Mini-CAT Question

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 Alleve 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?

PICO 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?

P → older adults (≥ 65y/o)
I → chronic use of NSAIDs
C → no NSAID use or alternative pain control (acetaminophen, opioids, physical therapy, etc.)
O → adverse effects (gastrointestinal bleeding, renal impairment, mortality)

Search Strategy

PICO Search Terms

P	**I**	**C**	**O**
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

Databases & Articles Returned

- PubMed – 294 results after filters applied
- Cochrane – 12 results after filters applied
- Trip Database – 48 results after filters applied

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

Articles [5]

1. **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)
   PMID: 34888761

- Abstract:
  - Aim:
    - Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used analgesics among older adults. Adverse effects may be avoided by careful patient selection. We aimed to evaluate the incidence of acute kidney injury (AKI) and/or hyperkalemia, risk factors, and the accuracy of an NSAID risk prediction model in a cohort of Asian older adults.
  - Methods:

        - We conducted a retrospective cohort study of older adults, age 65 years and above, who received prescriptions between March 2015 and December 2017 from Singapore's largest cluster of public healthcare institutions. Factors associated with 30-day incident acute kidney injury and/or hyperkalemia were evaluated with multivariable regression analysis. Calibration and discrimination of the Nash prediction model were assessed using the Hosmer-Lemeshow goodness-of-fit test and C-statistic, respectively.
    - Results:
        - The primary outcome occurred in 16.7% of 12,798 older adults. Topical NSAIDs (adjusted OR 1.29, 95% CI 1.15-1.45), systemic NSAIDs of 1-14 days' duration (adjusted OR 1.43, 95% CI 1.27-1.62), and systemic NSAIDs > 14 days (adjusted OR 1.84, 95% CI 1.37-2.49) were independently associated with the primary outcome, compared with no NSAID. Diabetes mellitus, cardiovascular disease, lower estimated glomerular filtration rate (eGFR), and diuretics were also independently associated with increased incident AKI and/or hyperkalemia. When applied to older adults with systemic NSAIDs > 14 days (n = 305), the Nash risk model had poor calibration ($p < 0.001$) and poor discrimination with C-statistic 0.527 (0.438, 0.616).
    - Conclusions:
        - Longer NSAID duration and systemic compared with topical route were associated with incremental odds for acute renal events. Further studies are required to improve the available risk model to guide NSAID prescriptions in older adults.
- Background: Older adults commonly use non-steroidal anti-inflammatory drugs (NSAIDs) for pain management. However, these medications can increase the risk of acute kidney injury (AKI) and hyperkalemia. This study aimed to evaluate the incidence of these adverse outcomes and assess the accuracy of an existing NSAID risk prediction model in a cohort of Asian older adults.
- Methods: A retrospective cohort study was conducted involving older adults aged 65 and above who received NSAID prescriptions between March 2015 and December 2017 from Singapore's largest public healthcare institutions. The primary outcomes were 30-day incident AKI and/or hyperkalemia
- Results: Among 12,798 older adults, 16.7% experienced the primary outcome
    - Longer NSAID duration and systemic administration were associated with higher odds of AKI and/or hyperkalemia:
        - Topical NSAIDs: adjusted OR 1.29 (95% CI 1.15–1.45)
        - Systemic NSAIDs (1–14 days): adjusted OR 1.43 (95% CI 1.27–1.62)
        - Systemic NSAIDs (>14 days): adjusted OR 1.84 (95% CI 1.37–2.49)
    - Additional independent risk factors included diabetes mellitus, cardiovascular disease, lower estimated glomerular filtration rate (eGFR), and diuretic use.
- Conclusion: Longer NSAID use and systemic administration are associated with increased risks of AKI and hyperkalemia in older adults
- Link: https://pubmed.ncbi.nlm.nih.gov/34888761/

2. 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)
PMID: 30908885

- Abstract:
    - Objective:
        - Despite an extensive body of research on NSAIDs in osteoarthritis, the duration of their efficacy and timeline of adverse event (AE) onset have been understudied. We conducted a systematic

review and meta-analyses from 2 to 26 weeks to characterize the efficacy and AE trajectories of oral NSAIDs in knee osteoarthritis.

