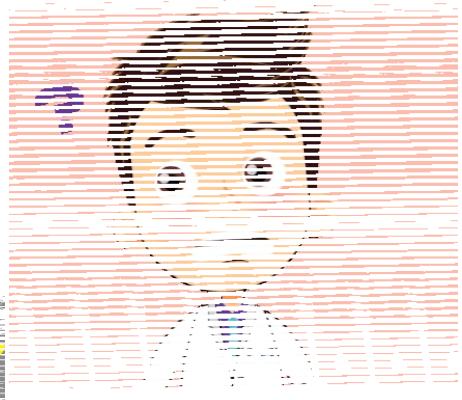
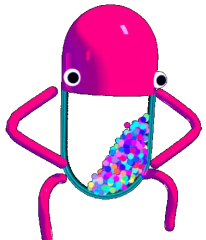
Your patient is a 95-year-old who is generally in good health, but has chronic knee pain despite having a knee replacement 10 years ago. She tells you that taking Aleve (Naproxen Sodium) twice a day helps her with the pain, but you are concerned about the risks to her of using an NSAID on a regular basis. She says “I’m an old woman, how serious a risk is it?”

What can you tell her about the degree of risk of chronic NSAID use for her?

Peter Lin, Elizabeth Pina, Kevin Zhang, Sharon (Xixuan) Wu, Lisette Romo

Clinical Question





In older adults using NSAIDs chronically, what is the risk of serious adverse effects (GI bleeding, renal dysfunction, cardiovascular events, etc.) compared to those not using NSAIDs or using alternative pain treatments?

PICO Search Terms

Patient	Intervention	Comparison	Outcome
Older adults	NSAIDs	No NSAID use	Adverse effects
Geriatric patients	Nonsteroidal anti-inflammatory drugs	Non-NSAID analgesics	Gastrointestinal bleeding
	Chronic use	Acetaminophen	Renal impairment
		Placebo	Peptic ulcer
			Mortality

Search Strategy Summary

Filters

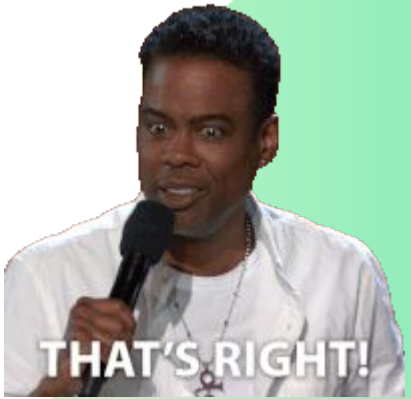
Age: Older Adults (≥ 65y/o)
Year of Publication: within the past 10 years
Article Types: Systematic Reviews, Meta-Analyses, RCTs, Cohort Studies, Case-Control Studies

Databases Searched

PubMed – 294 results after filters applied
- Many were not relevant to our clinical question

Cochrane Library – 12 results after filters apple
- None were relevant to our clinical question

Trip Database – 48 results after filters applied
- None were relevant to our clinical question



Articles Used

Based on the most recent research and relevancy of the articles to our topic…
- **PubMed** – 5 articles

Appraised Articles

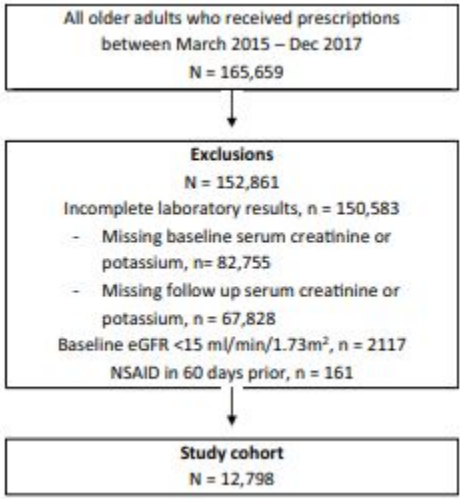
ARTICLE 01	Non-Steroidal Anti-Inflammatory Drugs and Risk of Acute Kidney Injury and Hyperkalemia in Older Adults: A Retrospective Cohort Study and External Validation of a Clinical Risk Model [Lim C, et al., 2022]
ARTICLE 02	Duration of Symptom Relief and Early Trajectory of Adverse Events for Oral Nonsteroidal Antiinflammatory Drugs in Knee Osteoarthritis: A Systematic Review and Meta-Analysis [Osani M C, et al., 2020]
ARTICLE 03	Effectiveness and Safety of Non-steroidal Anti-inflammatory drugs and Opioid treatment for knee and Hip Osteoarthritis: Network Meta-analysis [Da Costa BR, et al., 2021]
ARTICLE 04	Risk of Acute Myocardial Infarction with NSAIDs in Real World Use: Bayesian Meta-Analysis of Individual Patient Data [Trelle S. et al., 2017]
ARTICLE 05	Comparative Efficacy of Exercise Therapy and Oral Non-Steroidal Anti-Inflammatory Drugs and Paracetamol for Knee or Hip Osteoarthritis: A Network Meta-analysis of Randomized Controlled Trials [Weng Q. et al., 2023]

