Pain, Outpatient Management

Does taking an NSAID for acute pain make you more likely to develop chronic pain? Looks like it, so acetaminophen (Tylenol) is a better as a first choice.


Does Benadryl help acute pain in the ER?

- Yes, but see further below...


BACKGROUND: Diphenhydramine, commonly prescribed as an antihistamine drug, is not known for its analgesic effect and its use in acute pain management has not been thoroughly investigated. AIM: In this study, we aim to explore the analgesic properties of diphenhydramine and its role in acute pain reduction in the emergency department (ED). METHODS: A systematic review and meta-analysis were performed. The inclusion criteria were randomised controlled trials that investigated the effect of intravenous diphenhydramine on the management of acute pain. Acute pain reduction was defined as a reduction in the visual pain score within one hour of drug administration. We excluded non-English articles, articles that measured the impact of diphenhydramine beyond the acute period, and those that used a pain score other than the 10-point visual pain scale. The information sources included PubMed, Google Scholar, Cochrane, PROSPERO, and grey literature (ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform) databases for articles published between 1963 and January 2022, along with the articles referenced at the end of the reviews, for the keywords ‘diphenhydramine’, ‘antihistamine’, ‘pain’, and ‘analgesia’. The researchers used the RoB 2 Cochrane risk-of-bias tools for randomised controlled trials. RESULTS: We included four studies out of 128,902 involving 438 patients, out of whom 218 received diphenhydramine for pain control. The mean pain score in patients who received diphenhydramine was reduced by 28%; t(6)= -2.879, 95% CI [-2.87 to -0.23], p=0.028. When the baseline pain score was included in the analysis, we noted a reduction of 48% from the initial pain score. The pooled effect size or mean difference in acute pain reduction favouring diphenhydramine, taken from a random-effects model, was -1.53 (95% CI: [-2.35 to -0.70]) using Cohen’s d. CONCLUSION: This meta-analysis confirms the analgesic advantages of diphenhydramine and supports its consideration as an adjunct for acute pain management in the ED.

- However, the above study didn't address the drawbacks of Benadryl for pain in the ED, including sedation that lasts for up to 12 hours and is worse than having an alcohol of 0.1 (higher than the 0.8 that is legally drunk in most states)


**Is a combination of a NSAID and acetaminophen better than a narcotic plus acetaminophen for initial treatment of musculoskeletal pain in the ED, because there is less nausea and vomiting?**
- Yes.


**STUDY OBJECTIVE:** We compare the efficacy and adverse effects of 5 oral analgesics in emergency department (ED) patients aged 21 to 64 years with acute musculoskeletal pain. **METHODS:** This was a randomized clinical trial conducted in 2 urban EDs. Patients received 400 mg ibuprofen/1,000 mg acetaminophen, 800 mg ibuprofen/1,000 mg acetaminophen, 30 mg codeine/300 mg acetaminophen, 5 mg hydrocodone/300 mg acetaminophen, or 5 mg oxycodone/325 mg acetaminophen. The primary outcome was change in pain before administration of medication (baseline) to 1 hour postbaseline. A numeric rating scale was used, varying from 0="no pain" to 10="worst imaginable pain." Secondary outcomes included receipt of rescue medication and adverse effects at 1 and 2 hours postbaseline. ANOVA was used to test differences in the primary outcome between treatment groups. **RESULTS:** Six hundred participants, predominantly men and Latino, were enrolled. Change in pain from baseline to 60 minutes did not differ by treatment (P=.69). The mean change in pain in numeric rating scale units was 400 mg ibuprofen/1,000 mg acetaminophen 3.0 (95% confidence interval [CI] 2.6 to 3.5); 800 mg ibuprofen/1,000 mg acetaminophen 3.0 (95% CI 2.5 to 3.5), 30 mg codeine/300 mg acetaminophen 3.4 (95% CI 2.9 to 3.9), 5 mg hydrocodone/300 mg acetaminophen 3.1 (95% CI 2.7 to 3.5), and 5 mg oxycodone/325 mg acetaminophen 3.3 (95% CI 2.8 to 3.7). Rescue medication was received before 1 hour had elapsed by 2 patients receiving 400 mg ibuprofen/1,000 mg acetaminophen (1.7%), 3 patients receiving 800 mg ibuprofen/1,000 mg acetaminophen (2.5%), zero patients receiving 30 mg codeine/300 mg acetaminophen (0.0%), 3 patients receiving 5 mg hydrocodone/300 mg acetaminophen (2.5%), and zero patients receiving 5 mg oxycodone/325 mg acetaminophen (0.0%) (P=.21). More patients who received opioids were nauseated or vomited compared with those who did not: 6.7% versus 1.7% (5.0% difference; 95% CI 1.7% to 8.2%). The findings at 2 hours were similar. **CONCLUSION:** No analgesic was more efficacious than others 1 or 2 hours after baseline. There was significantly more nausea and vomiting among patients treated with opioids.

