸	Prospective RCT in adults undergoing elective coronary artery bypass grafting; mean age, 62.6 years	Diclofenac 100 mg pr + acetaminophen 1 g pr for 24 hours (n = 17); diclofenac 100 mg pr (n = 17) for 18 hours	PBO (n = 20)	PCA morphine 1 mg bolus, 5-minute lockout	Morphine use reduced by 27% in diclofenac group and 41% in diclofenac + acetaminophen group compared with PBO (P $<$ 0.05)	Pain scores were significantly lower in treatment groups than controls after 24 h ($P <$ 0.05)	One case of epigastric pain and melena in diclofenac group and 4 cases of severe PONV in PBO group

Fredman B et al, 2000; Major orthopedic surgery in geriatric patients ¹⁹	RCT in ASA physical status I–III geriatric patients aged ≥ 65 years	Diclofenac 0.7 mg/kg IV + constant infusion diclofenac 0.15 mg/kg/h during surgery (n = 20)	PBO (n = 20)	PCA morphine 1 mg bolus, 6-minute lockout	No difference between groups in PCA attempts or morphine delivered	No statistically significant difference between groups	NR
Gombotz H et al, 2010; Hip arthroplasty ³³	RCT in ASA physical status I–III adults aged 18–85 years	Diclofenac/orphenadrine combination 2 x 250 mL infusions (n = 60) during first 24 hours post-op	PBO (n = 60)	PCA morphine 2 mg bolus or piritramide 2.9 mg bolus, 10-minute lockout; max 5 boluses/h	Treatment group used 31% less morphine than PBO group ($P \leq 0.0004$)	No statistically significant difference between groups	No significant difference in AEs; 3 serious AEs in 2 patients in PBO group, none in treatment group;
Ng A et al, 2002; Abdominal hysterectomy ²³	RCT in ASA physical status I or II adults aged 20–60 years	Diclofenac 75 mg pr (n = 18) during three 12-hourly intervals	PBO (n = 16)	PCA morphine (no further information provided)	Mean morphine consumption was 47% lower in diclofenac group than PBO group ($P = 0.02$)	Pain scores were significantly lower in treatment groups than controls after 24 h ($P = 0.04$)	Sedation and nausea scores were significantly higher in PBO group
Olofsson CI et al, 2000; Cesarean delivery ¹²	RCT in healthy women; mean age, 31.6 years	Diclofenac 3 x 50 mg pr (n = 25) during first 24 hours post-op	PBO (n = 25)	PCA ketobemidone 1 mg bolus, 6-minute lockout, 10 mg/h max	Total ketobemidone dose 39% less in diclofenac group ($P < 0.01$) vs PBO group	Significantly lower pain scores in diclofenac group up to 3 h post-op	No complications due to post-op bleeding
Silvanto M et al, 2002; Knee arthroplasty ¹¹	RCT in ASA physical status I–III adults; mean age, 65.4 years	Diclofenac 75 mg IV + 50 mg po TID (n = 24); ketoprofen 100 mg IV + 100 mg po TID (n = 24) until the third post-op day	PBO (n = 16)	PCA oxycodone 30 µg/kg bolus, 12-minute lockout	Oxycodone use by diclofenac group was about half that of the PBO group from 25 h to 60 h post-op ($P < 0.05$)	Pain scores were significantly lower in diclofenac group than PBO group	Significantly more irritation at injection site and fewer cases of nausea in diclofenac group vs PBO
Thaweekul Y et al, 2011; Laparoscopic gynecologic surgery ²⁰	RCT in adults scheduled for laparoscopic gynecologic surgery; mean age, 44.3 years	Single dose diclofenac 75 mg IM post-op (n = 23)	PBO (n = 23)	PCA morphine 1 mg bolus; 5-minute lockout	Median morphine consumption was 41% lower in the diclofenac group than in PBO group ($P = 0.041$)	No statistically significant difference between groups at 24 h	No significant difference in AEs

AEs = adverse events; ASA = American Society of Anesthesiologists (I: normal healthy patient; II: patient with mild systemic disease; III: patient with severe systemic disease); BID = twice daily; IM = intramuscular; IV = intravenous; NR = not reported; PBO = placebo; PCA = patient-controlled analgesia; po = orally; PONV = post-operative nausea and vomiting; pr = per rectum; prn = as needed; RCT = randomized, controlled trial; TID = 3 times daily; VAS = visual analog scale.

