Mini-CAT Assignment

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Clinical Scenario:
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 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?

Clinical Question:
"In elderly patients, what are the risks and adverse effects of chronic NSAID use?"

PICO Terms:

P	I	C	O
Elderly patients	Chronic NSAID use	N/A	Harms
Elderly women	Non-steroidal anti -inflammatory drugs		Risks
Elderly patients with osteoarthritis	Naproxen/Aleve		Adverse Effects
Elderly patients with knee pain	Oral NSAID use		

Search Strategy:
Cochrane:

- Search criteria "chronic NSAID use adverse effects" gave 33 results, none of which matched our clinical question well.
- Notes: We searched "chronic nsaid use adverse effects" and returned 33 results. After reviewing the articles, none were included, either because they focused on NSAID therapeutic effects and not on adverse events or because they were not accessible via the York College library.

PubMed:

- PubMed Clinical Queries: oral NSAID use knee pain → 19 results for Systematic Reviews
- PubMed Clinical Queries: chronic NSAID use harm → 32 results for Systematic Reviews
- PubMed: naproxen/adverse effects: → 90 results. Filters: Article type, Publication Date (10 years), Species (Humans), Language (English), Sex (Female).

Trip:

- "Chronic NSAID use adverse effects" - 101 Systematic Reviews. Organized by relevance yielded article 5 (Tramer, et. al.)

Articles Used:

-Based on most recent research, sample size, type of NSAIDs use and article availability ,we chose the following articles:
-PubMed - 4 articles
-Trip Database - 1 article

Selection Methods: Criteria to determine which articles to include in our CAT

- Article 1 (Osani, et. al.): A very recent (3/25/19) systematic review and meta-analysis that included 72 RCTs (26,424 participants) to study the efficacy and adverse events of oral NSAIDs in knee OA.
- Article 2 (Zhang, et. al.): Systematic review and Meta-analysis with a total of 1,609,163 participants. It was also published in 2017 and indexed for MEDLINE.
- Article 3 (Wheling, M.): Systematic Review assessing NSAID risk on each body system, especially focusing on the elderly. Published in 2014.
- Article 4 (Solomon, et. al.): Very large RCT (24,081 patients) comparing Aleve (naproxen) with other NSAIDs on drug risks and toxicity.
- Article 5 (Tramer et. al.): An international meta analysis and systematic review of 15 RCTs, 3 cohort studies, 6 case-controls, 20 case series/reports involving 249,250 patients. Ultimately, it covered uncommon clinically-relevant adverse effects of chronic NSAID use.

Articles Chosen for Inclusion:

1. Duration of Symptom Relief and Early Trajectory of Adverse Events for Oral NSAIDs in Knee Osteoarthritis: A Systematic Review and Meta-analysis.

Osani MC, Vaysbrot EE, Zhou M, McAlindon TE, Bannuru RR.
Arthritis Care Res (Hoboken). 2019 Mar 25. doi: 10.1002/acr.23884. [Epub ahead of print]
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.

2. Non-steroidal anti-inflammatory drug induced acute kidney injury in the community dwelling general population and people with chronic kidney disease: systematic review and meta-analysis.
Zhang X, Donnan PT, Bell S, Guthrie B.
BMC Nephrol. 2017 Aug 1;18(1):256. doi: 10.1186/s12882-017-0673-8. Review.
PMID:28764659
Abstract
BACKGROUND:
Non-steroidal anti-inflammatory drugs (NSAIDs) are a common cause of adverse drug events (ADEs), but renal risks of NSAIDs are less well quantified than gastrointestinal and cardiac risks. This paper reports a systematic review of published population-based observational studies examining the risk of acute kidney injury (AKI) associated with NSAIDs in community-dwelling adults and those with pre-existing chronic kidney disease (CKD).

METHODS:
MEDLINE and EMBASE databases were searched until June 2016, and 3789 papers screened. Ten studies reporting NSAID risk of AKI in the general population were included in random effects meta-analysis, of which five additionally reported NSAID risk in people with CKD.