**More on pain meds in general**

</D-Analg.TXT>

</D-NSAID.TXT>

**Do one out of ten ibuprofen users take more than they should?**
- Yes.

[Kaufman, D. W., et al. (2018). "Exceeding the daily dosing limit of
nonsteroidal anti-inflammatory drugs among ibuprofen users."

**Are NSAIDs safe for fractures?**
- This point-counterpoint avoids a discussion of the risks of opioids vs NSAIDs and thus the "use NSAIDs" side wins.

**Trigger Point Injections**
- Safe and simple and done for many decades by many including me with impressive anecdotal success.
- Need to find a trigger point to inject it: tender, harder than surrounding muscle.
- Starting to get some evidence:

**My recommendation for outpatient pain management, assuming healthy patient:**
- naproxen = generic Aleve; cheaper than brand name, better compliance with BID dosing than Motrin = ibuprofen's QID dosing. 220 mg (OTC dose) BID with food, ideally with a big meal like breakfast and dinner. Unlike Motrin or even more prescription NSAIDs, not associated with cardiovascular risk.
Use Motrin instead if pregnant (except for last 6 weeks) or breastfeeding.
Add:
- acetaminophen (generic Tylenol) 500 mg (extra-strength Tylenol) 2 PO TID, or 325 mg (regular-strength Tylenol) 3 PO TID. This results in ~3000 mg = 3 g which is the recommended max daily dose (can go up to 4 g daily if inpatient and monitoring LFTs).
  If needed, add:
- Neurontin (gabapentin) 300 mg PO TID
- tramadol 50 mg, 1-2 PO QID, or oxycodone 5-10 mg, 1-2 PO QID

**Is the OTC dose of ibuprofen (Motrin) or naproxen (Aleve) as good as the higher prescription dose?**
- For musculoskeletal pain, for dental pain, for DJD or for back pain, yes.
  + Single doses of 400, 600 and 800 mg ibuprofen the same for acute pain in the ED.
STUDY OBJECTIVE: Nonsteroidal anti-inflammatory drugs (NSAIDs) are used extensively for the management of acute pain, with ibuprofen being one of
the most frequently used oral analgesics in the emergency department (ED). We compare the analgesic efficacy of oral ibuprofen at 3 different doses for adult ED patients with acute pain. METHODS: This was a randomized, double-blind trial comparing analgesic efficacy of 3 doses of oral ibuprofen (400, 600, and 800 mg) in adult ED patients with acute painful conditions. Primary outcome included difference in pain scores between the 3 groups at 60 minutes. RESULTS: We enrolled 225 subjects (75 per group). The difference in mean pain scores at 60 minutes between the 400- and 600-mg groups was -0.14 (95% confidence interval [CI] -0.67 to 0.39); between the 400- and 800-mg groups, 0.14 (95% CI -0.65 to 0.37); and between the 600- and 800-mg groups, 0.00 (95% CI -0.47 to 0.47). Reductions in pain scores from baseline to 60 minutes were similar for all subjects in each of the 3 groups. No adverse events occurred in any group. CONCLUSION: Oral ibuprofen administered at doses of 400, 600, and 800 mg has similar analgesic efficacy for short-term pain relief in adult patients presenting to the ED with acute pain.

+ A gram of Tylenol and 800 of Motrin is no better than a gram of Tylenol and 400 of Motrin.

+ However, if using short-acting ibuprofen instead of the naproxen I recommend, which I do if it's lunchtime or midnight, so the patient can then switch to a breakfast-and-dinner with-food schedule for naproxen, I give a single 800 mg loading dose to make sure it lasts until the first naproxen dose.

+ Doses of ibuprofen 1800 mg/day as effective as 2400 mg/day in soft tissue sports injuries
In a double-blind, placebo-controlled study of forty-six patients with acute ligamentous damage of the knee, ibuprofen in dosages 1800 mg and 2400 mg produced significant improvements in joint mobility, weight bearing ability and match fitness. Joint effusion, pain on stress and pain severity was significantly improved by all three treatments. Only two patients reported side-effects (one while taking placebo and one taking ibuprofen 2400 mg). The study confirmed the efficacy and excellent tolerance to ibuprofen in patients with sports injuries to the knee.]

+ Ibuprofen at 1200 mg a day appears to be as effective (for osteoarthritits) as 2400 mg ibuprofen or acetaminophen.