Table 2. Opioid-Sparing Studies of Ketorolac

Reference; Condition	Study Design/ Population	Intervention Arm(s) (n)	Control Arm (n)	Background Analgesia	Opioid Use Reduction	Pain Scores	Adverse Events
Alexander R et al, 2002; Major orthopedic surgery ³¹	RCT in ASA physical status I or II patients aged 18 to 80 years scheduled for prosthetic hip or knee replacement	Single dose ketorolac 60 mg IV (n = 31); diclofenac 75 mg IV (n = 36) before induction of anesthesia	PBO (n = 32)	PCA morphine 1 mg bolus, 5-minute lockout (max in 4 h: 30 mg); morphine 2 mg (rescue)	Ketorolac 24-h morphine use 9% lower than PBO group ($P < 0.01$)	Compared with PBO, ketorolac group mean VAS pain scores 18% lower ($P = 0.025$); verbal pain scores 20% lower ($P = 0.048$)	PONV more frequent in PBO group ($P < 0.05$); pruritus more common in PBO group ($P < 0.01$)
Cepeda MS et al, 2005; Surgery ¹⁶	RCT in adult subjects aged 18–60 years	Ketorolac 30 mg IV + morphine 0.1 mg/kg IV (n = 503) until pain intensity of ≤ 4 on numerical rating scale where 0 represents no pain and 10 represents the worst pain imaginable	Morphine 0.1 mg/kg IV (n = 500)	Morphine 2.5 mg/10 minutes until pain intensity ≤ 4 given as rescue	Ketorolac group required 59% less morphine than morphine-only group ($P = 0.00001$)	Pain significantly greater in ketorolac group during initial 30 minutes (a time where this treatment group had only received ketorolac); both groups received morphine thereafter, and no pain difference was observed thereafter	Fewer patients in the morphine-only group reported no AEs ($P = 0.007$), and the morphine-only group had a higher incidence of sedation, dizziness, and pruritus
Chen J-Y et al, 2005; Colorectal resection ³⁹	RCT in ASA physical status I or II subjects aged 35–75 years	PCA with ketorolac (1.2 mg/mL) + morphine (1 mg/mL; n = 39) until VAS for pain on movement was less than 3 on two consecutive evaluations	PCA morphine 1 mg/mL (n = 35)	PCA 2 mL bolus, 10-minute lockout	Morphine consumption 24% lower in ketorolac + morphine group than in morphine-only group ($P < 0.05$)	No statistically significant difference between groups	No statistically significant difference between groups
Chen J-Y et al, 2009; Colorectal resection ⁴⁰	Prospective RCT in ASA physical status I–III subjects aged 30–80 years	PCA with ketorolac (1.2 mg/mL) + morphine (1 mg/mL; n = 52) until VAS for pain on movement was less than 3 on two consecutive evaluations	PCA morphine 1 mg/mL (n = 50)	PCA 2 mL bolus, 10-minute lockout	Morphine consumption in first 3 days was 18% lower in ketorolac + morphine group than in morphine-only group ($P < 0.05$)	No statistically significant difference between groups except for VAS on movement on third day post-op	No statistically significant difference between groups

