Published in final edited form as:
Ann Longterm Care. 2010 ; 18(9): 24–27.

Recognizing the Risks of Chronic Nonsteroidal Anti-Inflammatory Drug Use in Older Adults

Zachary A. Marcum, PharmD and **Joseph T. Hanlon, PharmD, MS**
Drs. Marcum and Hanlon are in the Division of Geriatric Medicine, Department of Medicine, School of Medicine, University of Pittsburgh, PA; and Dr. Hanlon is also at the Geriatric Research Education and Clinical Center (GRECC), and the Center for Health Equity Research and Promotion (CHERP), Veterans Affairs Pittsburgh Healthcare System (VAPHS).

Abstract

Older adults commonly take nonsteroidal anti-inflammatory drugs (NSAIDs) chronically. Studies of older adults show that chronic NSAID use increases the risk of peptic ulcer disease, acute renal failure, and stroke/myocardial infarction. Moreover, chronic NSAID use can exacerbate a number of chronic diseases including heart failure and hypertension, and can interact with a number of drugs (eg, warfarin, corticosteroids). Preferred analgesics in older adults that may have a lower risk of these adverse drug reactions include acetaminophen, a nonacetylated salicylate (eg, salsalate), a short half-life NSAID (eg, ibuprofen), or low-dose opioid/opioid-like agents in combination with acetaminophen (in appropriate patients).

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a common class of analgesics used chronically for persistent pain due to osteoarthritis and other musculoskeletal disorders in older adults.[1-3] Specifically, an estimated 40% of people age 65 years and older fill one or more prescriptions for a NSAID each year.[4] Considering that NSAIDs are also currently available over the counter, it is clear to see that even larger numbers of older adults are exposed to NSAIDs in the United States.

While these agents can be effective in treating inflammation and pain, older adults are at increased risk for adverse drug reactions (ADRs) due to age-related loss of physiological organ reserve, increased comorbidities, polypharmacy, and changes in pharmacokinetics.[5] As a result, NSAID use causes an estimated 41,000 hospitalizations and 3300 deaths each year among older adults.[2] Some specific ADRs of concern with chronic use of NSAIDs include gastrointestinal (GI), renal, cardiovascular (CV), cerebrovascular, and central nervous system (CNS) adverse effects.[6] This review will begin by describing key evidence for these organ-specific ADRs associated with the chronic use of NSAIDs in older adults and finish with general recommendations for healthcare providers to avoid/minimize these ADRs.

GI Risks Associated with Chronic NSAID Use

The spectrum of potential NSAID-related GI adverse effects is wide, ranging from dyspepsia to life-threatening gastric bleeding.[2] A nested case control study from nearly two decades ago (before the introduction of cyclooxygenase-2 [COX-2] selective NSAIDs) showed that NSAIDs increase the risk of fatal peptic ulcers by nearly fivefold in older

The authors report no relevant financial relationships.

adults;[7] other studies have shown that the risk of peptic ulcer complications is increased by three- to fivefold in older adults using NSAIDs.[2] This risk is much more pronounced in those taking concomitant systemic corticosteroids and warfarin.[8,9] In addition, the risk is increased as early as within the first month of treatment and is sustained over time.[3,10] Often, these peptic ulcers are asymptomatic but can lead to significant morbidity and mortality. The evidence for which NSAIDs are less risky is limited. One retrospective cohort study found that celecoxib, as compared to nonselective NSAIDs (ibuprofen, diclofenac, naproxen) carried the least risk of hospitalization for GI bleeding among elderly persons.[11] Of note, all NSAIDs (ie, nonselective and COX-2 selective) carry a boxed warning for adverse GI events. Overall, the rate of hospitalizations for peptic ulcer disease (PUD) increases with age, from 1 per 1000 per year in populations younger than age 50 years to 2-6 per 1000 per year in older adults (> 65 yr), with an estimated 15-35% of all peptic ulcer complications being due to NSAID use.[2,12]