BACKGROUND: The optimal short-term, symptomatic therapy for osteoarthritis of the knee has not been fully determined. Accordingly, we compared the efficacy of a nonsteroidal antiinflammatory drug, ibuprofen, given in either an antiinflammatory dose (high dose) or an analgesic dose (low dose), with that of acetaminophen, a pure analgesic. METHODS: In a randomized, double-blind trial, 184 patients with chronic knee pain due to osteoarthritis were given either 2400 or 1200 mg of ibuprofen per day or 4000 mg of
acetaminophen per day. They were evaluated after a washout period of three to seven days before the beginning of the study, and again after four weeks of treatment. The major measures of outcome included scores on the pain and disability scales of the Stanford Health Assessment Questionnaire (range of possible scores, 0 to 3), scores on the visual-analogue scales for pain at rest and pain while walking, the time needed to walk 50 ft (15 m), and the physician's global assessment of the patient's arthritis. RESULTS: Seventy-eight percent of the patients completed four weeks of therapy. No significant differences were noted among the three treatment groups with respect to failure to complete the trial because of noncompliance or adverse events. All three groups had improvement in all major outcome variables, and the groups did not differ significantly in the magnitude of improvement in most variables. The mean improvement (change) in the scores on the pain scale of the Health Assessment Questionnaire was 0.33 with acetaminophen (95 percent confidence interval, 0.14 to 0.52), 0.30 with the low dose of ibuprofen (95 percent confidence interval, 0.09 to 0.51), and 0.35 with the high dose of ibuprofen (95 percent confidence interval, 0.13 to 0.57). Side effects were minor and similar in all three groups. CONCLUSIONS: In short-term, symptomatic treatment of osteoarthritis of the knee, the efficacy of acetaminophen was similar to that of ibuprofen, whether the latter was administered in an analgesic or an antiinflammatory dose.


The analgesic efficacy of single oral doses (400 mg, 800 mg) of ibuprofen on argon laser-induced pain was studied in a double-blind, placebo controlled, three way cross-over comparison. Ten healthy volunteers participated. 2. Pain thresholds and plasma concentrations of the S- and R-enantiomers of ibuprofen were measured every hour up to 8 h after medication. 3. Ibuprofen (400 mg) produced an analgesic effect significantly superior (P less than 0.05) to placebo 1-4 h after medication. Ibuprofen (800 mg) was significantly superior to placebo 2-4 h after administration. No differences were found between 400 mg and 800 mg, when hourly threshold differences were compared. 4. Comparing total analgesic effect (area under effect curve), both active medications were superior to placebo (P less than 0.01-0.05), and 400 mg was superior to 800 mg (P less than 0.05). 5. Peak plasma concentrations of S- and R-ibuprofen occurred between 1.2 and 1.5 h. Concentrations after the 800 mg dose were higher than those after the 400 mg dose at all times.

- For renal or biliary colic, or dysmenorrhea, the higher doses may be more effective. However, this has not been studied in a controlled manner. Most of the studies looked at OTC doses and found them effective.

- This one study looked at pain in general, including renal colic, and though it studied ketorlac (TORADOL) IV instead of OTC pain meds by mouth, it found that lower doses (10 mg) were just as good as bigger doses (30 mg). Sadly, they didn't do subgroup analysis for renal colic. But it suggests that the lower doses are just as good for renal and biliary colic.


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Are NSAIDs (in OTC doses) stronger than acetaminophen?
- Yes, about twice as strong.
  BACKGROUND: Quantitative reviews of postoperative pain management have demonstrated that the number of patients needed to treat for one patient to achieve at least 50% pain relief (NNT) is 2.7 for ibuprofen (400 mg) and 4.6 for paracetamol (1000 mg), both compared with placebo. However, direct comparisons between paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) have not been extensively reviewed. The aims of this review are (i) to compare the analgesic and adverse effects of paracetamol with those of other NSAIDs in postoperative pain, (ii) to compare the effects of combined paracetamol and NSAID with those of either drug alone, and (iii) to discuss whether the adverse effects of NSAIDs in short-term use are justified by their analgesic effects, compared with paracetamol.
  METHODS: Medline (1966 to January 2001) and the Cochrane Library (January 2001) were used to perform a systematic, qualitative review of postoperative pain studies comparing paracetamol (minimum 1000 mg) with NSAID in a double-blind, randomized manner. A quantitative review was not performed as too many studies of high scientific standard (27 out of 41 valid studies, including all major surgery studies) would have been excluded.
  RESULTS: NSAIDs were clearly more effective in dental surgery, whereas the efficacy of NSAIDs and paracetamol seemed without substantial differences in major and orthopaedic surgery, although firm conclusions could not be made because the number of studies was limited. The addition of an NSAID to paracetamol may confer additional analgesic efficacy compared with paracetamol alone, and the limited data available also suggest that paracetamol may enhance analgesia when added to an NSAID, compared with NSAIDs alone.
  CONCLUSION: Paracetamol is a viable alternative to the NSAIDs, especially because of the low incidence of adverse effects, and should be the preferred choice in high-risk patients. It may be appropriate to combine paracetamol with NSAIDs, but future studies are required, especially after major surgery, with specific focus on a potential increase in side-effects from their combined use.
- No, they're about the same.