Non-Steroidal Anti-Inflammatory Drugs and Risk of Acute Kidney Injury and Hyperkalemia in Older Adults: A Retrospective Cohort Study and External Validation of a Clinical Risk Model

CRITERIA

Age ≥ 65 years old who received prescriptions between March 2015 and December 2017 from Singapore's largest cluster of public healthcare institutions

12,798 older adults were identified



METHODS/PROCEDURE

Divided into 4 groups:

1. prescribed oral or IV for > 14 days
2. prescribed for 1-14 days
3. prescribed topical NSAID
4. no NSAID prescription

Exclusion Criterias [3]:

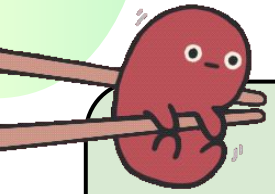
1. prescriptions for NSAIDs within 60 days prior to cohort entry
2. Missing Cr and/or K+ values within 6 months before and 30 days after cohort entry
3. Advanced or Severe Kidney Dysfunction (GFR < 15 – ESRD)

Primary Measurement

AKI & Hyperkalemia

- AKI was defined if Cr ≥ 26.5 or ≥50% from baseline
- Hyperkalemia was defined if baseline K+ was <5.5 and increased to ≥5.5

Non-Steroidal Anti-Inflammatory Drugs and Risk of Acute Kidney Injury and Hyperkalemia in Older Adults: A Retrospective Cohort Study and External Validation of a Clinical Risk Model



RESULTS

NSAID Use Prevalence

7,210 (56.3%) were prescribed NSAIDs

- 3,640 (28.4%) received **systemic NSAIDs**
  - 305 (2.4%) used >14 days (chronic use)
  - 3,335 (26.1%) used 1-14 days (short course)
- 3,570 (27.9%) received **topical NSAIDs**

Primary Outcome (30-day AKI and/or HyperK+)

Witnessed in 2,137 individuals (16.7%)

↑ **Incidence in Systemic NSAID use for >14 days**

Odds Ratio (vs. no NSAIDs)

Topical NSAIDs: OR 1.29 (95% CI 1.15-1.45)

Systemic NSAIDs 1-14 days: OR 1.43 (95% CI 1.27-1.62)

Systemic NSAIDs > 14 days: OR 1.84 (95% CI 1.37-2.49)

LIMITATIONS

Prescription ≠ True Consumption: may underestimate results

- Adherence & OTC NSAID use were not captured

Selection Bias: the study only included patients with baseline and follow-up labs of Cr & K+

- These individuals likely had labs done due to higher perceived renal risk → may overestimate AKI incidence

Confoundings

- Patients with underlying conditions that require chronic NSAID use (e.g. gout, RA) may be at already increased risk for AKI & HyperK+
- Study is conducted in Singapore → results may not apply globally due to differences in diet, genetics, healthcare access, comorbidities, etc.