Lu C-H et al, 2006; Laparoscopic-assisted vaginal hysterectomy ²⁵	RCT in ASA physical status I or II subjects; mean age, 45.4 years	Perioperative ketorolac 60 mg IV + dextromethorphan 40 mg IM (n = 20); perioperative ketorolac 60 mg IV alone (n = 20); perioperative dextromethorphan 40 mg alone (n = 20)	PBO (n = 20)	Chorpheniramine 20 mg IM; PCA morphine 1 mg bolus, 5-minute lockout	Patients in the combination group used 66% less morphine (<i>P</i> = 0.0001) and the ketorolac group used 31% less morphine (<i>P</i> = 0.004) than the control group	Significantly lower pain scores in combination and ketorolac-only groups through 2 h post-op	No significant difference in AEs
Pavy TJG et al, 2001; Cesarean delivery ¹³	RCT in ASA physical status I or II women; mean age, 31 years	Ketorolac 30 mg IV, then 120 mg IV over 24 h (n = 24)	PBO (n = 20)	PCEA meperidine 24 mg incremental dose, 15-minute lockout	Ketorolac group used 36% less meperidine in the 24 h post-op (<i>P</i> < 0.05)	No statistically significant difference between groups at 24 h	Significantly fewer patients free of pruritus at 48 h in ketorolac group (4%) than in PBO group (40%; <i>P</i> = 0.006)
Sousa AM et al, 2016; Laparoscopic gynecologic surgery ²¹	RCT in ASA physical status I or II women; mean age, 49.3 years	Periprocedural ketorolac 30 mg IV (n = 18); periprocedural magnesium sulfate 20 mg/kg (n = 18)	PBO (n = 18)	PCA morphine 2 mg bolus, 10-minute lockout + metamizole 30 mg/kg bolus	Patients in ketorolac group used 59.6% less morphine than the PBO group (<i>P</i> = 0.002)	Significantly less pain in ketorolac group at 24 h than PBO (<i>P</i> < 0.001)	Fewer patients in ketorolac group experienced nausea than in PBO group (<i>P</i> = 0.01)

AEs = adverse events; ASA = American Society of Anesthesiologists (I: normal healthy patient; II: patient with mild systemic disease; III: patient with severe systemic disease); IM = intramuscular; IV = intravenous; PBO = placebo; PCA = patient-controlled analgesia; PCEA = patient-controlled epidural analgesia; PONV = post-operative nausea and vomiting; RCT = randomized, controlled trial; VAS = visual analog scale.

Table 3. Opioid-Sparing Studies of Ibuprofen

Reference; Condition	Study Design/ Population	Intervention Arm(s) (n)	Control Arm (n)	Background Analgesia	Opioid Use Reduction	Pain Scores	Adverse Events
Gago Martínez A et al, 2016; Abdominal and orthopedic surgery ³⁰	RCT in subjects aged 18–80 years	Ibuprofen 800 mg IV q6h (n = 87) for 24 hours (abdominal surgery), 48 hours (hip, shoulder, ligament surgery), and 72 hours (knee and spine surgery)	PBO (n = 79)	PCA morphine 1 mg bolus, 5-minute lockout; max 30 mg in 4 h	Patients in the ibuprofen group used 46% less morphine than the PBO group ($P = 0.01$)	Ibuprofen group had significantly lower pain scores at 24 h post-op than PBO group ($P = 0.0119$)	No statistically significant difference between groups
Pinar HU et al, 2017; Spinal surgery ³⁶	RCT in ASA physical status I or II subjects aged 18–65 years	Pre-op ibuprofen 800 mg IV (n = 21)	PBO (n = 21)	Pregabalin 150 mg po; PCA morphine 1 mg bolus, 10-minute lockout, 30 mg/4 h max	Significantly less morphine consumption in ibuprofen group at 2 h, 4 h, 8 h, 12 h, and 48 h post-op ($P < 0.05$)	Significantly lower pain scores in ibuprofen group at 0 h, 1 h, 2 h, 36 h, and 48 h post-op ($P < 0.05$)	No difference between groups for sedation, nausea, vomiting, dizziness, and visual disturbances
Singla N et al, 2010; Orthopedic surgery ²⁸	RCT in subjects aged 18–80 years	Ibuprofen 800 mg IV q6h (n = 99) for 7 days	PBO (n = 86)	PCA morphine 1–2 mg bolus; 5-minute lockout	Ibuprofen group used 31% less morphine than PBO group ($P < 0.001$)	Ibuprofen group had significantly lower pain scores than PBO group ($P < 0.001$)	No significant difference in AEs
Southworth S et al, 2009; Orthopedic or abdominal surgery ³²	RCT in subjects aged 18–70 years	Ibuprofen 800 mg IV q6h (n = 138); ibuprofen 400 mg IV q6h (n = 134) up to 5 days	PBO (n = 134)	PCA morphine 1–2 mg every 5 min	Ibuprofen 800 mg group used 22% less morphine than PBO group in first 24 h ($P = 0.03$)	Ibuprofen 800 mg group had significantly lower pain scores than PBO group in 1–24, 6–24, and 12–24 h time periods ($P \leq 0.001$ for each time period vs PBO); ibuprofen 400 mg group had significantly lower pain scores than PBO group in 6–24 h and 12–24 h time periods ($P < 0.05$ for each comparison)	Both doses of ibuprofen associated with fewer cases of pyrexia, nausea, and GI AEs ($P < 0.05$); ibuprofen 800 mg associated with more dizziness ($P = 0.011$)
White PF et al, 2011; Ambulatory surgery ¹⁵	RCT in subjects scheduled for superficial surgical procedures; mean age, 48.7 years	Ibuprofen 1200 mg/d (n = 60); celecoxib 400 mg/d (n = 60) for 4 days	PBO (n = 60)	Hydrocodone 5 mg/acetaminophen 500 mg po as rescue medication	Ibuprofen group used fewer rescue medication pills at 48 h and 72 h than PBO group ($P < 0.05$)	Lower overall pain scores (0–72 h) in ibuprofen group than in PBO group ($P < 0.05$)	Post-operative constipation higher in PBO group ($P < 0.05$); no unusual bleeding, wound, or cardiovascular AEs