Is the higher, anti-inflammatory dose of ibuprofen or naproxen more toxic than the lower, OTC doses?
- Yes.
- Both COX-2 inhibitors and NSAIDs result in fluid retention, edema, and hypertension, and the effects are dose-dependent.
  [Hawkey, C. J. (2002). "NSAID toxicity: where are we and how do we go forward?" J Rheumatol 29(4): 650-652.]
- GI toxicity is also dose-dependent.
OBJECTIVE: To compare the relative risks of serious gastrointestinal complications reported with individual non-steroidal anti-inflammatory drugs. DESIGN: Systematic review of controlled epidemiological studies that found a relation between use of the drugs and admission to hospital for haemorrhage or perforation. SETTING: Hospital and community based case-control and cohort studies. MAIN OUTCOME MEASURES: (a) Estimated relative risks of gastrointestinal complications with use of individual drugs, exposure to ibuprofen being used as reference; (b) a ranking that best summarised the sequence of relative risks observed in the studies. RESULTS: 12 studies met the inclusion criteria. 11 provided comparative data on ibuprofen and other drugs. Ibuprofen ranked lowest or equal lowest for risk in 10 of the 11 studies. Pooled relative risks calculated with exposure to ibuprofen used as reference were all significantly greater than 1.0 (interval of point estimates 1.6 to 9.2). Overall, ibuprofen was associated with the lowest relative risk, followed by diclofenac. Azapropazone, tolmetin, ketoprofen, and piroxicam ranked highest for risk and indomethacin, naproxen, sulindac, and aspirin occupied intermediate positions. Higher doses of ibuprofen were associated with relative risks similar to those with naproxen and indomethacin. CONCLUSIONS: The low risk of serious gastrointestinal complications with ibuprofen seems to be attributable mainly to the low doses of the drug used in clinical practice. In higher doses ibuprofen is associated with a similar risk to other non-steroidal anti-inflammatory drugs. Use of low risk drugs in low dosage as first line treatment would substantially reduce the morbidity and mortality due to serious gastrointestinal toxicity from these drugs.

Are acetaminophen and a NSAID combined superior to either?
- We looked but, uuhh... well... our study was not powered to show a difference. [Motov, S., et al. (2020). "Comparison of Oral Ibuprofen and Acetaminophen with Either Analgesic Alone for Pediatric Emergency Department Patients with Acute Pain." The Journal of Emergency Medicine.]

BACKGROUND: There has been a trend over recent years for combining a nonsteroidal anti-inflammatory drug (NSAID) with paracetamol (acetaminophen) for pain management. However, therapeutic superiority of the combination of paracetamol and an NSAID over either drug alone remains controversial. We evaluated the efficacy of the combination of paracetamol and an NSAID versus either drug alone in various acute pain models. METHODS: A systematic literature search of Medline, Embase, Cumulative Index to Nursing and Allied Health Literature, and PubMed covering the period from January 1988 to June 2009 was performed to identify randomized controlled trials in humans that specifically compared combinations of paracetamol with various NSAIDs versus at least 1 of these constituent drugs. Identified studies were stratified into 2 groups: paracetamol/NSAID combinations versus paracetamol or NSAIDs. We analyzed pain intensity scores and supplemental analgesic requirements as primary outcome measures. In addition, each study was graded for quality
using a validated scale. RESULTS: Twenty-one human studies enrolling 1909 patients were analyzed. The NSAIDs used were ibuprofen (n = 6), diclofenac (n = 8), ketoprofen (n = 3), ketorolac (n = 1), aspirin (n = 1), tenoxicam (n = 1), and rofecoxib (n = 1). The combination of paracetamol and NSAID was more effective than paracetamol or NSAID alone in 85% and 64% of relevant studies, respectively. The pain intensity and analgesic supplementation was 35.0% +/- 10.9% and 38.8% +/- 13.1% lesser, respectively, in the positive studies for the combination versus paracetamol group, and 37.7% +/- 26.6% and 31.3% +/- 13.4% lesser, respectively, in the positive studies for the combination versus the NSAID group. No statistical difference in median quality scores was found between experimental groups. CONCLUSION: Current evidence suggests that a combination of paracetamol and an NSAID may offer superior analgesia compared with either drug alone.

