**CHRONIC NSAID USE IN THE ELDERLY**

**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 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?

**Clinical Question:**

Is long-term NSAID use safe in an older population (65 yrs +)?

**PICO Question:**

What are the associated risks of chronic NSAID use in a 95-year-old woman?

**P:** 95 y/o woman, elderly woman, patient 65+ years

**I:** oral NSAID use, 1200 mg oral NSAID

**C:** topical NSAID, acetaminophen, Diclofenac 1% gel

**O:** acute renal failure, acute MI, GI complications, CVA

**Search Strategy:**

Searched terms: “Chronic NSAID use risk”

Database and Articles Returned:

* Trip: 3,450 before filters, 59 after filters
* Cochrane: 17 before filters, 17 after filters
* PubMed: 2546 before filters, 193 after filters

Filters: English, within the last 5 years, systematic review

Selection Methods:

* Females included in the study with an attempt to include larger female study populations
* Focused on individuals aged 65+
* Oral NSAID use vs topical NSAID use
* Examination of risks associated with long-term use of oral NSAIDs (acute kidney disease, risk of MI, GI bleed, etc.)

**Articles Chosen for Inclusion:**

**[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.](https://www.ncbi.nlm.nih.gov/pubmed/25163793)**

**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.

Link: <https://www.ncbi.nlm.nih.gov/pubmed/25163793>

**[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.](https://www.ncbi.nlm.nih.gov/pubmed/28764659)**

**Zhang X, Donnan PT, Bell S, Guthrie B.**

**BMC Nephrol. 2017 Aug 1;18(1):256. doi: 10.1186/s12882-017-0673-8.**

**PMID:28764659**

#### 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).

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#### 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.

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#### 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).

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#### 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.

Link: <https://www.ncbi.nlm.nih.gov/pubmed/28764659>

**Osteoarthritis Research Society International Guidelines**

OBJECTIVE: To develop concise, up-to-date, patient-focused, evidence-based, expert consensus guidelines for the management of knee osteoarthritis (OA), intended to inform patients, physicians, and allied healthcare professionals worldwide.

METHOD: Thirteen experts from relevant medical disciplines (primary care, rheumatology, orthopedics, physical therapy, physical medicine and rehabilitation, and evidence-based medicine), three continents and ten countries (USA, UK, France, Netherlands, Belgium, Sweden, Denmark, Australia, Japan, and Canada) and a patient representative comprised the Osteoarthritis Guidelines Development Group (OAGDG). Based on previous OA guidelines and a systematic review of the OA literature, 29 treatment modalities were considered for recommendation. Evidence published subsequent to the 2010 OARSI guidelines was based on a systematic review conducted by the OA Research Society International (OARSI) evidence team at Tufts Medical Center, Boston, USA. Medline, EMBASE, Google Scholar, Web of Science, and the Cochrane Central Register of Controlled Trials were initially searched in first quarter 2012 and last searched in March 2013. Included evidence was assessed for quality using Assessment of Multiple Systematic Reviews (AMSTAR) criteria, and published criticism of included evidence was also considered. To provide recommendations for individuals with a range of health profiles and OA burden, treatment recommendations were stratified into four clinical sub-phenotypes. Consensus recommendations were produced using the RAND/UCLA Appropriateness Method and Delphi voting process. Treatments were recommended as Appropriate, Uncertain, or Not Appropriate, for each of four clinical sub-phenotypes and accompanied by 1e10 risk and benefit scores.

RESULTS: Appropriate treatment modalities for all individuals with knee OA included biomechanical interventions, intra-articular corticosteroids, exercise (land-based and water-based), self-management and education, strength training, and weight management. Treatments appropriate for specific clinical subphenotypes included acetaminophen (paracetamol), balneotherapy, capsaicin, cane (walking stick), duloxetine, oral non-steroidal anti-inflammatory drugs (NSAIDs; COX-2 selective and non-selective), and topical NSAIDs. Treatments of uncertain appropriateness for specific clinical sub-phenotypes included acupuncture, avocado soybean unsaponfiables, chondroitin, crutches, diacerein, glucosamine, intra- articular hyaluronic acid, opioids (oral and transdermal), rosehip, transcutaneous electrical nerve stimulation, and ultrasound. Treatments voted not appropriate included risedronate and electrotherapy (neuromuscular electrical stimulation).

CONCLUSION: These evidence-based consensus recommendations provide guidance to patients and practitioners on treatments applicable to all individuals with knee OA, as well as therapies that can be considered according to individualized patient needs and preferences.

Link:<https://www.oarsi.org/sites/default/files/docs/2014/non_surgical_treatment_of_knee_oa_march_2014.pdf>

# **A review of the gastrointestinal safety data--a gastroenterologist's perspective.**

[Lanas A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lanas%20A%5BAuthor%5D&cauthor=true&cauthor_uid=20407138)1.