Renal Risks Associated with Chronic NSAID Use

Similar to NSAID-related GI adverse effects, NSAID-induced renal dysfunction has a wide spectrum of negative effects, including decreased glomerular perfusion, decreased glomerular filtration rate, and acute renal failure (ARF). While it is important to recognize that ARF can develop at any point during long-term NSAID therapy, the risk may be highest among those who have recently initiated therapy. Specifically, in a nested case control study of older adults, the risk of ARF was increased nearly twofold for all NSAIDs (nonselective and COX-2 selective NSAIDs) within 30 days of initial use/prescribing.[13] This is consistent with previous studies reporting that NSAIDs increase the risk of ARF in the elderly.[14,15] This risk is further increased in those older adults with preexisting chronic kidney disease (CKD) and in those who use long half-life NSAIDs.[16] Thus, diligent monitoring of renal function (eg, blood urea nitrogen/serum creatinine to estimate creatinine clearance) is critical in older adults receiving NSAIDs, especially those who are at increased risk.[14] Of note, salsalate may be preferred among the NSAIDs as it is rarely associated with nephrotoxicity.[5] Overall, it is estimated that 2.5 million individuals in the United States experience adverse renal effects from NSAID use annually,[17] with older adults being in the highest-risk group in the population.

CV/Cerebrovascular Risks Associated with Chronic NSAID Use

NSAIDs have been shown to worsen/increase the risk of various CV and cerebrovascular outcomes, with some studies suggesting a greater risk associated with COX-2 selective NSAIDs as compared to nonselective NSAIDs.[11,18-23] One retrospective cohort study of older adults showed that naproxen carried the least risk of hospitalization for acute myocardial infarction (MI) among users of aspirin as compared to other nonselective NSAIDs (ibuprofen, diclofenac) and COX-2 selective NSAIDs (celecoxib, rofecoxib) used with aspirin.[11] In contrast, a prospective, population-based cohort study found an increased risk of stroke with the use of nonselective NSAIDs (including naproxen), as well as with COX-2 selective NSAIDs (including celecoxib) in those not taking aspirin. On an individual NSAID analysis, naproxen users were found to have more than a twofold increased risk of stroke.[20] Of note, all NSAIDs (ie, nonselective and COX-2 selective) carry a boxed warning for adverse CV events, including MI and stroke. Further research is needed to confirm individual NSAID adverse CV risk profiles.

One clinical trial of patients with hypertension (HTN) showed that piroxicam and ibuprofen blunted the effects of antihypertensive drugs (lisinopril/hydrochlorothiazide), significantly increasing systolic blood pressure (SBP) by 7.7-9.9%. An acetaminophen (APAP) period (in place of the NSAID) led to a significant decrease in blood pressure toward baseline, and a

second exposure to the NSAIDs led to another significant increase in SBP of 7.0-7.7%, adding strong support to the evidence of causality.[21] In addition, a cohort study of community-dwelling elderly individuals

> The NSAID should be used at the lowest effective dose for the shortest period of time.

found that those who were taking antihypertensive therapy and NSAIDs had SBPs approximately 5 mmHg higher than those not taking NSAIDs, and were more likely to have SBP higher than 140 mmHg.[18]

NSAIDs have also been shown to cause or exacerbate heart failure (HF) in older adults. Specifically, a cohort study of older adults found that rofecoxib and nonselective NSAIDS (naproxen, ibuprofen, and diclofenac), but not celecoxib, were significantly associated with an increased risk of admission for HF as compared to those not taking NSAIDs.[19] In contrast, another cohort study found that among patients who had survived their first hospitalization because of HF, subsequent use of any NSAID (including celecoxib, as well as ibuprofen, diclofenac, naproxen, and other NSAIDs) led to a significantly increased risk of death.[22]

Finally, an important point of clinical debate is the interaction between low-dose, cardioprotective aspirin and NSAIDs potentially interfering with the antiplatelet effect of aspirin. The American Geriatrics Society[5] recommends avoiding the coadministration of aspirin and ibuprofen based on a 2006 Food and Drug Administration warning. However, it is important to recognize that evidence suggests that this warning should also apply to naproxen, but not celecoxib.[23,24]