RESULTS:
In the general population, the pooled odds ratio (OR) of AKI for current NSAID exposure was 1.73 (95%CI 1.44 to 2.07), with somewhat higher risk observed in older people (OR 2.51, 95%CI 1.52 to 2.68). In people with CKD, individual study OR of AKI due to current NSAID exposure ranged from 1.12 to 5.25, with pooled estimate OR 1.63 (95% CI 1.22 to 2.19).

CONCLUSIONS:
No study reported baseline risk of AKI in different populations meaning absolute risks could not be estimated, but baseline risk and therefore the absolute risk of NSAID exposure is likely to be higher in people with CKD and older people. Large population based studies measuring AKI using current definitions and estimating the absolute risk of harm are needed in order to better inform clinical decision making.

3. Non-steroidal anti-inflammatory drug use in chronic pain conditions with special emphasis on the elderly and patients with relevant comorbidities: management and mitigation of risks and adverse effects.
Wehling M.
Eur J Clin Pharmacol. 2014 Oct;70(10):1159-72. doi: 10.1007/s00228-014-1734-6. Epub 2014 Aug 28. Review.
PMID: 25163793

PURPOSE:
Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used drugs, and this widespread use is complicated by safety issues.

METHOD:
A Literature review was conducted.

RESULTS:
NSAIDs are a leading cause of drug-related morbidity, especially in the elderly and patients with comorbidities. Most adverse effects are related to generalized inhibition of the major targets of NSAIDs: cyclooxygenases I and II. These enzymes are not only involved in pain and inflammation pathogenesis but are also required in the gastrointestinal (GI) tract for mucosal protection and gut motility, and in the kidneys for functional integrity. Thus, the mechanisms of NSAID toxicity are well understood, but the consequences are largely uncontrolled in clinical practice. GI ulcers, including bleeding ulcers, may occur in several percent of all chronic unprotected, high-dose NSAID users. Renal side effects may precipitate renal failure, resulting in acute dialysis and chronic retention. This includes sodium retention, resulting in arterial hypertension, heart failure, and atherosclerotic events. Cardiovascular risk may be tripled by chronic high-dose NSAID use in long-term clinical trials though "real-life studies" indicate lower risk ratios. Off-target side effects include allergic reactions, drug-induced liver injury, and central nervous system effects.

CONCLUSIONS:
Management of pain and inflammation must consider those risks and find alternative drugs or approaches to limit the negative impact of NSAIDs on mortality and morbidity. Alternative drugs, low-dose/short-term use, but especially non-pharmacologic approaches, such as physiotherapy, exercise, neurophysiologic measures, and local therapies, need to be further utilized. The appalling equation "less pain-more deaths/morbidity" ultimately necessitates treatment optimization in the individual patient.

4. The Risk of Major NSAID Toxicity with Celecoxib, Ibuprofen, or Naproxen: A Secondary Analysis of the PRECISION Trial.: A Post-Hoc analysis of a Randomized Control Trial. [Solomon, et. al, 2017]

The Risk of Major NSAID Toxicity with Celecoxib, Ibuprofen, or Naproxen: A Secondary Analysis of the PRECISION Trial.
Solomon DH, Husni ME, Libby PA, Yeomans ND, Lincoff AM, Lüscher TF, Menon V, Brennan DM, Wisniewski LM, Nissen SE, Borer JS.
Am J Med. 2017 Dec;130(12):1415-1422.e4. doi: 10.1016/j.amjmed.2017.06.028. Epub 2017 Jul 26.
PMID:28756267
BACKGROUND: The relative safety of long-term use of nonsteroidal anti-inflammatory drugs is unclear. Patients and providers are interested in an integrated view of risk . We examined the risk of major nonsteroidal anti-inflammatory drug toxicity in the PRECISION trial.

