

Opioid vs Nonopioid Single Dose Medications for Acute Extremity Pain in the Emergency Department (ED) - Critical Appraisal & Insights from the [Chang et al RCT](#)¹

BOTTOM LINE ⇒ supports a nonopioid option of acetaminophen + an NSAID over opioid options for acute pain in the ED

- No statistically significant or clinically important differences in pain reduction were seen 2 hours after the administration of a single dose nonopioid combination (ibuprofen 400mg + acetaminophen 1000mg po x1) vs. oral opioid combinations
- Trends that may be of interest (given arbitrary nature of minimally clinically important difference in pain, P value, & limited power of trial):
 - ♦ combinations of (ibuprofen + acetaminophen) and (oxycodone + acetaminophen) trended slightly better
 - ♦ combinations of weaker opioids, (hydrocodone + acetaminophen) and (codeine + acetaminophen) trended slightly worse
- Adverse event information was not collected and contextualization of results requires consideration of those who may not be suitable candidates (e.g. see exclusions) for an NSAID + acetaminophen based regimen, although single dose minimizes risk.
- For moderate-severe acute pain, opioid analgesic combinations do not outperform nonopioid combinations. Unless NSAID + acetaminophen combination is contraindicated, it is an excellent pharmacological choice for acute extremity pain in the ED.

BACKGROUND¹

- Opioids are often considered to provide stronger analgesia for acute injury, but this is not necessarily supported in the literature. The study discussion suggests that it is time to let the evidence challenge that aspect of the WHO Analgesic Ladder. Many postsurgical studies have found combination nonopioids to be as effective, or more effective than opioid combinations.²
- There is considerable desire to address the current burden of opioid related harms such as addiction, overdose and opioid related death.
- Comparing common opioid combinations in ER settings against a nonopioid combination-provides practical insight.

TRIAL BACKGROUND/DESIGN¹ {Published - Nov 2017}

DESIGN: randomized, double blind; active control of 1 nonopioid vs 3 opioid combination strategies; allocation concealed.

INTERVENTION:

Nonopioid Combination:	ibuprofen 400mg + acetaminophen 1000mg po x1	<div style="border: 1px solid black; padding: 5px; background-color: #e0ffe0;"> Non-pharmacologic interventions: Elastic bandage, splint, cast, ice, other. </div>
Opioid Combinations:	oxycodone 5mg + acetaminophen 325mg po x1, or hydrocodone 5mg + acetaminophen 300mg po x1, or codeine 30mg + acetaminophen 300mg po x1	

- rescue analgesic (5mg oxycodone) allowed within the 2hr study period at discretion of ED physician; additional analgesia permitted.
- analysis: ITT; multiple imputation using chained equations used to impute scores (calculate missing NRS data) for patients receiving rescue meds; Bonferroni method used to account for multiple comparisons

INCLUSION: adult, age 21-64; presenting to ED (in Bronx NY) with an acute extremity pain (shoulder & distal upper; hip & distal lower); indication for radiological imaging (proxy for more severe injury, and allowed time for 1 & 2 hour pain scoring)

EXCLUSION: past use of methadone, chronic condition requiring frequent pain management, hx of adverse reaction to study med, hx of opioid use in last 24 hours, hx of ibuprofen or acetaminophen within last 8 hours, pregnant, breastfeeding, hx of peptic ulcer disease, any prior use of recreational narcotics, medical condition that might affect metabolism of opioids, acetaminophen, or ibuprofen (hepatitis, renal insuff., hypo- or hyperthyroid, Addison or Cushing disease), potential drug interaction (e.g. on SSRI, TCA)

POPULATION at baseline: n=416 (411 analyzed after 5 patients excluded based on analgesic use prior to randomization); mean age ≈37; ~48% female; diagnosis: 59-67% sprain or strain, 21-24% extremity fracture, 8-12% muscle pain, 4-7% contusion, ~4% other; mean pain score = 8.7

Table 1: Results – Pain Scores - Numerical Rating Scale (NRS): 11 point where 0 = no pain; pain scores & decline in pain scores

Minimum clinically important difference was NRS score of 1.3	Ibuprofen + Acetaminophen n=101	Oxycodone + Acetaminophen n=104	Hydrocodone + Acetaminophen n=103	Codeine + Acetaminophen n=103	P Value (by analysis of variance)
Primary Endpoint: - Decline in NRS score at 2hr	4.3 (3.6 – 4.9)	4.4 (3.7-5.0)	3.5 (2.9-4.2)	3.9 (3.2-4.5)	.053 (NS)
Baseline score	8.9	8.7	8.6	8.6	.47
NRS – 1hr	5.9	5.5	6.2	5.9	.25
NRS – 2hr	4.6	4.3	5.1	4.7	.13
Receiving rescue analgesic	17.8%	13.5%	17.5%	22.3%	.42
Rescue analgesic dose in MED	1.6	1.1	1.7	2.0	.27
Total analgesic dose in MED	1.6	8.6	6.7	6.5	<.001

STRENGTHS, LIMITATIONS, UNCERTAINTIES

STRENGTHS	<ul style="list-style-type: none"> • Compared commonly used analgesic regimens, which allows for generalizability to other EDs and acute care settings.
LIMITATIONS	<ul style="list-style-type: none"> • The high percentage of patients receiving opioid rescue analgesia may have favored finding no difference • There is significant room for adverse effects to the medications used and unfortunate that no data was collected • A set dose was given as study medication with no room for individualized adjustment, as may occur in real life • Other: variation in injury severity, baseline population; some individual results could vary from the average³
UNCERTAINTIES	<ul style="list-style-type: none"> • Did not assess benefit (or harm) at later time point than 2 hours (such as 24 hours); might there be a difference? • Imputation of scores for patients receiving rescue opioid analgesia could be inaccurate and have an impact on the overall result, especially given how close the p value and confidence ranges were for a) decline in score and b) comparison of between group differences.

- The predefined minimally clinically important difference of 1.3 in pain score could be inadequate for some patients.

Hx=history **MED/day**=morphine equivalent dose per day **NS**=non-statistically significant **NSAID**=non-steroidal anti-inflammatory drug **po**=by mouth
SSRI=selective serotonin reuptake inhibitor **TCA**=tricyclic antidepressant

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Related RxFiles Links:

- <http://www.rxfiles.ca/rxfiles/uploads/documents/RxFiles-Pain-and-Opioid-Resource-Links.pdf>

References:

- ¹ Chang AK, Bijur PE, Esses D, Barnaby DP, Baer J. Effect of a Single Dose of Oral Opioid and Nonopioid Analgesics on Acute Extremity Pain in the Emergency Department: A Randomized Clinical Trial. JAMA. 2017 Nov 7;318(17):1661-1667. Full article and supplemental content available at: <https://jamanetwork.com/journals/jama/fullarticle/2661581>
- ² Bandolier. Oxford league table of analgesics in acute pain. 2007. Accessed online 16 July 2018 at <http://www.bandolier.org.uk/booth/painpag/Acutrev/Analgesics/Leagtab.html>
- ³ Beaudoin FL. Combination of ibuprofen and acetaminophen is no different than low-dose opioid analgesic preparations in relieving short-term acute extremity pain. BMJ Evid Based Med. 2018 Oct;23(5):197-198.