AEs = adverse events; ASA = American Society of Anesthesiologists (I: normal healthy patient; II: patient with mild systemic disease); GI = gastrointestinal; IV = intravenous; PBO = placebo; PCA = patient-controlled anesthesia; po = orally; q6h = every 6 hours; RCT = randomized, controlled trial.

Table 4. Opioid-Sparing Studies of Ketoprofen and Dexketoprofen

Reference; Condition	Study Design/ Population	Intervention Arm(s) (n)	Control Arm (n)	Background Analgesia	Opioid Use Reduction	Pain Scores	Adverse Events
Ketoprofen							
Hanna MH et al, 2003; Orthopedic surgery ²⁷	RCT in ASA physical status I or II subjects aged 18–75 years	Ketoprofen 2 x 100 mg IM (n = 56) Dexketoprofen trometamol 2 x 50 mg IM (n = 58); first dose of both administered immediately post-op and second administered 12 hours later	PBO (n = 54)	PCA morphine 1 mg bolus, 5-minute lockout	Statistically significant decrease in morphine use by 36% in ketoprofen group vs PBO	Significantly lower pain scores in ketoprofen group than in PBO group at the 1 h–6 h time period ($P = 0.0001$) but not between hours 9–12 or 13–24	PONV more frequent in PBO group (47%) than ketoprofen group (34%); 1 incident of GI bleeding in ketoprofen group, none in PBO
Oberhofer D et al, 2005; Major abdominal surgery ¹⁷	RCT in subjects undergoing major abdominal surgery; mean age, 64.5 years	Ketoprofen 100 mg IV post-op (n = 21) at 1 hour and 9 hours post-op	PBO (n = 22)	Tramadol 200 mg IV + metamizole 5 g IV; tramadol 25 mg bolus (rescue)	Tramadol consumption was 18% lower in ketoprofen group ($P < 0.001$)	Pain scores were significantly lower in ketoprofen group at 12 h post-op; no difference at 24 h	PONV more frequent in PBO group (n = 7) than ketoprofen group (n = 4); no excessive bleeding in ketoprofen group
Rao AS et al, 2000; Abdominal surgery ⁴²	RCT in subjects aged 18–60 years	Ketoprofen 100 mg IV (n = 20) given 0.5 hours before end of surgery and 12 hours later	PBO (n = 19)	PCA morphine 1 mg bolus, 5-minute lockout	Significantly less morphine consumption in ketoprofen group in the recovery room (55% reduction; $P = 0.013$) and significantly less at 8, 12, and 24 hours post operatively ($P < 0.05$ for each time point)	No statistically significant difference between groups	4 cases of PONV in ketoprofen group vs 6 cases in PBO group; 1 patient with transient oliguric renal failure in the ketoprofen group
Silvanto M et al, 2002; Knee arthroplasty ¹¹	RCT in ASA physical status I–III adults; mean age, 65.4 years	Ketoprofen 100 mg IV + 100 mg po TID (n = 24); diclofenac 75 mg IV + 50 mg po TID (n = 24) until the third post-op day	PBO (n = 16)	PCA oxycodone 30 µg/kg bolus, 12-minute lockout	The ketoprofen groups used 34% and 66% less oxycodone than the PBO group from 13 to 24 h and 61 to 72 h post-op, respectively ($P < 0.05$)	Pain scores were significantly lower in ketoprofen group than PBO controls 2 days post-op ($P < 0.05$)	Significantly more irritation at injection site in ketoprofen group vs PBO ($P < 0.01$)