Observational Study

- Cannot infer causality & generalizability to all older adults

Duration of Symptom Relief and Early Trajectory of Adverse Events for Oral Nonsteroidal Antiinflammatory Drugs in Knee Osteoarthritis: A Systematic Review and Meta-Analysis

CRITERIA

72 randomized controlled trials involving non-steroidal anti-inflammatory drugs (NSAIDs) in human subjects with knee osteoarthritis (OA) were included in this study

Total 26,424 participants

Mean age: 53 to 69 years old
Follow-up duration: 1 week to 2 years (96% of the trials had a duration of 13 weeks or less)
Percentage of female participants: 49% to 85%

METHODS/PROCEDURE

NSAIDs were group into three classes

1. Traditional (non-selective) NSAIDs: (e.g., Diclofenac, Ibuprofen, Naproxen)
2. Selective COX-2 Inhibitors: (Celecoxib)
3. Intermediate COX Inhibitors: (e.g., Etodolac, Meloxicam, Nabumetone)

Outcome Measures

- Efficacy outcomes: included pain and functional outcomes
- Safety outcomes: included serious adverse events, treatment-related adverse events, incidence of gastrointestinal and cardiovascular AE

Duration of Symptom Relief and Early Trajectory of Adverse Events for Oral Nonsteroidal Antiinflammatory Drugs in Knee Osteoarthritis: A Systematic Review and Meta-Analysis

RESULTS

Overall Efficacy: NSAIDs produced statistically significant pain and function improvements

Peak Effect: At 2 weeks (SMD −0.43 [−0.48, −0.38])

- Benefits decreased progressively over time. Treatment effects lost clinical significance by 8 weeks

Class Comparison: Traditional NSAIDs performed consistently better on pain and functional outcomes, but it has the least favorable safety profile of all the classes

- Highest risk of GI AEs & 92% greater likelihood of reporting CV AEs

Adverse Events:

- GI AEs was significantly higher in NSAID users (RR 1.36 [1.25, 1.49]); was evident as early as 4 weeks after initiation
- CV AEs was also higher in NSAID users (RR 1.37 [1.05, 1.77])

LIMITATIONS

Short Follow-Up:

- Median follow up= 6 weeks; 96% of trials ≤13 weeks
- Limits conclusions on chronic NSAID use

Attrition Bias:

- More placebo withdrawals due to lack of efficacy, and more NSAID withdrawals due to AEs
- May understate treatment effects

Exclusion of High-Risk Patients:

- Knee OA population included in the RCTs was more restricted and less representative of the general OA population
- Trials often excluded those with GI/CV comorbidities → likely underestimates real-world risks

Inability to Evaluate Serious Events:

- Unable to assess major vascular events (MI, stroke) or serious GI complications (GI bleed, perforation, obstruction) due to rarity in the study and short follow-up

Effectiveness and Safety of Non-Steroidal Anti-Inflammatory drugs and Opioid treatment for knee and hip Osteoarthritis: Network Meta-analysis

CRITERIA

Randomized Controlled Trials: **192 RCTs** involving adults diagnosed with knee or hip Osteoarthritis. This includes a scope amongst international trials until 2021.

Total participants: **102,829**

Age range: **48 to 72** years old

Treatments studied: **Oral & Topical NSAIDS, opioids, paracetamol (acetaminophen), placebo**

Trial Size: ≥100 participants per study

METHODS/PROCEDURE

Major databases: **(MEDLINE, Cochrane CENTRAL, Embase)**

Network Meta-analysis approach: Comparison of multiple drugs with the *Bayesian random-effects model*

90 active drug regimens were compared:
68 NSAIDs, 19 opioids, 3 paracetamol

Outcomes measured: **pain relief, physical function, adverse events, treatment discontinuation**

Effectiveness and Safety of Non-Steroidal Anti-Inflammatory drugs and Opioid treatment for knee and hip Osteoarthritis: Network Meta-analysis

RESULTS

Pain Relief:
Only **4** oral NSAIDs achieved about **99% probability** of pain reduction: Diclofenac, Etoricoxib, Rofecoxib (25mg & 50mg)

Physical Function: Opioids showed the least improvement

Treatment Discontinuation:
Opioids - 83.3% increased risk of drop outs due to side effects

Oxymorphone (opioid) had the worst results with the highest side effect profile

LIMITATIONS

Heterogeneity in the medications with varying drug type, dose, and duration

Short length of duration for studies ranging on average 4 to 12 weeks → long term adverse events were not considered

Large studies with ≥100 participants were considered, which excluded small studies → relevant information left out

Network Meta Analysis only relies on indirect comparisons → **evidence is skewed**

Risk of Acute Myocardial Infarction with NSAIDs in Real World Use: Bayesian Meta-Analysis of Individual Patient Data

CRITERIA

Population: 446,763 middle-aged to older adults who had confirmed acute myocardial infarction events with concurrent NSAID use vs nonusers