CNS Risks Associated with Chronic NSAID Use

NSAID use has been shown to be associated with a number of CNS effects including aseptic meningitis, psychosis, and cognitive dysfunction.[1,2] This latter point may seem to be inaccurate, but the literature suggests otherwise. At the time of this writing, the studies to date have not consistently shown a benefit from chronic NSAID use in reducing the risk of dementia or cognitive impairment.[25] Interestingly, though, several studies have shown that high-dose NSAIDs (ie, anti-inflammatory doses) may actually increase the risk of cognitive impairment.[26,27] In particular, indomethacin appears to cause more CNS effects than other NSAIDs in the elderly.[28]

What Should Clinicians Do to Avoid/Minimize ADRs Associated with Chronic NSAID Use in Older Adults?

One approach to reducing ADRs associated with NSAIDs is to avoid the use of specific agents and use preferred alternative analgesics (Table). This is particularly important in those older adults with preexisting HTN, CKD, HF, and/or PUD, or those taking concomitant warfarin or corticosteroids. An alternative option would be to use APAP, which has been shown to be equally effective to NSAIDs in a number of studies of patients with mild-to-moderate osteoarthritis pain. Of note, patients who say that APAP does not work for them may not have used an optimal dose (3-4 g/day in divided doses for at least 2 wk), which would be required in order to show a lack of effectiveness. If APAP does not work and NSAID use is not contraindicated, a trial of analgesic dosing of a nonacetylated salicylate (eg, salsalate) or ibuprofen or celecoxib may be acceptable. For those with moderate-to-moderately severe osteoarthritis pain, a trial of a low-dose opioid or opioid-like agent (eg, codeine, tramadol) in combination with APAP is another option. The rationale for this approach is to combine two different mechanisms of analgesic action. In those elderly

persons who require chronic NSAIDs, a proton pump inhibitor or misoprostol should be used to avoid the risk of PUD.[9,12] In general, long half-life NSAIDs (eg, naproxen, oxaprozin, piroxicam) and specific other NSAIDs (eg, indomethacin, ketorolac) should be avoided because their risk outweighs their potential benefits.[28]

Conclusion

This review has summarized the potential risks associated with chronic NSAID use in older adults, including GI, renal, CV/cerebrovascular, and CNS adverse effects. Although only ADRs affecting these four organ systems were discussed in this review, it is important to recognize that NSAIDs can cause various other adverse effects (eg, hepatotoxicity, cutaneous toxicity).[2] Moreover, it is important to note that nonpharmacological approaches (weight reduction, increasing physical activity) may also help patients who are experiencing musculoskeletal pain.[29] For patients already taking NSAIDS chronically, healthcare providers should assess whether the patient could switch to APAP or salsalate. If the patient still requires a NSAID, GI prophylaxis should be considered in all older patients, especially those with other risk factors; importantly, the NSAID should be used at the lowest effective dose for the shortest period of time.

As the aging population rapidly grows over the next few decades, the risks associated with chronic NSAID use will remain an important public health issue. Hopefully, health-care providers armed with the above information who carefully and consistently monitor chronic NSAID use in their older patients will avoid these preventable complications.

Acknowledgments

The writing of this paper was supported by National Institute on Aging grants (R01AG027017, P30AG024827, T32 AG021885, K07AG033174, R01AG034056), a National Institute of Mental Health grant (R34 MH082682), a National Institute of Nursing Research grant (R01 NR010135), and an Agency for Healthcare Research and Quality grant (R01 HS017695).