Dexketoprofen							
Hanna MH et al, 2003; Orthopedic surgery ²⁷	RCT in ASA physical status I or II subjects aged 18– 75 years	Dexketoprofen trometamol 2 x 50 mg IM (n = 58); ketoprofen 2 x 100 mg IM (n = 56); first dose of both administered immediately post- op and second administered 12 hours later	PBO (n = 54)	PCA morphine 1 mg bolus, 5- minute lockout	Statistically significant decrease in morphine use by 39% in dexketoprofen group vs PBO	Significantly lower pain scores in dexketoprofen group compared with placebo group across 3 time periods (1–6 h, 9–12 h, and 13–24 h; <i>P</i> < 0.05)	PONV more frequent in PBO group (47%) than in dexketoprofen group (21%); 2 incidents of GI bleeding in dexketoprofen group, none in PBO group
Kesimci E et al, 2011; Laminectomy ³⁵	Prospective RCT in ASA physical status I or II subjects aged 18– 65 years	Single pre-op dose dexketoprofen 25 mg po (n = 25) or acetaminophen 500 mg po (n = 25)	PBO (n = 25)	PCA morphine 1 mg bolus, 15- minute lockout, 0.3 mg/h background infusion	24-h morphine consumption in dexketoprofen group was 36% lower than in the PBO group (<i>P</i> < 0.006) and 31% lower than in the acetaminophen group	Mean pain scores were not different between groups	No significant difference in AEs
Sivrikoz N et al, 2014; Major orthopedic surgery ²⁹	RCT in ASA physical status I–III subjects; mean age, 61 years	Dexketoprofen 50 mg IV BID the day of surgery (n = 40); lornoxicam 8 mg IV BID the day of surgery (n = 40)	PBO (n = 40)	PCA morphine 0.01 mg/kg bolus, 10-minute lockout	Dexketoprofen group used 50% less morphine than PBO (<i>P</i> < 0.001)	Dexketoprofen group had significantly lower pain scores at rest at 1, 2, 4, 8, 12, and 24 h post-op vs PBO group (<i>P</i> value between 0.01 and 0.001 for each time point listed)	NR

AEs = adverse events; ASA = American Society of Anesthesiologists (I: normal healthy patient; II: patient with mild systemic disease; III: patient with severe systemic disease); BID = twice daily; GI = gastrointestinal; IM = intramuscular; IV = intravenous; NR = not reported; PBO = placebo; PCA = patient-controlled anesthesia; po = orally; PONV = post-operative nausea and vomiting; RCT = randomized, controlled trial; TID = 3 times daily.