METHODS: We conducted a post hoc analysis of a double-blind, randomized, controlled, multicenter trial enrolling 24,081 patients with osteoarthritis or rheumatoid arthritis at moderate or high cardiovascular risk. Patients were randomized to receive celecoxib 100 to 200 mg twice daily, ibuprofen 600 to 800 mg thrice daily, or naproxen 375 to 500 mg twice daily. All patients were provided with a proton pump inhibitor. The outcome was major nonsteroidal anti-inflammatory drug toxicity, including time to first occurrence of major adverse cardiovascular events, important gastrointestinal events, renal events, and all-cause mortality.

RESULTS: During follow-up, 4.1% of subjects sustained any major toxicity in the celecoxib arm, 4.8% in the naproxen arm, and 5.3% in the ibuprofen arm. Analyses adjusted for aspirin use and geographic region found

that subjects in the naproxen arm had a 20% (95% CI 4-39) higher risk of major toxicity than celecoxib users and that 38% (95% CI 19-59) higher risk. These risks translate into numbers needed to harm of 135 (95% CI, 72-971) for naproxen and 82 (95% CI, 53-173) for ibuprofen, both compared with celecoxib.

CONCLUSIONS: Among patients with symptomatic arthritis who had moderate to high risk of cardiovascular events, approximately 1 in 20 experienced a major toxicity over 1 to 2 years. Patients using naproxen or ibuprofen experienced significantly higher risk of major toxicity than those using celecoxib.

5. Quantitative estimation of rare adverse events which follow a biological progression: a new model applied to chronic NSAID use.
Tramèr MR, Moore RA, Reynolds DJ, McQuay HJ.
Pain. 2000 Mar;85(1-2):169-82.
PMID:10692616

Full article: https://www.sciencedirect.com/science/article/pii/S0304395999002675
Randomised controlled trials (RCTs) alone are unlikely to provide reliable estimates of the incidence of rare events because of their limited size. Cohort, case control, and other observational studies have large numbers but are vulnerable to various kinds of bias. Wanting to estimate the risk of death from bleeding or perforated gastroduodenal ulcers with chronic usage of non-steroidal anti-inflammatory drugs (NSAIDs) with greater precision, we developed a model to quantify the frequency of rare adverse events which follow a biological progression. The model combined data from both RCTs and observational studies. We searched systematically for any report of chronic (≥2 months) use of NSAIDs which gave information on gastroduodenal ulcer, bleed or perforation, death due to these complications, or progression from one level of harm to the next. Fifteen RCTs (19 364 patients exposed to NSAIDs for 2–60 months), three cohort studies (215 076 patients redeeming a NSAID prescription over a 3–12 month period), six case-control studies (2957 cases) and 20 case series (7406), and case reports (4447) were analysed. In RCTs the incidence of bleeding or perforation in 6822 patients exposed to NSAIDs was 0.69%; two deaths occurred. Of 11 040 patients with bleeding or perforation with or without NSAID exposure across all reports, 6–16% (average 12%) died; the risk was lowest in RCTs and highest in case reports. Death from bleeding or perforation in all controls not exposed to NSAIDs occurred in 18 out of 849 489 (0.002%). From these numbers we calculated the number-needed-to-treat for one patient to die due to gastroduodenal complications with chronic (≥2 months) NSAIDs as $1/((0.69\times\{6–16\%, \text{average } 12\%\})-0.002\%))=909–2500$ (average 1220). On average 1 in 1200 patients taking NSAIDs for at least 2 months will die from gastroduodenal complications who would not have died had they not taken NSAIDs. This extrapolates to about 2000 deaths each year in the UK.

