

## NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

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1. Abramson SB. Treatment of gout and crystal arthropathies with nonsteroidal antiinflammatory drugs: uses and mechanisms of action. *Curr Opin Rheum* 4:295-300, 1992

*Review of prostaglandin dependent and independent mechanisms of NSAID action.*

2. Amin AR, Vyas P, Attur M, et al. The mode of action of aspirin-like drugs: effect on inducible nitric oxide synthase. *Proc Natl Acad Med* 92:7926-7930, 1995

*Salicylates inhibit nitric oxide synthesis independently from effects on cyclooxygenase.*

3. **Ashcroft** DM, Chapman SR, Clark WK, Millson DS. Upper gastroduodenal ulceration in arthritis patients treated with celecoxib. *Ann Pharmacother* 35:829-834, 2001.

*In this meta-analysis of five trials that evaluated endoscopic endpoints in RA and OA patients, celecoxib was associated with a diminished incidence of gastroduodenal ulcers when compared with diclofenac, ibuprofen, and naproxen.*

4. **Bensen** WG, Fiechtner JJ, McMillen JI, Zhao WW, Yu SS, Woods EM et al. Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: A randomized controlled trial. *Mayo Clin Proc* 74:1095-1105, 1999.

*Celecoxib is an effective agent for the treatment of pain due to knee OA and produced relief comparable to naproxen.*

5. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med* 343:1520-8, 2000+

*In this trial involving rheumatoid arthritis patients, rofecoxib was associated with fewer confirmed upper GI events (perforations, ulcers, and bleeds, as well as symptomatic gastroduodenal ulcers), compared with naproxen.*

6. Bradley JD, Brandt KD, Katz, BP, et al. Comparison of an antiinflammatory dose of ibuprofen, an analgesic dose of ibuprofen and acetaminophen in the treatment of osteoarthritis of the knee. *N Engl J Med* 325:87-91,1985

*Influential article demonstrates equal analgesic efficacy of acetaminophen at four weeks for chronic mild-moderate OA.*

7. Brandt KD. Effects of nonsteroidal anti-inflammatory drugs on chondrocyte metabolism in vitro and in vivo. *Am J Med* 83:29-34, 1987+

*Controversy exists as to whether NSAIDS may be deleterious to OA-affected cartilage.*

8. **Cannon** GW, Caldwell JR, Holt P, McLean B, Seidenberg B, Bolognese J et al. Rofecoxib, a specific inhibitor of cyclooxygenase 2, with clinical efficacy comparable with that of diclofenac sodium: results of a one- year, randomized, clinical trial in patients with osteoarthritis of the knee and hip. Rofecoxib Phase III Protocol 035 Study Group. *Arthritis Rheum* 43:978-987, 2000.

*Akin to reference 4, this study establishes the efficacy of the COX-2 inhibitor rofecoxib in the treatment of symptomatic OA of the knee and hip.*

9. Catania A, Arnold HM, Nacakysi A, et al. Inhibition of acute inflammation in the periphery by central action of salicylates. *Proc Natl Acad Sci USA* 88:8544-8547, 1991

*Interesting documentation of central CNS action of salicylates, but not indomethacin, on peripheral carageenin-induced inflammation.*

10. Crofford LJ, Wilder RL, Ristimaki AP, et al. Cyclooxygenase-1 and -2 expression in rheumatoid synovial tissues: effects of interleukin-1B, phorbol ester, and corticosteroids. *J Clin Invest* 93:1095-1101, 1994

*Demonstration of COX-2 up-regulation, and the inhibition of its expression to steroids, in synovial tissue obtained from patients with RA.*

11. **Dalen** JE, Goldberg RJ. Prophylactic aspirin and the elderly population. *Clin Geriatr Med* 8:119-126, 1992.

*In spite of the potential GI adverse events detailed in reference 12, low dose ASA remains important in primary prevention of cardiovascular disease in the cohort of individuals over age 50.*

12. **Derry** S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. *BMJ* 321:1183-1187, 2000.

*Even at doses < 163 mg/day, long term aspirin therapy is associated with a significant increase in the incidence of GI hemorrhage, according to this meta-analysis of 24 randomized, clinical trials.*

13. Diaz-Gonzalez F, Gonzalez-Alvero I, Campanero MR, et al. Prevention of in vitro neutrophil-endothelial attachment through shedding of L-selectin by nonsteroidal antiinflammatory drugs. *J Clin Invest* 95:1756-1765, 1995

*NSAIDS inhibit neutrophil-endothelial cell interaction by causing the shedding of endothelial L-selectin, a molecule responsible for initial rolling of neutrophils, which is required for subsequent attachment and egress.*

14. **Ehrlich** EW, Davies GM, Watson DJ, Bolognese JA, Seidenberg BC, Bellamy N. Minimal perceptible clinical improvement with the Western Ontario and McMaster Universities osteoarthritis index questionnaire and global assessments in patients with osteoarthritis. *J Rheumatol* 27:2635-2641, 2000.