- No


Non-opioid analgesics are often administered to emergency department (ED) patients with musculoskeletal pain but if inadequate, opioids are given with associated potential adverse events. We tested the hypothesis that the reduction in pain scores with the combination of ibuprofen and acetaminophen would be at least 15 mm greater than with either of the agents alone. We conducted a double-blind, randomized, controlled trial of adult ED patients with acute musculoskeletal pain. Patients were randomized to oral ibuprofen 800 mg, acetaminophen 1 g, or their combination. Pain scores across the groups were compared with repeated measures analysis of variance at 20, 40, and 60 minutes. A sample of 30 patients in each group had 80% power to detect a 15 mm difference in pain scores across the groups (alpha = .05). Thirty patients were randomized to each study group. Mean (SD) age was 36 (15), 54% were male, 73% were white, and 13% were Hispanic. Groups were well balanced in baseline characteristics including initial pain scores (59, 61, and 62 for ibuprofen, acetaminophen, and their combination). Pain decreased over the one hour study period for all groups (P < .001) with mean (SD) scores about 20 mm lower on the Visual Analogue Scale than the mean initial score. However, there was no significant difference among treatments (P = .59). The need for rescue analgesics was similar across groups. We conclude that the combination of ibuprofen and acetaminophen did not reduce pain scores or the need for rescue analgesics compared with either agent alone in ED patients with pain secondary to acute musculoskeletal injuries.

- Yes, if you believe the drug company


BACKGROUND: Acetaminophen is often used with a non-steroidal anti-inflammatory drug for acute pain. Hitherto, these drugs have had to be given separately, typically at different time intervals. Maxigesic tablets combine acetaminophen and ibuprofen in clinically appropriate doses to simplify administration and dosage regimen. We compared this combination with each of the constituent drugs for the relief of pain after extraction of third molar teeth. METHODS: Adults (more than 16 yr) having one or more wisdom teeth removed under general or local anaesthesia were instructed to take two
tablets before operation, then two tablets every 6 h for up to 48 h of: (i) a combination of acetaminophen 500 mg and ibuprofen 150 mg per tablet (Maxigesic); (ii) acetaminophen 500 mg per tablet alone; or (iii) ibuprofen 150 mg per tablet alone. The primary outcome measure was the area under the curve (AUC) of the 100 mm visual analogue scale pain measurements taken for up to 48 h after surgery, divided by time, at rest and on activity. Pharmacokinetic data were collected in a subset of patients. RESULTS: The mean (sem) time-corrected AUC on rest and activity, respectively, were: combination group 22.3 (3.2) and 28.4 (3.4); acetaminophen group 33.0 (3.1) and 40.4 (3.3); and ibuprofen group 34.8 (3.2) and 40.2 (3.4); P<0.01 for each of the four comparisons of combination vs constituent drug. There was no pharmacokinetic interaction between acetaminophen and ibuprofen administered together. CONCLUSIONS: Maxigesic tablets provide superior pain relief after oral surgery to acetaminophen or ibuprofen alone.

- No.


BACKGROUND AND OBJECTIVE: The analgesic potency of non-steroidal anti-inflammatory drugs and acetaminophen are still being debated. We have assessed the relative analgesic effect of ibuprofen, acetaminophen or the combination of both after orthopaedic surgery. METHODS: Sixty-one ASA I patients, scheduled for an elective anterior cruciate ligament reconstruction under general anaesthesia were randomized, in a double blind fashion, into one of three groups. The ibuprofen group (n = 17) received ibuprofen 800 mg orally 1 h before operation and again at 6 and 12 h after the initial dose. The acetaminophen group (n = 20) received of acetaminophen 1 g orally at the same time intervals. The combination group (n = 24) received both ibuprofen 800 mg and acetaminophen 1 g. Surgery was performed under general anaesthesia with propofol and fentanyl for induction and maintenance with propofol and nitrous oxide in oxygen. The patients were monitored for 24 h thereafter, and the following variables were assessed: pain by visual analogue and verbal scales, need for rescue intravenous opioid analgesia (i.e. ketobemidone) and adverse events. RESULTS: The ibuprofen group and the combination group experienced significantly less pain during the first 6 h after surgery than the acetaminophen group using the visual analogue and the verbal scales. The acetaminophen group also had a significantly higher average consumption of opioids during the first 6 and 24 h. There were no significant differences between the ibuprofen group and the combination group in respect of experienced pain or consumption of rescue analgesia. The incidence of side-effects, postoperative haemoglobin concentration and renal function, judged by creatinine clearance, were identical between the groups. CONCLUSION: Ibuprofen 800 mg thrice daily reduced pain to a greater degree than acetaminophen 1 g thrice daily, after anterior cruciate ligament reconstruction under general anaesthesia. The combination of acetaminophen and ibuprofen did not provide any superior analgesic effect.