NSAIDs Used in Research: ibuprofen, naproxen, diclofenac, celecoxib, rofecoxib

Dose and Duration: Based on World Health Organization's Defined Daily Dose system to categorize each NSAID into low dose vs high dose

METHODS/PROCEDURE

Systematic review from four large prescription and medical databases in Canada, Finland, and the United Kingdom followed by one stage Bayesian individual patient meta analysis

The study was categorized based on the:

- The type of NSAID exposure
- Dose: varying for each NSAID depending on DDD system
- Duration: Days 1-7, Days 8-30, >30 days
- The risk percentage and odds ratio of an acute myocardial infarction from NSAID use

Risk of Acute Myocardial Infarction with NSAIDs in Real World Use: Bayesian Meta-Analysis of Individual Patient Data

RESULTS

All NSAIDs increased the risk of acute myocardial infarction in comparison to non NSAID users in middle-aged and older adults.

There were 61,460 reports of AMI from 446, 763 individuals.

The risk increased quickly within **days 1-7 day** of NSAID use

Higher doses of NSAIDS increased the risk of AMI

Rofecoxib has the highest risk.

NSAID use for **more than 30 days** did not further increase the risk significantly

LIMITATIONS

Selection Bias: 4 potential eligible studies were excluded due to the lack of permission to access patient data.

Confounding Variables: Important risk factors such as smoking, obesity, socioeconomic status, and lifestyle was not measured. These can underestimate or overestimate the risk of acute myocardial infarction

Observational Data: The study used medical database, which records prescriptions and drug dispensing, but did not record whether patients actually took the medications.

Comparative Efficacy of Exercise Therapy and Oral Non-Steroidal Anti-Inflammatory Drugs and Paracetamol for Knee or Hip Osteoarthritis: A Network Meta-analysis of Randomized Controlled Trials

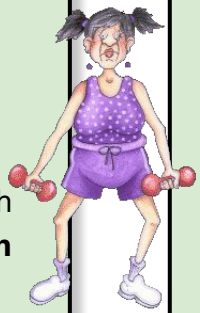
CRITERIA

Randomized Controlled Trials (RCTs)

Participants must be diagnosed with knee or hip osteoarthritis (OA)

Studies must directly compare exercise therapy with oral NSAID or paracetamol (acetaminophen) on **pain relief** and **functional improvement**

Any form of exercise eligible, regardless of duration, frequency or intensity:
Aerobic, muscle strengthening, flexibility/neuromotor skills training or mind-body exercise



METHODS/PROCEDURE

Based on five major databases (PubMed, Embase, Scopus, Cochrane Library, Web of Science)

Total of 152 RCTs

- 17,431 participants
- Average age = 53.0 to 65.9 years
- Majority were female (62.5% to 85.1%)
-

83.6% of the trials involved participants with only knee OA

7.9% of the trials involved only hip OA

8.6% involved a mix of both knee and hip OA

Comparative Efficacy of Exercise Therapy and Oral Non-Steroidal Anti-Inflammatory Drugs and Paracetamol for Knee or Hip Osteoarthritis: A Network Meta-analysis of Randomized Controlled Trials

RESULTS

There was **no statistical difference** between exercise and oral NSAIDs and paracetamol for pain relief and functional improvement at 4, 8, or 24 weeks.

Pain Relief

- 4 weeks: SMD=-0.12 (95% CrI -1.74 to 1.50)
- 8 weeks: SMD=0.22 (95% CrI -0.05 to 0.49)
- 24 weeks: SMD=0.17 (95% CrI -0.77 to 1.12)

Physical Function

- 4 weeks: SMD=0.09 (95% CrI -1.69 to 1.85)
- 8 weeks: SMD=0.06 (95% CrI -0.20 to 0.33)
- 24 weeks: SMD=0.05 (95% CrI -1.15 to 1.24)

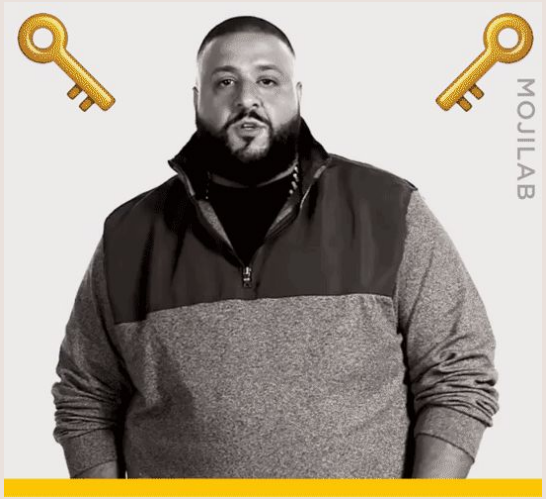
LIMITATIONS

Limited generalizability to other joints: Included trials were restricted to those with knee or hip OA. Therefore, the study's conclusion may not be generalisable to OA at other joints.