- Methods:
    - We searched MEDLINE, EMBASE, Web of Science, Google Scholar, and the Cochrane Database from inception to May 2018. RCTs assessing the efficacy and/or safety of FDA-approved NSAIDs in knee osteoarthritis patients were included. Two independent reviewers assessed quality and extracted data. We calculated standardized mean differences and risk ratios with 95% confidence intervals.
- Results:
    - We included 72 RCTs (26,424 participants). NSAIDs demonstrated moderate, statistically significant effects on pain that peaked at 2 weeks (SMD −0.43 [−0.48, −0.38]), but the magnitude of the effects decreased over time. The results for function were similar. The incidence of GI AEs was significantly higher in NSAID users than placebo users as early as 4 weeks (RR 1.38 [1.21, 1.57]). The incidence of CV AEs in NSAID users was not significantly different from placebo. Most GI and CV AEs were transient and of minor severity.
- Conclusion:
    - NSAIDs produced significant pain and function improvements that peaked at 2 weeks but decreased over time. The incidence of minor GI and CV AEs consistently rose, reaching significance as early as 4 weeks. Clinicians should weigh the durability of efficacy with the early onset of minor AEs along with patient tolerability and preferences when formulating an NSAID regimen.

- Background: Oral nonsteroidal anti-inflammatory drugs are commonly prescribed for knee osteoarthritis, but their duration of symptomatic relief and timeline of adverse events are not well established. The study aimed to clarify how long NSAIDs remain effective and when adverse effects (such as gastrointestinal and cardiovascular) begin to emerge.
- Methods: This is a systematic review and meta-analysis that uses multiple databases (MEDLINE, Embase, Google Scholar and the Cochrane Central Register of Controlled Trials) for randomized controlled trials (RCTs) comparing oral NSAIDs with placebo or other comparators in adults with knee OA. The outcomes of interest were efficacy of the NSAIDs (pain and functional outcomes) and the safety (gastrointestinal (GI) and cardiovascular (CV) AEs).
- Results: 72 RTC articles were used for analyses. The mean age of included participants ranged from 53 to 69 years.
    - “NSAIDs showed statistically significant, clinically important effects on pain as early as two weeks from baseline, with a SMD of −0.43 (95% CI −0.48, −0.38). This treatment effect remained statistically significant up to 26 weeks (SMD −0.21 [95% CI −0.39, −0.03]), though the effects attenuated progressively over time and lost clinical significance”
    - “With respect to functional improvement, NSAIDs again showed consistent statistically significant benefits compared with placebo, from 2 weeks (SMD −0.45 [−0.52, −0.38]) to 26 weeks (SMD −0.19 [−0.32, −0.07])”
    - Most commonly reported GI AEs were transient and mild, and included upper abdominal pain, diarrhea, dyspepsia, and nausea. Edema and hypertension were the most commonly reported CV AEs
    - Patients receiving NSAIDs were more likely to experience a minor GI AE as early as 4 weeks after initiating treatment and at 26 weeks
    - The overall risk of developing a minor CV AE was higher in patients using NSAIDs vs. placebo but not statistically significant
    - Traditional NSAIDs (including Naproxen) demonstrated the largest effects with regard to efficacy outcomes, but also the least favorable safety profile of all the classes

- Conclusion: Oral NSAIDs provide rapid but time-limited symptom relief in knee OA, with peak benefits around 2 weeks and the effects attenuated and lost clinical significance by 8 weeks. “The incidence of minor GI and CV AEs in NSAID users rose as early as 2 weeks after treatment initiation and remained elevated thereafter. The use of Traditional NSAIDs was associated with the least favorable safety profile.” The study suggests that chronic use of NSAIDs may lack long-term efficacy and increase the risks of adverse treatment effects.
- Link: https://pubmed.ncbi.nlm.nih.gov/30908885/