- Yes, in mice


The antinociception induced by the intraperitoneal coadministration of
combinations of paracetamol with the nonsteroidal anti-inflammatory drugs (NSAIDs) diclofenac, ibuprofen, ketoprofen, meloxicam, metamizol, naproxen, nimesulide, parecoxib and piroxicam was studied by isobolographic analysis in the acetic acid abdominal constriction test of mice (writhing test). The effective dose that produced 50% antinociception (ED50) was calculated from the log dose-response curves of fixed ratio combinations of paracetamol with each NSAID. By isobolographic analysis, this ED50 was compared to the theoretical additive ED50 calculated from the ED(50) of paracetamol and of each NSAID alone obtained from ED50 dose-response curves. As shown by isobolographic analysis, all the combinations were synergistic, the experimental ED50s being significantly smaller than the theoretically calculated ED50s. The results of this study demonstrate potent interactions between paracetamol and NSAIDs and validate the clinical use of combinations of these drugs in the treatment of pain conditions.

- No


STUDY OBJECTIVE: We compare paracetamol with a combination of paracetamol, ibuprofen, and codeine for pain relief in acute minor musculoskeletal injuries. METHODS: This was a prospective, double-blind, randomized, active-controlled, parallel-arm study at an urban tertiary hospital emergency department. Participants were aged 18 to 65 years and had acute (<48 hours) closed limb or trunk injuries with moderate pain (greater than 3/10). A single dose of 1 g of paracetamol, 400 mg of ibuprofen, and 60 mg of codeine was compared with a single dose of 1 g of paracetamol, placebo ibuprofen, and placebo codeine. The minimum detectable difference in pain was taken as 1.3.

RESULTS: Baseline characteristics and pain were similar. There were clinically detectable reductions in pain at rest at 60 minutes for paracetamol: -1.6; 95% confidence interval (CI) -2.2 to -1.1; n=59 and the combination -2.0; 95% CI -2.5 to -1; n=59; difference -0.4; 95% CI -1.1 to 0.29; P=.26. At 120 minutes, the reduction in pain was -2.4; 95% CI -3.2 to -1.6 for paracetamol (n=30) and -2.9; 95% CI -3.7 to -2.2 for the combination (n=35); difference -0.5; 95% CI -1.6 to 0.5; P=.32. Rescue analgesia was required by 4 of 59 patients in the paracetamol group and 5 of 60 in the combination group (P>.99). More participants in the combination group had adverse events: 14 of 60 versus 5 of 59 in the paracetamol group, relative risk 2.8; 95% CI 1.1 to 7.2. No adverse events were serious. CONCLUSION: Combining oral paracetamol, ibuprofen, and codeine as the initial treatment for pain associated with acute musculoskeletal injuries was not superior to paracetamol alone for pain reduction at 60 minutes or need for rescue analgesia, with more adverse events in the combination group.

- Dynamed Rater Comments on this article:
  + "Emergency Medicine rater: This is intriguing because much has been written about combination OTC and mild opioid analgesia. I think this calls for a systematic review of acetaminophen or equivalents against other comparisons. Too early to close the door on this given the small study sample."
  + "Emergency Medicine rater: As an emergency physician and anaesthesiologist, I would suspect that the study size and population studied were contributing factors to not finding a difference here as the trends showed the combination therapy (Paracetamol 1 gm Ibuprofen 400mg and codeine 60 mg was
trending better (though only slightly) than the Paracetamol 1 gm alone at 60 minutes. Longer assessment interval at 120 min with the whole population even if assessed by phone (as they used a verbal rating scale) may have shown a difference. My personal practice is to often use acetaminophen (North American equivalent of paracetamol) and ibuprofen in combination with good effect after 1-2 hrs in similar patients (mostly upper/lower extremity sprains)."

"Emergency Medicine rater: A combination of paracetamol (APAP), ibuprofen and codeine did not have a clinically relevant improvement in pain control in the emergency department versus paracetamol alone. That said, when telling a patient that you are giving them an analgesic that they could have received from their own house (as opposed to a "chance" at getting a study drug that includes codeine), they frequently experience less pain relief - at least in the unblinded setting of clinical care. Also, by probability theory, it is practically guaranteed that providing 3 drugs concurrently will increase the chance of adverse effects (versus one). It would have been interesting if the other combinations were tried (ibu + APAP, ibu + cod, APA + cod) as it is possible that ibu + APAP could have been better since patients would have felt less of the effects of the cod, which is likely to cause the most AE."