Heterogeneity of interventions: Exercise therapy varied widely across trials in terms of type, frequency, intensity and duration, making it difficult to pinpoint which specific exercise protocols are most effective.

Variability in outcome measures: Different trials used different pain and function scales, which may introduce inconsistency

Generalizability: Most participants were older adults and predominantly female, which may limit applicability to younger population or men.



SUMMARY OF KEY FINDINGS

Lim C, et. al., 2022

↑ Systemic NSAID use (>14 days) is associated with higher risk of AKI and hyperkalemia in older adults

- Topical < Short-Term Systemic < Long-Term Systemic

Osani M. C., et al., 2020

Oral NSAIDs provide rapid symptom relief with peak benefit at 2 weeks, but effects wane by 8 weeks as GI and CV adverse events emerge early and persist, making chronic use less effective and more risky, especially for frail elderly with comorbidities

Weng Q. et al., 2023

Exercise therapy was shown to be a clinically effective treatment for reducing pain and improving physical function in patients with knee or hip OA. The study recommends prioritizing exercise as a first-line treatment.

Da Costa BR, et al., 2021

Oral NSAIDs gave the strongest pain relief. Topical NSAIDs were recognized as the safest option, and opioids had little to no clinical benefits in management, with the highest risk of side effects.

Trelle S. et al., 2017

The risk for AMI occurs quickly, within the first 1-7 days of NSAID use and is greater at higher doses. However, after 30 days, the risk for AMI does not significantly increase in comparison to the risk within the first 30 days.

Clinical Bottom Line

What are the risks of chronic NSAID use in older adults?

Chronic systemic NSAIDs **increase risk of AKI, hyperkalemia, GI bleeding, and CV events (e.g. MI)**, especially in older adults as these adverse effects **can become life-threatening.**

Use the **lowest effective dose for the shortest time, monitor kidney function, and consider safer alternatives** (**PT**, warm compresses, **exercise**, topical NSAIDs).

HOWEVER...

Geriatric Care

Patient Autonomy, Quality of Life, and Shared-Decision Making

Quality of Life often takes precedence in elderly patients → goal shifts from long-term disease prevention to **comfort, independence, and function**

This leads to the clinician having to balance **nonmaleficence** with respect for **patient autonomy**, acknowledging the patient's values and goals.

In a 95-year-old, the goal is not zero risk → it's a person-centered balance between safety and meaningful pain relief. This is when shared-decision making comes in hand.

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Lim, C., et. al (2022). Non-Steroidal Anti-Inflammatory Drugs and Risk of Acute Kidney Injury and Hyperkalemia in Older Adults: A Retrospective Cohort Study and External Validation of a Clinical Risk Model. Drugs & aging, 39(1), 75–82. https://doi.org/10.1007/s40266-021-00907-w

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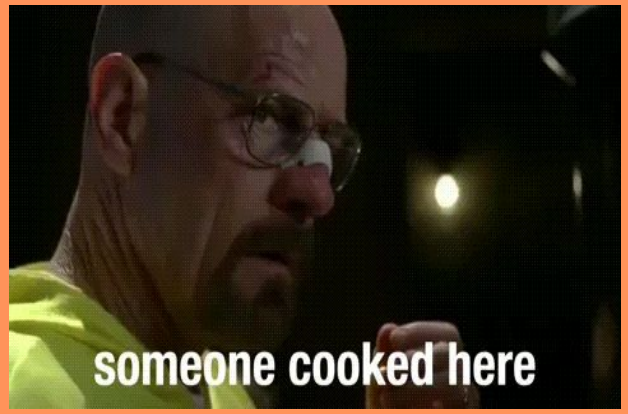

WAITING FOR FEEDBACK