3. 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

- Abstract:
    - Objective
        - Clinical guidelines recommend exercise as a core treatment for knee or hip osteoarthritis (OA). However, how its analgesic effect compares to analgesics, for example, oral non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol—the most commonly used analgesics for OA, remains unknown.
    - Design
        - Network meta-analysis.
    - Data sources
        - PubMed, Embase, Scopus, Cochrane Library and Web of Science from database inception to January 2022.
    - Eligibility criteria for selecting studies
        - Randomised controlled trials (RCTs) comparing exercise therapy with oral NSAIDs and paracetamol directly or indirectly in knee or hip OA.
    - Results
        - A total of n=152 RCTs (17 431 participants) were included. For pain relief, there was no difference between exercise and oral NSAIDs and paracetamol at or nearest to 4 (standardised mean difference (SMD)=−0.12, 95% credibility interval (CrI) −1.74 to 1.50; n=47 RCTs), 8 (SMD=0.22, 95% CrI −0.05 to 0.49; n=2 RCTs) and 24 weeks (SMD=0.17, 95% CrI −0.77 to 1.12; n=9 RCTs). Similarly, there was no difference between exercise and oral NSAIDs and paracetamol in functional improvement at or nearest to 4 (SMD=0.09, 95% CrI −1.69 to 1.85; n=40 RCTs), 8 (SMD=0.06, 95% CrI −0.20 to 0.33; n=2 RCTs) and 24 weeks (SMD=0.05, 95% CrI −1.15 to 1.24; n=9 RCTs).
    - Conclusions
        - Exercise has similar effects on pain and function to that of oral NSAIDs and paracetamol. Given its excellent safety profile, exercise should be given more prominence in clinical care, especially in older people with comorbidity or at higher risk of adverse events related to NSAIDs and paracetamol.
- Background: Oral NSAIDs and paracetamol (acetaminophen) are commonly prescribed for pain relief and functional improvement of knee or hip osteoarthritis (OA) but carry GI and CV risks, especially in older adults with comorbidities. This study aimed to evaluate and compare the effectiveness of exercise therapy with these commonly used medications for patients with OA and whether it can be used as a replacement therapy.
- Methods: This is a systematic review and network meta-analysis based on a comprehensive search of five major databases (PubMed, Embase, Scopus, Cochrane Library, and Web of Science). A total of 152 randomized controlled trials (RCTs) involving 17,431 participants were included to assess the comparative effects of exercise therapy versus oral NSAIDs or paracetamol on pain relief and functional improvement in adults with OA.
- 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)

- Conclusion: Exercise therapy was shown to be a clinically effective treatment for reducing pain and improving physical function in patients with knee or hip OA. Its efficacy was comparable to that of oral NSAIDs and paracetamol across short (4 weeks), medium (8 weeks), and long term (24 weeks) follow-up. Given its similar effectiveness and superior safety profile, the study recommends prioritizing exercise as a first-line treatment, particularly for older adults or those with comorbidities at risk for medication-related adverse effects.
- Link: https://pmc.ncbi.nlm.nih.gov/articles/pmid/36593092/

4. **Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis**

   PMID: 34642179

   Abstract:

    - Objective:
        - To assess the effectiveness and safety of different preparations and doses of non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and paracetamol for knee and hip osteoarthritis pain and physical function to enable effective and safe use of these drugs at their lowest possible dose.
    - Design:
        - Systematic review and network meta-analysis of randomised trials.
    - Data sources:
        - Cochrane Central Register of Controlled Trials (CENTRAL), Medline, Embase, regulatory agency websites, and ClinicalTrials.gov from inception to 28 June 2021.
    - Eligibility criteria for selecting studies:
        - Randomised trials published in English with ≥100 patients per group that evaluated NSAIDs, opioids, or paracetamol (acetaminophen) to treat osteoarthritis.
    - Outcomes and measures:
        - The prespecified primary outcome was pain. Physical function and safety outcomes were also assessed.
    - Review methods:
        - Two reviewers independently extracted outcomes data and evaluated the risk of bias of included trials. Bayesian random effects models were used for network meta-analysis of all analyses. Effect estimates are comparisons between active treatments and oral placebo.
    - Results:
        - 192 trials comprising 102 829 participants examined 90 different active preparations or doses (68 for NSAIDs, 19 for opioids, and three for paracetamol). Five oral preparations (diclofenac 150 mg/day, etoricoxib 60 and 90 mg/day, and rofecoxib 25 and 50 mg/day) had ≥99% probability of more pronounced treatment effects than the minimal clinically relevant reduction in pain. Topical diclofenac (70-81 and 140-160 mg/day) had ≥92.3% probability, and all opioids had ≤53% probability of more pronounced treatment effects than the minimal clinically relevant reduction in pain. 18.5%, 0%, and 83.3% of the oral NSAIDs, topical NSAIDs, and opioids, respectively, had an increased risk of dropouts due to adverse events. 29.8%, 0%, and 89.5% of oral NSAIDs,

topical NSAIDs, and opioids, respectively, had an increased risk of any adverse event. Oxymorphone 80 mg/day had the highest risk of dropouts due to adverse events (51%) and any adverse event (88%).