"Family Medicine (FM)/General Practice (GP) rater: Very limited conclusions can be drawn from this small study of acute pain treatment for only the first two hours after treatment was begun. The question is important but needs further research."

"Family Medicine (FM)/General Practice (GP) rater: We need more comparative studies of analgesics. Fascinating result that 1 gm plain acetaminophen/paracetamol is as effective as 1 gm acetaminophen plus 400 mg ibuprofen plus codeine. We have been sold a bill of goods on NSAIDS ("anti-inflammatory") and narcotics for years."

"General Internal Medicine-Primary Care (US) rater: I find the premise of this study troubling. In my practice I do not use codeine, so I found the combination arm undoable, at least for me. Also, a lot of patients I care for have contraindications to NSAIDs. What I took away from this study is that for MSK injuries, Tylenol works just as well as a somewhat problematic combination of medications."

- No, in the sense that it doesn't make you get better faster which I don't care about, I just want to know if it provides better temporary pain relief.  
  [Friedman, B. W., et al. "Ibuprofen + acetaminophen versus ibuprofen alone for acute low back pain. An ED-based randomized study." Academic Emergency Medicine n/a(n/a).]

Abstract Objectives Patients with low back pain (LBP) are often treated with non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are modestly effective for LBP, but many patients with LBP continue to suffer despite treatment with these medications. We compared pain and functional outcomes one week after ED discharge among patients randomized to a one-week course of ibuprofen + acetaminophen versus ibuprofen + placebo. Methods This was a randomized, double-blind study conducted in two urban EDs. Patients presenting with acute, non-traumatic, non-radicular LBP of no more than 2 weeks duration were eligible for enrollment immediately prior to discharge from an ED if they had a score > 5 on the Roland-Morris Disability Questionnaire (RMDQ), a 24-item
validated instrument, indicating more than minimal functional impairment. All patients were given a standardized ten-minute LBP educational session prior to discharge. The primary outcome was improvement on the RMDQ between ED discharge and one week later. One secondary outcome was pain intensity, as measured on a 4-point descriptive scale (severe, moderate, mild, none) at one week. Results Enrollment began in October 2018. 120 patients met selection criteria and were randomized. Baseline demographic characteristics were comparable between the two groups. By one week after the ED visit, patients randomized to ibuprofen + placebo reported a mean improvement in the RMDQ 9.7 of 11.9 (SD), while those randomized to ibuprofen + acetaminophen reported a mean improvement of 11.1 (SD 10.7). The 95%CI for the between-group difference of 0.8 was -3.0, 4.7. At one week, moderate or severe pain was reported by 15/53 (28%) patients in the ibuprofen + placebo group and 16/57 (28%) patients in the ibuprofen + acetaminophen group (95%CI for between group difference of 0%: -17, 17%). Conclusion Among ED patients with acute, non-traumatic, non-radicular LBP, adding acetaminophen to ibuprofen does not improve outcomes within one week.

Are ibuprofen, and, particularly, naproxen, safer than prescription NSAIDs as far as cardiovascular and cerebrovascular risk?
- Yes. Ibuprofen poses no CV risk at OTC doses, and naproxen poses no CV risks even at higher levels.