Summary of the Evidence:

Author (Date)	Level of Evidence	Sample/ Setting	Outcome(s) studied	Key Findings	Limitations and Biases
1. Osani, et. al. (2019)	Systematic Review & Meta-analysis	- 72 RCTs - 26,424 participants with knee OA using NSAIDs. -1,607 potentially relevant abstracts → 191 eligible for full text review → 72 RCTs eligible for study. -Sample sizes: 47-844 -Mean Age: 53-69 -Dates: 1976-2017	-Pain & function -Discontinuation rate due to lack of efficacy -Discontinuation rate due to AEs -Incidence of treatment-related AEs -Incidence of GI, CV & serious AEs	-The treatment effect remained statistically significant up to 26 weeks, however the effects did diminish progressively over time and lost clinical significance. -The incidence of GI AEs was significantly higher in NSAID users than placebo users as early as 4 weeks. -The incidence of CV AEs in NSAID users was not significantly different from placebo users. -The most common GI AEs were transient and mild (upper abdominal pain, diarrhea, dyspepsia, nausea). -The most common CV AEs were edema and HTN and were also mildly severe. -Traditional NSAIDs - least favorable safety profile of all the classes (Ibuprofen, Naproxen, etc).	-Potential attrition bias and reporting bias were the most common reasons for High Risk of Bias ratings. -Lack of data at and after 26 weeks, since only 2 studies reported efficacy results at 26 weeks, and Celecoxib was the only treatment represented at this point. Additionally, the follow-up time (26 weeks) limited the safety analyses to the observation of minor AEs. -The risk estimates might be smaller than those observed in clinical practice. -Composite rates of events were collected to maximize data, so the raw event rates may be a small overestimation of the actual number of patients who experienced GI and/or CV AEs.
2. Zhang, et. al. (2017)	Systematic Review &	total of 1,609,163 participants in the	quantify AKI risk from taking NSAIDs:	quantify the risk of AKI due to NSAIDs in the general population and in	-The selection criteria included NSAIDs and COX-2 inhibitors,

	Meta-Analysis	community setting	general population and CKD patients	people with pre-existing CKD	but left out "low dose aspirin" -They did not assess for publication bias in the included studies -The result of this meta-analysis is only as reliable as the results from the included studies. -Reported "heterogeneity" between studies, attributed to the differences within the respective studies' population, and the methods of measuring AKI in each
3. Wheling, M. (2014)	Systematic Review & Meta-Analysis	Methods were not mentioned.	NSAID adverse effects on the following systems: -gastrointestinal -renal -cardiovascular -hepatic -immunologic -CNS.	Gastrointestinal NSAIDs can inhibit the mucosal defences of the GI system and thus about chronic NSAID users will develop GI adverse effects such as, discomfort, bloating, GERD, mild pain, or loss of appetite. One study found GI bleeding in 6.14% of chronic NSAID users compared with 0.54% of the general population. Furthermore, increasing age is a prominent risk factor for hospitalisation for peptic ulcers. Renal	-Methods were not clearly described. -Many of the studies used were admittedly not strong and more research must be conducted before confirming these links. -Wehling previously worked for AstraZeneca R&D and received consulting fees from several pharmaceutical companies.

				NSAIDs inhibit renal COX enzymes, which can negatively affect renal function. Being that adults over 80 years old already are at about 50% of normal creatinine clearance, NSAIDs may push these patients into dialysis. Cardiovascular- Not enough research has been conducted to confirm specific cardiovascular dangers, however some studies have found that it may increase blood pressure and increase the relative risk of cardiovascular events. Hepatic- The metabolism of NSAIDs in the liver can result in cellular damage and thus, damage to the liver. Immunologic- The most prominent allergic reaction to NSAIDs is to aspirin, which may result in hypotension, tachycardia, and anaphylaxis. CNS- The elderly are the most susceptible to CNS effects of NSAIDs which may include, dizziness, confusion, or falls, however there is not enough evidence to confirm. On the other hand, NSAIDs are currently being considered as a potential medication for dementia because of the	