### Abstract

Although NSAIDs have a well-established place for certain indications in the management of OA and RA, they are associated with significant gastrointestinal (GI) toxicity. The risk of NSAID-related upper GI events, such as dyspepsia or peptic ulcer and complications such as perforation or bleeding, is well characterized. Non-selective NSAIDs increase the risk of peptic ulcer disease approximately 5-fold, and that of upper GI bleeding 4-fold, whereas selective cyclo-oxygenase-2 (COX) inhibitors are associated with a significantly lower GI toxicity than non-selective agents. There is evidence that, while the incidence of NSAID-related upper GI complications has decreased in recent years, that of lower GI complications is increasing. Observational studies and analyses from studies, primarily designed to investigate upper GI events, suggest that lower GI complications are relatively common in NSAID users and that COX-2 selective inhibitors are associated with a lower risk of these events. Such events have been poorly characterized, but are associated with significant mortality; indeed, they may have even more serious consequences than the better characterized upper GI events. There is thus a strong case for evaluating the impact of such complications in prospective outcome studies. To facilitate such studies a new endpoint, Clinically Significant Upper or Lower GI Events, has been introduced that captures both upper and lower GI events.

Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2857792/

**Summary of the Evidence:**

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| --- | --- | --- | --- | --- | --- |
| **Author (Date)** | **Level of Evidence** | **Sample/Setting****(# of subjects/ studies, cohort definition etc. )** | **Outcome(s) studied** | **Key Findings** | **Limitations and Biases** |
| **Article 1** |  |  |  |  |  |
| Wehling, Martin, 2014 | Literature Review of controlled clinical trials, systematic reviews, and meta-analyses | This literature review looked at 125 articles gathered from a search in PubMed, using the term NSAID yielding 190,854 results | Discusses recent data on:• the inappropriate use of NSAIDs in at-risk patients• mechanisms underlying NSAIDs associated toxicity• utilization of alternative approaches to optimize treatment for chronic pain conditions and age-related conditions | - GI: • impairment of mucosal defense mechanisms by NSAIDs was the most serious SE• elderly are at a high risk of developing ulcers and to be hospitalized • NSAIDs contribute to bleeding from angiodysplasias in the lower GI tract in the elderly- Renal:• one study showed that 36% of elderly pts w/ ESRD required renal replacement therapy, outcome partially caused by NSAIDs (were on NSAIDs during the preceding 3 years)• MC complication in the elderly was chronic renal impairment- Cardiovascular:• NSAID use increase BP significantly• chronic use of diclofenac, NSAID, associated w/ 3x increase in CV risk compared w/ non-users• observational studies showed that there is no safe dose for NSAIDs in pts w/ CV disease (increased risk from the start of NSAID use)- Hepatic: • oxidation of NSAIDs can lead to reactive intermediaries which may damage cellular structures • overall hepatic risk of most NSAIDs is low - CNS:• SE of NSAID use, typically seen in elderly include dizziness, confusion, falls, and deliriant states• systematic studies on the CNS risk elicited by NSAIDs are lacking• NSAID withdrawal is considered as a cause for confused/deliriant elderly pt (once other causes have been considered and corrected)• CV damage from NSAIDs more clinically relevant in terms of CNS SEs | Biases: • Drug discussed (topical NSAID) is manufactured by the same organization that funded the literature review • Author received lecturing, reporting, and/or consulting fees from numerous pharmaceutical organizations (including the one funding the literature review)Limitations:• low generalizability to population• parameters “elderly” were not consistently defined• only one database used (PubMed)• subjective search terms used “NSAIDs”• methodology/exclusions are not explained• uncontrolled use is defined as “not prescribed by a doctor” but does not include specific dosage• review of other literature - multiple factors involved that cannot be all accounted for |
| **Article 2** |  |  |  |  |  |
| Lanas, 2010 | Systematic Review  | This systematic review is comprised of 44 articles which consist of case control, meta-analysis, randomized double blind trial, observational study, retrospective cohort, and randomized placebo- controlled studies. | The risk of GI complications associated with non-selective NSAIDs vs COX 2 inhibitors  | • NSAIDs are associated with GI toxicity – including asymptomatic mucosal damage, abdominal pain, dyspepsia with or without mucosal damage and bleeding ulcers. • There is evidence showing that the incidence of lower GI adverse effects associated with NSAID use is increasing but these results have been found incidentally while studying upper GI complications, therefore, it may be beneficial to conduct studies focused on lower GI or whole GI tract complications associated with NSAIDs. • NSAIDs can aggravate lesions and induce GI complications from pre-existing disease such as IBD, diverticulosis or angiodysplasia. • As per CSULGIEs (Clinically Significant Upper or Lower GI Events) NSAID use for patients without lesions have the following concerns: Acute GI hemorrhage of unknown origin, including presumed SB hemorrhage, clinically significant anemia of presumed occult GI origin, including possible SB blood loss. • A systematic literature review reported that mucosal breaks or small intestine injuries were present in up to 71% of NSAID users and 88% of patients with lower GI bleeding were NSAID users. • Upper GI complications is increased ~4 fold in NSAID users compared to non NSAID users. • COX2 inhibitors have been found to have LESS adverse reactions than NSAID use (p = 0.04) NSAID adverse events have been decreased with the use of gastro protective drugs such as PPIs.  | • The author failed to mention how many articles were used in the study and how these articles were selected. • Author failed to mention age groups in all of the discussed articles, only some mentioned age 65+ yrs. • Many of the statistics in this article are vague as study population is not mentioned but percentages are.  |
| **Article 3** |  |  |  |  |  |
| Zhang, Donnan, Bell, Guthrie, 2017 | Systematic review, meta-analysis | • 10 studies with 1,609,163 participants – PICO to search for NSAIDs, renal diseases, and renal function measurements in MEDLINE (n=1625) and EMBASE (n=3004), then removed duplicates (n=3789). Records screened publication year, study design, population, definition of AKI, type of NSAID, period and length of NSAID usage.• Included only cross-sectional, cohort, and case-control studies in English.  | • Presence or not of AKI (acute kidney injury).• AKI risk among current NSAID users in general population. | • 8 of 10 studies reported a statistically significant association between NSAID exposure and AKI.• Non-statistically significant association between higher COX-2 selectivity of NSAID with lower increased odds of AKI (p=0.07).•People aged 50+ had higher odds of AKI associated with NSAID exposure than general population.• Current exposure to NSAIDs are associated with 1.5x increase of developing AKI as compared to the general population. | • Consider-able heterogeneity between the 10 studies even though subgroup analyses were conducted.• Studies did not compare the same NSAIDs.• Studies varied in how they examined and measured AKI.• No inclusion of the absolute risk of developing AKI as it depends on the baseline risk of those exposed to NSAIDs. |
| **Article 4** |  |  |  |  |  |
| McAlindon, Bannuru, Sullivan, 2014 | Guidelines, systematic review | • Built upon previous literature search done by OARSI• Searched current (2010 - March 2013) literature, level of evidence was confined to: meta-analyses, systematic reviews and RCTs.• Expert panel composed of 13 voting members (7 rheumatologists, 2 orthopedic surgeons, 2 physical therapists, 1 primary care practitioner, 1 clinical guidelines methodologist and 1 physical therapy and rehabilitation specialist. • The role of the panel was to review the literature provided by the literature search and then vote on recommendations stratified by the degree of certainty, the inclusion of co-morbidities and single (knee) vs multiple-joint OA.  | • Impact of various treatment modalities (n=30) in the management of patients with knee osteoarthritis.• In order to advise the patient in our scenario we were concerned with only 3 recommendations (NSAIDs - oral non-selective; NSAIDs - oral COX-2 inhibitors; NSAIDS - topical). | -Only took into account recommendations related to NSAID use• Oral non-selective NSAIDs were determined appropriate for use in patient populations without co-morbidities, were uncertain for patients with moderate co-morbidities and were determined not appropriate for patients with significant co-morbidities (effect size for pain: 0.37, 0.26-0.49). Level of evidence: systematic review and meta-analysis of RCTs.• Oral COX-2 inhibitors were determined to be best used in a patient population with multiple-joint OA (which is not applicable to our patient).• Topical NSAIDs were recommended as an appropriate treatment for all patients with knee OA, irrespective of presence of co-morbidities (effect size for pain not available). Level of evidnce: systematic review and meta-analysis of RCTs. • Moderate co-morbidity risk was defined as: diabetes, advanced age, hypertension, CV disease, depression, or physical impairment limiting activity, including obesity.• High co-morbidity risk was defined as: history of GI bleed, MI, or chronic renal failure.  | • Potential conflicts of interest or bias on the part of the members of the expert panel were addressed through full disclosure of any sources of conflict of interest and oversight by the OARSI ethics committee. • Members of the panel deemed to have a conflict of interest were prohibited from voting on recommendations pertaining to that specific issue. • Limitations of this study include the fact that while the recommendations were founded on the basis of evidence-based research the recommendations themselves were the sole product of 13 experts.  |