BACKGROUND: Randomised trials have highlighted the cardiovascular risks of non-steroidal anti-inflammatory drugs (NSAIDs) in high doses and sometimes atypical settings. Here, we provide estimates of the comparative risks with individual NSAIDs at typical doses in community settings. METHODS AND FINDINGS: We performed a systematic review of community-based controlled observational studies. We conducted comprehensive literature searches, extracted adjusted relative risk (RR) estimates, and pooled the estimates for major cardiovascular events associated with use of individual NSAIDs, in different doses, and in populations with low and high background risks of cardiovascular events. We also compared individual drugs in pair-wise (within study) analyses, generating ratios of RRs (RRRs). Thirty case-control studies included 184,946 cardiovascular events, and 21 cohort studies described outcomes in >2.7 million exposed individuals. Of the extensively studied drugs (ten or more studies), the highest overall risks were seen with rofecoxib, 1.45 (95% CI 1.33, 1.59), and diclofenac, 1.40 (1.27, 1.55), and the lowest with ibuprofen, 1.18 (1.11, 1.25), and naproxen, 1.09 (1.02, 1.16). In a sub-set of studies, risk was elevated with low doses of rofecoxib, 1.37 (1.20, 1.57), celecoxib, 1.26 (1.09, 1.47), and diclofenac, 1.22 (1.12, 1.33), and rose in each case with higher doses. Ibuprofen risk was seen only with higher doses. Naproxen was risk-neutral at all doses. Of the less studied drugs etoricoxib, 2.05 (1.45, 2.88), etodolac, 1.55 (1.28, 1.87), and indomethacin, 1.30 (1.19, 1.41), had the highest risks. In pair-wise comparisons, etoricoxib had a higher RR than ibuprofen, RRR = 1.68 (99% CI 1.14, 2.49), and naproxen, RRR = 1.75 (1.16, 2.64); etodolac was not significantly different from naproxen and ibuprofen. Naproxen had a significantly lower risk than ibuprofen, RRR = 0.92 (0.87, 0.99). RR
estimates were constant with different background risks for cardiovascular
disease and rose early in the course of treatment. CONCLUSIONS: This review
suggests that among widely used NSAIDs, naproxen and low-dose ibuprofen are
least likely to increase cardiovascular risk. Diclofenac in doses available
without prescription elevates risk. The data for etoricoxib were sparse, but
in pair-wise comparisons this drug had a significantly higher RR than
naproxen or ibuprofen. Indomethacin is an older, rather toxic drug, and the
evidence on cardiovascular risk casts doubt on its continued clinical use.
Please see later in the article for the Editors' Summary.

p Does adding IV Tylenol to strong narcotics like Dilaudid IV help acute
pain control?
- Duh. No. It was sort of underpowered, but still...
  [Bijur, P. E., et al. (2020). "Randomized Clinical Trial of Intravenous (IV)
  Acetaminophen as an Adjunct to IV Hydromorphone for Acute Severe Pain in
  Emergency Department Patients." Acad Emerg Med.]

p Does taking acetaminophen increase risk-taking?
- Yes
  Acetaminophen, an analgesic and antipyretic available over-the-counter and
  used in over 600 medicines, is one of the most consumed drugs in the USA.
  Recent research has suggested that acetaminophen’s effects extend to the
  blunting of negative as well as positive affect. Because affect is a
determinant of risk perception and risk taking, we tested the hypothesis that
acute acetaminophen consumption (1000 mg) could influence these important
judgments and decisions. In three double-blind, placebo-controlled studies,
healthy young adults completed a laboratory measure of risk taking (Balloon
Analog Risk Task) and in Studies 1 and 2 completed self-report measures of
risk perception. Across all studies (total n = 545), acetaminophen increased
risk-taking behavior. On the more affectively stimulating risk perception
measure used in Study 2, acetaminophen reduced self-reported perceived risk
and this reduction statistically mediated increased risk-taking behavior.
These results indicate that acetaminophen can increase risk taking, which may
be due to reductions in risk perceptions, particularly those that are highly
affect laden.

p Is topical capsaicin good for acute musculoskeletal pain?
- Yes? This study showed it better than a topical NSAID which
  has been shown to work in other studies.
  piroxicam in the treatment of acute trauma-induced pain: A randomized double-
  blind trial." The American journal of emergency medicine 38(9): 1767-1771.
  Background: This study aimed to compare the analgesic efficacy of topical
capsaicin and topical piroxicam in acute musculoskeletal injuries.
  Methods: This is a prospective, randomized, controlled, double-blinded study.
  The data for the 67 patients in the piroxicam group and the 69 in the
capsaicin group were examined. The initial visual analog scale (VAS) scores
were compared with the 60th and 120th minute as well as the 24th and 72nd
hour values. Differences between the VAS scores, clinical effectiveness of
the treatment and side effects were evaluated.
Results: In the capsaicin group, the mean difference in the delta VAS scores was significantly higher at each measurement time. The mean of the percentage of reduction in the VAS scores of the topical capsaicin group was significantly higher than that in the topical piroxicam group. The highest difference in terms of both outcomes was determined at the 72nd hour VAS change. Mean differences were 1.53 (95% CI: 0.85–2.221) and 19.7 (95% CI: 12.4–27.2) respectively (p < 0.001). In the capsaicin group, the clinical effect of the treatment was found significantly higher (p < 0.01). The difference between the clinical effectiveness of the groups regarding the treatment outcomes was also statistically significant (p < 0.001). There was no significant difference between the patient groups regarding the presence of side effects.
Conclusion: Topical capsaicin can be used as an alternative to topical piroxicam initially and at follow-up in patients presenting to the emergency department with acute pain as there were no observable differences in side-effects between the two groups.