Table 5. Opioid-Sparing Studies of Other NSAIDs

Reference; Condition	Study Design/ Population	Intervention Arm(s) (n)	Control Arm (n)	Background Analgesia	Opioid Use Reduction	Pain Scores	Adverse Events
Anwari JS et al, 2008; Abdominal hysterectomy ²⁴	RCT in ASA physical status I or II females aged 25–60 years	Single dose meloxicam 15 mg pr (n = 23); diclofenac 100 mg pr (n = 24)	PBO (n = 23)	PCA morphine 1.5 mg bolus, 10-minute lockout, basal infusion of 1 mg/h	Meloxicam 24-h morphine use not different from diclofenac or PBO groups	No statistically significant difference between groups	No statistically significant difference between groups in sedation or PONV
De Decker K et al, 2001; Spine surgery ³⁴	RCT in ASA physical status I–III subjects aged 20–70 years	Piroxicam 40 mg IM (n = 15) pre-op; tenoxicam 40 mg IV (n = 15) pre-op; tenoxicam 40 mg IM pre-op (n = 15)	PBO (n = 15)	PCA morphine 3 mg loading dose; 1 mg bolus, 5-minute lockout; 1-h limit of 5 mg	During the entire 24-h study, the tenoxicam IV group used 41% less morphine ($P < 0.05$); tenoxicam treatment groups were no different than PBO	At 24 h, all 3 treatment groups had significantly lower resting pain scores than PBO group	Urinary retention observed frequently, tenoxicam IV group had significantly fewer events requiring catheterization than PBO group ($P = 0.037$)
Kotsovolis G et al, 2015; Laparoscopic cholecystectomy ⁴³	RCT in adults aged 18–70 years	A) Lornoxicam 8 mg IV + ketamine 0.3 mg/kg IV + gabapentin 600 mg po pre- and post-op + ropivacaine 0.75% local infiltration; B) gabapentin only; C) ketamine only; D) lornoxicam only; E) ropivacaine only (n = 28 for each group); all up to 24 hours	PBO (n = 28)	PCA morphine 1 mg bolus, 10-minute lockout	24-h morphine consumption was 68% lower in the combination group ($P < 0.001$), 53% lower in the gabapentin group ($P = 0.01$), and 54% lower in the lornoxicam group ($P = 0.008$) than PBO	No statistically significant difference between groups	Combination group had significantly fewer incidents of nausea than PBO group ($P = 0.018$); no other differences in AEs
Sivrikoz N et al, 2014; Major orthopedic surgery ²⁹	RCT in ASA physical status I–III subjects; mean age, 61 years	Lornoxicam 8 mg IV BID the day of surgery (n = 40); Dexketoprofen 50 mg IV BID the day of surgery (n = 40) PBO (n = 40)	PBO (n = 40)	PCA morphine 0.01 mg/kg bolus, 10-minute lockout	Lornoxicam group used 36% less morphine than PBO group ($P < 0.001$)	Lornoxicam group had lower pain scores than PBO group at 24 h ($P < 0.001$); dexketoprofen group had lower pain scores than lornoxicam group through 4 h ($P < 0.01$)	NR

Yamashita K et al, 2006; Spinal surgery ³⁷	RCT in ASA physical status I or II subjects scheduled for spinal fusion surgery; mean age, 61.7 years	Pre-op flurbiprofen axetil 1 mg/kg IV (n = 12); post-op flurbiprofen 1 mg/kg IV (n = 12)	PBO (n = 12)	PCA morphine 0.1 mg/kg bolus, 3 mL dose, 30-minute lockout	Morphine consumption was roughly 50% lower with pre-surgical flurbiprofen than with PBO or post-op flurbiprofen ($P < 0.05$)	Pain scores were significantly lower with pre-surgical flurbiprofen than with PBO through 24 h ($P < 0.05$)	No AEs reported in flurbiprofen treatment groups
Yeh Y-C et al, 2005; Cesarean delivery ²²	Prospective RCT in ASA physical status I or II women; mean age, 31.2 years	Tenoxicam 20 mg IV perioperatively: Primiparous (n = 20); Multiparous (n = 20)	PBO: Primiparous (n = 20); Multiparous (n = 20)	PCA morphine 2 mg bolus, 10-minute lockout	Tenoxicam reduced morphine use in primiparous women compared with PBO (38%; $P < 0.05$), but not in multiparous women	Tenoxicam reduced pain from uterine cramping in primiparous women ($P < 0.05$), but not in multiparous women	No statistically significant difference between groups

AEs = adverse events; ASA = American Society of Anesthesiologists (I: normal healthy patient; II: patient with mild systemic disease; III: patient with severe systemic disease); BID = twice daily; IM = intramuscular; IV = intravenous; NR = not reported; PBO = placebo; PCA = patient-controlled analgesia; po = orally; PONV = post-operative nausea and vomiting; pr = per rectum; RCT = randomized, controlled trial.