References

1. Hanlon JT, Fillenbaum GG, Studenski SA, et al. Factors associated with suboptimal analgesic use in community-dwelling elderly. Ann Pharmacother. 1996; 30(7-8):739–744. [PubMed: 8826552]
2. Griffin MR. Epidemiology of nonsteroidal anti-inflammatory drug-associated gastrointestinal injury. Am J Med. 1998; 104(3A):23S–29S. 41S–42S. [PubMed: 9572317]
3. Gupta M, Eisen GM. NSAIDs and the gastrointestinal tract. Curr Gastroenterol Rep. 2009; 11(5): 345–353. [PubMed: 19765361]
4. Ray WA, Stein MC, Byrd V, et al. Educational program for physicians to reduce use of non-steroidal anti-inflammatory drugs among community-dwelling elderly persons: A randomized controlled trial. Med Care. 2001; 39(5):425–435. [PubMed: 11317091]
5. American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. J Am Geriatr Soc. 2009; 57(8):1331–1346. Published Online: July 2, 2009. [PubMed: 19573219]
6. Hanlon, JT.; Guay, DRP.; Ives, TJ. Oral analgesics: efficacy, mechanism of action, pharmacokinetics, adverse effects, and practical recommendations for use in older adults. In: Gibson, SJ.; Weiner, DK., editors. Pain in Older Persons. IASP Press; Seattle, WA: 2005. p. 205-222.
7. Griffin MR, Ray WA, Schaffner W. Nonsteroidal anti-inflammatory drug use and death from peptic ulcer in elderly persons. Ann Intern Med. 1988; 109(5):359–363. [PubMed: 3261560]
8. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Concurrent use of nonsteroidal anti-inflammatory drugs and oral anticoagulants places elderly persons at high risk for hemorrhagic peptic ulcer disease. Arch Intern Med. 1993; 153(14):1665–1670. [PubMed: 8333804]

9. MacLean CH, Pencharz JN, Saag KG. Quality indicators for the care of osteoarthritis in vulnerable elders. J Am Geriatr Soc. 2007; 55(suppl 2):S383–S391. [PubMed: 17910561]
10. Schaffer D, Florin T, Eagle C, et al. Risk of serious NSAID-related gastrointestinal events during long-term exposure: A systematic review. Med J Aust. 2006; 185(9):501–506. [PubMed: 17137455]
11. Rahme E, Nedjar H. Risks and benefits of COX-2 inhibitors vs non-selective NSAIDs: Does their cardiovascular risk exceed their gastrointestinal benefit? A retrospective cohort study. Rheumatology (Oxford). 2007; 46(3):435–438. Published Online: January 25, 2007. [PubMed: 17255138]
12. Lanza FL, Chan FK, Quigley EM. Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009; 104(3):728–738. Published Online: February 24, 2009. [PubMed: 19240698]
13. Schneider V, Lévesque LE, Zhang B, et al. Association of selective and conventional nonsteroidal antiinflammatory drugs with acute renal failure: A population-based, nested case-control analysis. Am J Epidemiol. 2006; 164(9):881–889. Published Online: September 27, 2006. [PubMed: 17005625]
14. Griffin MR, Yared A, Ray WA. Nonsteroidal anti-inflammatory drugs and acute renal failure in elderly persons. Am J Epidemiol. 2000; 151(5):488–496. [PubMed: 10707917]
15. Winkelmayer WC, Waikar SS, Mogun H, Solomon DH. Nonselective and cyclooxygenase-2-selective NSAIDs and acute kidney injury. Am J Med. 2008; 121(12):1092–1098. [PubMed: 19028206]
16. Murray MD, Black PK, Kuzmik DD, et al. Acute and chronic effects of nonsteroidal antiinflammatory drugs on glomerular filtration rate in elderly patients. Am J Med Sci. 1995; 310(5):188–197. [PubMed: 7485222]
17. Zhang J, Ding EL, Song Y. Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmia events: Meta-analysis of randomized trials. JAMA. 2006; 296(13):1619–1632. Published Online: September 12, 2006. [PubMed: 16968832]
18. Chrischilles EA, Wallace RB. Nonsteroidal anti-inflammatory drugs and blood pressure in an elderly population. J Gerontol. 1993; 48(3):M91–M96. [PubMed: 8482817]
19. Mamdani M, Juurlink DN, Lee DS, et al. Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: A population-based cohort study. Lancet. 2004; 363(9423):1751–1756. [PubMed: 15172772]
20. Haag MD, Bos MJ, Hofman A, et al. Cyclooxygenase selectivity of nonsteroidal anti-inflammatory drugs and risk of stroke. Arch Intern Med. 2008; 168(11):1219–1224. [PubMed: 18541831]
21. Pavlicević I, Kuzmanić M, Rumboldt M, Rumboldt Z. Interaction between antihypertensives and NSAIDs in primary care: A controlled trial. Can J Clin Pharmacol. 2008; 15(3):e372–e382. Published Online: October 24, 2008. [PubMed: 18953082]
22. Gislason GH, Rasmussen JN, Abildstrom SZ, et al. Increased mortality and cardiovascular morbidity associated with use of nonsteroidal anti-inflammatory drugs in chronic heart failure. Arch Intern Med. 2009; 169(2):141–149. [PubMed: 19171810]
23. Capone ML, Sciulli MG, Tacconelli S, et al. Pharmacodynamic interaction of naproxen with low-dose aspirin in healthy subjects. J Am Coll Cardiol. 2005; 45(8):1295–1301. [PubMed: 15837265]
24. Renda G, Tacconelli S, Capone ML, et al. Celecoxib, ibuprofen, and the antiplatelet effect of aspirin in patients with osteoarthritis and ischemic heart disease. Clin Pharmacol Ther. 2006; 80(3):264–274. [PubMed: 16952493]
25. Coley N, Andrieu S, Gardette V, et al. Dementia prevention: Methodological explanations for inconsistent results. Epidemiol Rev. 2008; 30(1):35–66. Published Online: September 8, 2008. [PubMed: 18779228]
26. Saag KG, Rubenstein LM, Chrischilles EA, Wallace RB. Nonsteroidal antiinflammatory drugs and cognitive decline in the elderly. J Rheumatol. 1995; 22(11):2142–2147. [PubMed: 8596158]
27. Hanlon JT, Schmader KE, Landerman LR, et al. Relation of prescription nonsteroidal antiinflammatory drug use to cognitive function among community-dwelling elderly. Ann Epidemiol. 1997; 7(2):87–94. [PubMed: 9099396]

