The Comparative Safety of Analgesics in Older Adults with Arthritis (Solomon et al)[1]

Study Cohort:

- Analysis of a large drug plan claims administrative database for Medicare beneficiaries from Pennsylvania and New Jersey who received a traditional NSAID, coxib or opioid between 1999 – 2005.
- **Included**: low income adults, either osteoarthritis (OA) or rheumatoid arthritis, with new Rx for 1 of the 3 classes of analgesics. Subjects had to use health care system consistently in previous 365 days.
- **Excluded**: recent analgesic use (<180days), >1 analgesic class used simultaneously, malignancy/hospice use, <1yr follow up.

Study Validity:

Observational cohort, matched on high dimensional propensity scores (500 covariate) based on administrative database

- Matched for demographic, surgical & diagnosis (e.g. CV diagnosis/tx, osteoporosis/fractures, GI diagnosis/tx, liver & renal).
- Initial cohort = 163,714 subjects; & after exclusions = 23,647
- Cohort after propensity score matching = 12,840 (7.8% or 4,280 in each of the 3 tx groups)
- Well designed observational study; however, limited by the potential for unknown/unexpected confounders and impact of the inclusion/exclusion criteria on the population to which the results apply.
- Unknown/unexpected confounders [opioid group potentially sicker than other group (acute care hospital stay 2.4 days vs 1.9; higher comorbidity index 1.7 vs. 1.6; ↑ falls, ↑ osteoporosis, ↑ renal insufficiency, ↑ chronic back pain, ↑ gout; ↑ ACEI, ARBs, BB, surgery; huge difference in baseline characteristics in eTable 1 before propensity score-matched); variance in dose/duration & ASA/OTC analgesic use not factored in. All opioids in one group.]

Baseline population:

- ~ 90% OA, ~ 10% RA; Age mean= 80; 84% ♀; on an average of 4.7 different drugs; 32% diabetes, 32% hypertensive, 6% MI, ~7% previous fractures; 24% on a PPI; 1-2% renal insufficiency; co-morbidity index = 1.5
- Note: this population represents a relatively healthy older (80yr) female OA population with <2 co-morbidities.

Results: Safety Events Among Propensity Score-Matched Older Arthritic Adults Initiating Rx Analgesics

	HR & 95% CI		
Adverse Events (AE)	**NSAIDs**	**Coxibs**	**Opioids**
Composite Cardiovascular (CV)[a]	1 (reference)	1.28 1.01-1.62	1.77 1.39-2.24; NNH=17/yr Author's estimate
Upper/Lower GI Tract Bleed	1 (reference)	0.60 0.35-1.00	1.07 0.65-1.76
Composite Fracture [b]	1 (reference)	0.96 0.62-1.49	4.47 3.12-6.41; NNH=26/yr Author's estimate
Hospitalized AE	1 (reference)	1.12 0.91-1.38	1.68 1.37-2.07; NNH=19/yr Author's estimate
Death related to AE	1 (reference)	1.12 0.62-2.02	1.11 0.58-2.10
All-cause mortality	1 (reference)	1.16 0.85-1.57	1.87 1.39-2.53; NNH=27/yr Author's estimate
Individual AE HRs of note for opioid vs NSAID: **Bowel obstruction 4.87** 1.40-17.02; Fracture: hip 3.02 1.20-7.58 ; humerus 9.26 4.25-20.18			

[a] MI, stroke, hospitalization for HF, revascularization, CV death out of hospital. [b] hip, humerus, pelvis & wrist. ♀=female AE=adverse event CI=95% confidence interval CV=cardiovascular HR=hazard ratio NNH=number needed to harm (number of patients that need to be treated for 1yr to observe 1 excess adverse event when initiating an opioid vs a NSAID) rx=prescription yr=year

Considerations:

- Very well done observational study; however, potential for unrecognized confounding leaves the results, especially those with more marginal HRs (e.g. CV & mortality) open to question.
- It is quite likely that opioid use in the elderly is associated with increased fracture risk and related morbidity/mortality as well as bowel obstruction. The HR for these outcomes is more convincing.
- The higher CV risk associated with opioids was unexpected and since HR is much smaller (<2), and since opioids are often chosen for those in whom NSAIDs/Coxibs are contraindicated, this result is open to question.

Bottom Line (Opioids relative to NSAIDs & Coxibs):

- Although opioids are sometimes considered "preferred" in elderly patients due to the well recognized GI, CV and renal risks of NSAIDS/Coxibs, opioids do present their own potential array of harms. One should be aware of the increased risk of falls/fractures and bowel obstruction, and carefully weigh this against any potential benefit.
- Opioids may be associated with an increase in CV events and mortality; however, given the limitations of the study and the modest hazard ratios, this may be the result of confounding and not represent true causality.
  {Opioids not usually associated with a direct adverse CV event (except for ↑QT interval with methadone). Opioids may be an indirect cause of CV events 2° to other adverse events. NSAIDs appear to ↑ CV events (CV risk: rofecoxib, diclofenac > ibuprofen & celecoxib at low doses > naproxen appears safest).[2,3] Opioid use has been indirectly associated with ↑ mortality and the recent ↑ in opioid utilization has occurred in association with a rise in opioid related deaths observational data.[4] }
- One should not extrapolate the findings of this study to elderly with several (>2) co-morbidities as NSAIDs & Coxibs may still present significant cardiovascular and renal risks relative to opioids.

[1] Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. Arch Intern Med. 2010 Dec 13;170(22):1968-76.
[2] Fosbøl EL, Folke F, Jacobsen S, et al. Cause-Specific Cardiovascular Risk Associated With Nonsteroidal Antiinflammatory Drugs Among Healthy Individuals. Circ Cardiovasc Qual Outcomes. 2010 Jun 8.
[3] Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, Egger M, Jüni P. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ. 2011 ;342:c7086.
[4] Fischer B, Rehm J. Deaths related to the use of prescription opioids. CMAJ.2009 Dec 8;181(12):881-2. Accessed online at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2789122/?tool=pubmed