- Conclusions:
    - Etoricoxib 60 mg/day and diclofenac 150 mg/day seem to be the most effective oral NSAIDs for pain and function in patients with osteoarthritis. However, these treatments are probably not appropriate for patients with comorbidities or for long term use because of the slight increase in the risk of adverse events. Additionally, an increased risk of dropping out due to adverse events was found for diclofenac 150 mg/day. Topical diclofenac 70-81 mg/day seems to be effective and generally safer because of reduced systemic exposure and lower dose, and should be considered as first line pharmacological treatment for knee osteoarthritis. The clinical benefit of opioid treatment, regardless of preparation or dose, does not outweigh the harm it might cause in patients with osteoarthritis.

Background: Osteoarthritis is recognized as a chronic and debilitating condition. Many experience pain affecting the knee and hip. This disease is disabling because it reduces physical functionality, which limits activities of daily living. Commonly prescribed for symptomatic relief include NSAIDs, opioids, and paracetamol, but each carries significant side effects targeting the systemic systems. This study aimed to evaluate both the efficacy and harms of these drug classes in patients with osteoarthritis through a systematic review and network meta-analysis of randomized controlled trials.

Methods: This systematic review and meta-analysis assessed adults with knee or hip OA using RCTs. MEDLINE, Embase, and CENTRAL databases were used to compare NSAIDs, opioids, topicals, and a placebo. The main outcomes tracked were reductions in pain and physical function in patients, and other outcomes measured included adverse effects of the medications and treatment discontinuation.

Results: 192 RCTs were conducted with a total of 102,829 participants.

- 90 drug treatments were initiated to be tested in the trials (68 NSAIDs, 19 opioids, 3 paracetamol) and demonstrated:

    i. Only four oral treatments resulted in a ≥ 99% probability of achieving a reduction in pain versus the placebo. “Diclofenac 150 mg/day, etoricoxib 60 mg/day, rofecoxib 25 and 50 mg/day had the highest probability of achieving clinically meaningful pain reduction.”

    ii. Topical Diclofenac demonstrated ≥ 92.3% probability of clinically reducing pain

    iii. Opioids demonstrated a ≤ 53% probability of clinically reducing pain

- Adverse drug reactions leading to participants **dropping out** of the studies:

    i. Patients on opioids had the highest increased rate of discontinuation of treatment at 83.3% compared to oral NSAIDs at 18.5%

    ii. There were no treatment discontinuations involved with topical NSAIDs at 0%

- Overall Adverse risk events: The type of side effects was not specified.

    i. Oral NSAIDs: 29.8%

    ii. Topical NSAIDs: 0%

    iii. Opioids: 89.5%

    iv. Oxymorphone was the worst medication for patients to be placed on for pain relief, with 88% experiencing side effects and a 51% chance of dropping out

Conclusion: Oral NSAIDs were the most effective in managing hip and knee osteoarthritis in providing pain relief and restoring a certain level of functionality in movements. Both Diclofenac and Etoricoxib demonstrated the greatest efficacy, and while they are safer to use than the other classes of medications tested, they still carry adverse reactions with chronic use and in patients who have multiple comorbidities. Next, Topical NSAIDs remain the safest to use, with no increase in adverse risks or drop-outs involved, and are considered first-line for

management along with the oral NSAIDs. While Opioids are amongst the strongest category for pain relief, with osteoarthritic patients, there was a higher risk-to-benefit ratio, with more potential for harm, and should be considered as the last possible option before initiation of other suitable medications.
Link: https://pubmed.ncbi.nlm.nih.gov/34642179/

5. **Risk of acute myocardial infarction with NSAIDs in real-world use: Bayesian meta-analysis of individual patient data**

   PMCID: 28487435

   Abstract:

   - Objective
     - To assess the effectiveness and safety of different preparations and doses of non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and paracetamol for knee and hip osteoarthritis pain and physical function to enable effective and safe use of these drugs at their lowest possible dose.
   - Design
     - Systematic review and network meta-analysis of randomised trials.
   - Data sources
     - Cochrane Central Register of Controlled Trials (CENTRAL), Medline, Embase, regulatory agency websites, and ClinicalTrials.gov from inception to 28 June 2021.
   - Eligibility criteria for selecting studies
     - Randomised trials published in English with ≥100 patients per group that evaluated NSAIDs, opioids, or paracetamol (acetaminophen) to treat osteoarthritis.
   - Outcomes and measures
     - The prespecified primary outcome was pain. Physical function and safety outcomes were also assessed.
   - Review methods
     - Two reviewers independently extracted outcomes data and evaluated the risk of bias of included trials. Bayesian random effects models were used for network meta-analysis of all analyses. Effect estimates are comparisons between active treatments and oral placebo.
   - Results
     - 192 trials comprising 102 829 participants examined 90 different active preparations or doses (68 for NSAIDs, 19 for opioids, and three for paracetamol). Five oral preparations (diclofenac 150 mg/day, etoricoxib 60 and 90 mg/day, and rofecoxib 25 and 50 mg/day) had ≥99% probability of more pronounced treatment effects than the minimal clinically relevant reduction in pain. Topical diclofenac (70-81 and 140-160 mg/day) had ≥92.3% probability, and all opioids had ≤53% probability of more pronounced treatment effects than the minimal clinically relevant reduction in pain. 18.5%, 0%, and 83.3% of the oral NSAIDs, topical NSAIDs, and opioids, respectively, had an increased risk of dropouts due to adverse events. 29.8%, 0%, and 89.5% of oral NSAIDs, topical NSAIDs, and opioids, respectively, had an increased risk of any adverse event. Oxymorphone 80 mg/day had the highest risk of dropouts due to adverse events (51%) and any adverse event (88%).
   - Conclusions
     - Etoricoxib 60 mg/day and diclofenac 150 mg/day seem to be the most effective oral NSAIDs for pain and function in patients with osteoarthritis. However, these treatments are probably not appropriate for patients with comorbidities or for long term use because of the slight increase in the risk of adverse events. Additionally, an increased risk of dropping out due to adverse events was found for diclofenac 150 mg/day. Topical diclofenac 70-81 mg/day seems to be effective and

generally safer because of reduced systemic exposure and lower dose, and should be considered as first line pharmacological treatment for knee osteoarthritis. The clinical benefit of opioid treatment, regardless of preparation or dose, does not outweigh the harm it might cause in patients with osteoarthritis.

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) are chronically used for pain management in older adults. However, NSAIDs have been associated with serious adverse effects such as gastrointestinal bleeding, renal impairement, and cardiovascular events such as acute myocardial infraction (AMI). This study was conducted to clarify how quickly NSAIDs increase the risk of AMI, and to determine if specific NSAIDs or doses have greater danger than others. This information is important to understand the risk-benefit when using or prescribing NSAIDs for chronic pain, especially in older.

Methods: This research is a systemic review from large drug prescription or medical databases from Canada, Finland, and the United Kingdom followed by one bayesian individual patient data meta-analysis. The observational studies selected for systemic review evaluated NSAID use and acute myocardial infraction. The study categorized NSAID exposure by specific drug, dose, duration of use, and recency of use. Based on this the researchers examined how different oral NSAIDs, doses, and the length of use affected the risk of AMI in 446, 000 participants.

Results: NSAIDs use for one week, one month, or more than one month was associated with an risk of acute myocardial infraction compared to non-use.

- Effects of Duration and Doses
    - NSAID used for **1 to 7 days for any dose** increased the probability of AMI by
        - 92% for celecoxib
        - 97% for ibuprofen
        - 99% for diclofenac, naproxen, and rofecoxib.
    - NSAID used for **8 to 30 days at high dose** was particularly harmful for
        - Ibuprofen >1200 mg/day: 97.5% probability of AMI compared to 59.3% at doses <1200 mg/day
        - Naproxen >750 mg/day: 99.2% probability of AMI compared to 92.1% at doses <750 mg/day
        - Refecoxib >25 mg/day: 99.8% probability of AMI compared to 88.6% at doses <25 mg/day
    - NSAID used for **long term (>30 days)** did not significantly increase the risk of AMI

Conclusions: The conclusion from the study is that the use of oral NSAIDs have an increased risk for acute myocardial infraction. The risk occurs quickly, within the first 1-7 days of 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. Out of all the NSAIDs, refecoxib has the highest risk for AMI and this may explain why AMI risk with NSAIDs was first uncovered through rofecoxib trials. These findings highlight that to prevent AMI it may be beneficial to avoid refecoxib in older adults, and to use the lowest effect dose for the shortest duration.

Link: https://pmc.ncbi.nlm.nih.gov/articles/PMC8506236/