**Conclusions:**

There are potentially life-threatening risks associated with long-term NSAID use, specifically: increased risk of an acute GI bleed, myocardial infarction, cerebrovascular accident and acute renal injury. NSAID use is appropriate for pain management in patient populations that do not possess concomitant co-morbidities. For those individuals that are living with some form of co-morbidity: advanced age, diabetes, hypertension, history of CV disease or PUD there may be an increased risk of adverse events with long-term oral NSAID use. Older populations in particular have an increased risk of AKI associated with chronic NSAID use. Topical NSAIDs are a potential option for those patients in need of pain relief, but for whom oral NSIADs may pose an undue risk, however, further research needs to be conducted as to the efficacy of topical NSAIDs and pain relief.

**Clinical Bottom Line:**

Older, otherwise healthy patients should be made aware of the full risks associated with oral NSAID use for joint pain. In discussing pain management options the clinician may suggest a trial of topical NSAIDs for pain relief, which have been found to be more effective for joints such as the knee and elbow and thus far have proven to have a lower side effect profile than oral NSAIDs. Patients with significant co-morbidities (CRD, history of MI, CVA or GI bleed) should be discouraged from the use of oral NSAIDs, and before considering other analgesics a trial of a topical NSAID should be attempted.

For our patient in particular, her age limits other avenues of pain management (i.e. a new exercise regimen or diet modifications). As such, a trial of a new type of analgesic with a lower side effect profile makes the most sense.