				potential link between Alzheimer's and inflammation.	
4. Solomon, et. al. (2016)	Post Hoc Analysis of an RCT	31,857 patients screened, 24,081 patients randomized. Data was collected from 923 centers in North America, Central America, South America, Asia, and Eastern Europe between Oct 2006 and April 2016. Patient group was stratified and randomized into three groups, each receiving 20-40 mg esomeprazole per day: Group 1: Celecoxib 100-200 mg twice per day Group 2: Ibuprofen 600-800 mg TID Group 3: Naproxen	The primary outcomes studied were the increased NSAID toxicity risk of major adverse CV events, renal events, serious GI events, and all-causes mortality. The secondary outcomes studied included heart failure exacerbations, hypertension admissions, and iron-deficiency anemia.	-Ibuprofen had the greatest percentage of primary and secondary outcomes (5.3%), followed by naproxen (4.8%) and then celecoxib (4.1%). For the primary outcomes, naproxen had a higher comparative HR when compared with celecoxib (1.2) and ibuprofen (1.38). For the secondary outcomes, the result trends were similar. These results showed that there is an increased risk of major NSAID toxicity for naproxen and ibuprofen in comparison to celecoxib. Celecoxib is a selective COX-2 inhibitor, while ibuprofen and naproxen are non-selective inhibitors. This may have contributed to the better safety profile of celecoxib.	- An "on-treatment" statistical analysis was performed with the advise of the FDA - an intention -to-treat analysis would have been also important to see. -There was a very high non-retention rate. 24,081 patients were enrolled and only 17,474 completed. -The study notes at the end that the doses of naproxen and ibuprofen were allowed to be uptitrated throughout the study. Celecoxib was not able to be uptitrated because of the US safety regulatory restrictions. This caveat was not mentioned in methods, and this may have altered the results. -Many of the not statistically significant results found in the forest plot for major

		375-500 mg BID			NSAID toxicity are not mentioned in the results or discussion. -Almost all of the researchers were involved in Pfizer in some capacity, whether having received grants, consulted regarding clinical trials etc. Pfizer produces celecoxib, and the main goal of the trial was to determine the safety of celecoxib. Additionally, one of the researchers served on an advisory panel for the FDA, who allowed the trial to be analyzed on an "on-treatment" analysis instead of the standard intention-to-treat analysis.
5. Tramer, et. al. (2000)	Systematic Review & Meta-Analysis	15 RCTs, 3 cohort studies, 6 case-controls, 20 case series/ reports - 249,250 patients	Uncommon adverse effects of chronic NSAID use	1 in 1200 pts taking NSAIDs chronically will die of gastroduodenal bleeding who would not have died if they were not taking NSAIDs	-Study was limited to the UK with correspondence with Switzerland. -Wide confidence interval for NNH. -80% of bleeding, 99.8% of deaths found in studies

					other than RCTs or cohorts

Conclusion(s):
Article 1: The results of this study suggest that repeated cycles of continuous NSAID use of longer duration can lack long-term efficacy and can increase the risks for minor and transient adverse effects.
Article 2: NSAID use in the "general population" and those with CKD was found to have 1.5-fold increased risk of developing AKI, and 2-fold increased risk in people >60 years old.
Article 3: Chronic NSAID use can be dangerous for several body systems, especially GI, regarding peptic ulcers and bleeding. These risks are exacerbated among the elderly, thus other alternatives should be explored when possible.
Article 4: Celecoxib may be a better NSAID for long-term use than ibuprofen or naproxen, because of its lower risk of NSAID toxicity. Further research is required to determine the safety profile of celecoxib.
Article 5: Rare though it may be, patients using NSAIDs chronically are at increased risk for gastroduodenal ulcers and can potentially die from associated complications.

Clinical Bottom Line:

- We can advise our patient to explore alternative methods of pain control: Tylenol, topical NSAIDs, alternative pain therapies, as well as exercise as tolerated.
- Most common adverse effects: GI issues (ie: bleeding, ulcers, upper abdominal pain, diarrhea, dyspepsia, nausea), CV (ie: edema, HTN), and AKI.
- If necessary to maintain her on an NSAID, we would try switching her to celecoxib because of its better safety profile.