28. Fick DM, Cooper JW, Wade WE, et al. Updating the Beers criteria for potentially inappropriate medication use in older adults: Results of a U.S. consensus panel of experts. Arch Intern Med. 2003; 163(22):2716–2724. published correction appears in *Arch Intern Med* 2004;164(3):298. [PubMed: 14662625]

29. American Geriatrics Society Panel on Exercise and Osteoarthritis. Exercise prescription for older adults with osteoarthritis pain: Consensus practice recommendations. A supplement to the AGS Clinical Practice Guidelines on the management of chronic pain in older adults. J Am Geriatr Soc. 2001; 49(6):808–823. published correction appears in *J Am Geriatr Soc* 2001;49(10):1400. [PubMed: 11480416]

Table

Preferred Analgesic Agents for Treatment of Nociceptive Pain in Older Adults

Drug	Initial Dosing	Special Considerations in Older Adults
Mild-to-Moderate Pain		
APAP	325-500 mg every 4 h or 500-1000 mg every 6 h; maximum daily dose of 4000 mg	Does not interfere with platelet function; reduce maximum dose 50% to 75% in patients with hepatic insufficiency or history of alcohol abuse
Celecoxib	100 mg daily	Higher doses associated with higher incidence of GI and CV side effects; patients with indications for cardioprotection require aspirin
Ibuprofen	200 mg 3-4 times/day; maximum daily dose of 3200 mg	Risk of GI bleeding increased in persons > 75 yr; misoprostol or PPI should be prescribed for long-term users
Salsalate	500-750 mg every 12 h; maximum daily dose of 3000 mg	Does not interfere with platelet function; GI bleeding and nephrotoxicity are rare
Moderate-to-Moderately Severe Pain		
APAP/Codeine	325/30 mg every 6 h; maximum daily dose of 12 tablets	Monitor for constipation, confusion, and falls; same considerations for APAP as listed above
APAP/Tramadol	325/37.5 mg every 6 h; maximum daily dose of 8 tablets	Renally adjusted dose when estimated creatinine clearance < 30 mL/min: maximum of 2 tablets every 12 h; treatment should not exceed 5 days; same considerations for APAP as listed above

APAP = acetaminophen; GI = gastrointestinal; CV = cardiovascular; PPI = proton pump inhibitor.

Contains information from references 5 *and* 6.

Ann Longterm Care. Author manuscript; available in PMC 2011 August 19.