*What change in the WOMAC score is clinically relevant when analyzing an NSAID treatment trial?*

15. Endres S, Cannon JG, Ghorbani R, Dempsey RA, Sisson SD, Lonnemann G et al. In vitro production of IL 1 beta, IL 1 alpha, TNF and IL2 in healthy subjects: distribution, effect of cyclooxygenase inhibition and evidence of independent gene regulation. *Eur J Immunol* 19:2327-2333, 1989+

*Exposing PBMCs in vitro to both indomethacin and lipopolysaccharide led to an upregulation of Interleukin-1 synthesis.*

16. Fiorucci S, Santucci L, Cirino G, Mencarelli A, Familiari L, Soldato P, and Morelli A. IL-1 $\beta$  converting enzyme is a target for nitric oxide-releasing aspirin: new insights in the anti-inflammatory mechanism of nitric oxide-releasing nonsteroidal anti-inflammatory drugs. *J Immunol* 165: 5245-5254; 2000+

*NO-releasing NSAIDS appear to be both anti-inflammatory and gastro-protective. This paper addresses the complex relationship between NO and inflammation.*

17. Fu J-Y, Masferrer JL, Seibert K, Raz A, Needleman P. The induction and suppression of prostaglandin H<sub>2</sub> synthase(cyclooxygenase) in human monocytes. *J Biol Chem* 265:16737-16740, 1990

*Landmark article in description of COX-2 isoform.*

18. Gurwitz JH, Everitt DE, Monane M, Glynn RJ, Choodnovskiy I, Beaudet MP, Avorn J. The impact of ibuprofen on the efficacy of antihypertensive treatment with hydrochlorothiazide in elderly persons. *J Gerontol: Med Sci*, 51:74-79, 1996

*Ibuprofen (1800 mg/d) induces a significant increase in systolic blood pressure in older hypertensive patients treated with hydrochlorothiazide. NSAID therapy may negatively impact the control of hypertension in elderly patients.*

19. **Hawkey** C, Laine L, Simon T, Beaulieu A, Maldonado-Cocco J, Acevedo E et al. Comparison of the effect of rofecoxib (a cyclooxygenase 2 inhibitor), ibuprofen, and placebo on the gastroduodenal mucosa of patients with osteoarthritis: a randomized, double-blind, placebo-controlled trial. The Rofecoxib Osteoarthritis Endoscopy Multinational Study Group. *Arthritis Rheum* 43:370-377, 2000.

*Akin to reference 3, this endoscopic study noted that rofecoxib was associated with a diminished incidence of gastroduodenal ulcers when compared with ibuprofen in a population of patients with OA.*

20. Kopp E, Ghosh S. Inhibition of NF-kB by sodium salicylate and aspirin. *Science* 265:956-959, 1994

*Inhibitory (and therefore potential antiinflammatory) effects of salicylate on NFk $\beta$  activation are independent of cyclooxygenase inhibition.*

21. Masferrer JL, Zweifel BS, Manning PT, et al. Selective inhibition of inducible cyclooxygenase 2 in vivo is antiinflammatory and nonulcerogenic. *Proc Natl Acad Sci USA* 91:3228-3232, 1994

*Animal model of inflammation demonstrates up-regulation of COX-2 in air pouch lining cells at site of carageenin injection. Selective COX-2 inhibitor blocks COX-2 dependent prostaglandin production, reduces inflammatory cell infiltrate but does not induce gastric ulceration.*

22. **Mukherjee** D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA* 286:954-959, 2001.

*An excellent theoretical discourse concerning why highly selective (or specific) COX-2 inhibitors might be thrombogenic.*

23. **Pincus** T, Koch GG, Sokka T, Lefkowitz J, Wolfe F, Jordan JM et al. A randomized, double-blind, crossover clinical trial of diclofenac plus misoprostol versus acetaminophen in patients with osteoarthritis of the hip or knee. *Arthritis Rheum* 44:1587-1598, 2001.

*Contrary to the results noted in reference 6, using a 6 week trial for patients with hip and/or knee OA, these investigators noted a significant improvement in pain scores for those taking diclofenac/misoprostol, compared with those taking acetaminophen.*

24. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *JAMA*; 284:1247-1255, 2000+

*In this trial of both osteoarthritis and rheumatoid arthritis patients, celecoxib was associated with fewer confirmed upper GI events (perforations, ulcers, and bleeds, as well as symptomatic gastroduodenal ulcers) compared with diclofenac and ibuprofen (secondary endpoint). However, the primary endpoint of upper GI perforations, ulcerations, and bleeds did not achieve statistical significance.*

25. Simon LS. Actions and toxicity of nonsteroidal anti-inflammatory drugs. *Curr Op Rheum* 7: 159-166, 1995.

*Excellent review of the literature regarding the mechanisms of action as well as adverse reactions associated with NSAIDs.*

26. Simon LS. Nonsteroidal antiinflammatory drugs and their effect. The importance of COX "selectivity". J Clin Rheum 2: 135-140, 1996

*Excellent review, including new concepts of COX-1/COX-2 inhibition with regard to understanding efficacy and toxicities of NSAIDs.*

27. Singh G. Gastrointestinal complications of prescription and over-the-counter nonsteroidal anti-inflammatory drugs: a view from the ARAMIS database. Am J Ther 7: 115-121, 2000 +

*A concise description of prescription and OTC NSAID GI complications as noted in the prospective Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) database.*

28. Vane J. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nature 231:232-234, 1971

*Classical, Nobel Prize winning article.*

29. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. N Engl J Med 340:1888-1899, 1999 +

*Excellent review of epidemiology and treatment of NSAID-induced gastropathy.*

**Proposed deletions:**

11. Silverstein FE, Graham DY, Senior JR, Davies HW, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. Annals Int Med 123:241-249, 1995.

**Replace with Wolfe, et al (#21).**

14. Soll AH, Weinstein WM, Kurata J, et al. Nonsteroidal antiinflammatory drugs and peptic ulcer disease. Ann Int Med 114: 307-319, 1991

**Replace with Wolfe, et al (#21).**

15. Taha AS, Hudson N, Hawkey CJ, Swannell AJ, Trye PN, Cottrell J, Mann SG, Simon TJ, Sturrock RD, Russell RI. Famotidine for the prevention of gastric and duodenal ulcers caused by nonsteroidal antiinflammatory drugs. N Engl J Med 334:1435- 1439, 1996

**Replace with Wolfe, et al (#21).**