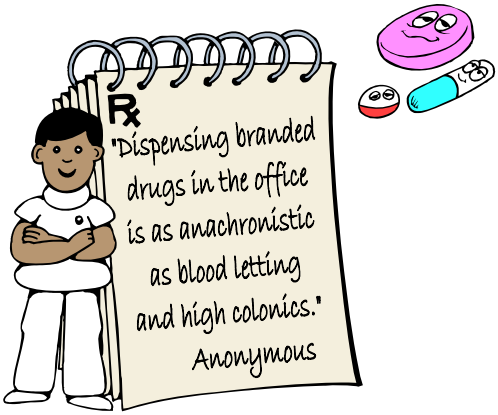
The Prudent Prescriber

Phil Mohler, M.D. • pmohler69@gmail.com
2775 Crossroads Blvd • P.O. Box 10600 • Grand Junction, CO 81502-5600



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NSAID Update: Four New Ideas from the Literature to Hone Your Skills

Pharm Reps ≠ Rational Prescribing (PR) (RP)

1) NSAIDS for Chronic Low Back Pain

The latest, most definitive word is from Enthoven et al Cochrane Database Systemic Review (2016; 2: CDO12087). This study reviewed 13 clinical trials, including 4,807 patients, average age 50 years, who were seen in general practice and outpatient settings in 28 countries.

Results:
NSAIDs were associated with greater statistical improvement in pain intensity and disability compared with placebo; however, *none of the studies demonstrated clinically important improvements of NSAIDs over placebo.*

The European Guidelines of the Management of Chronic Low Back Pain recommend using NSAIDS for up to three months. The American College of Physicians and the American Pain Society guidelines on chronic back pain recommend the shortest duration possible.

CHF?

Think:
Ace
Aldactone
B-blocker
Dig
Diuretic

Avoid these expensive "me-too" drugs:
Intermezzo
Vimovo
Livalo
Pristiq
Viibyrd
Edarbi
Daliresp

Treat patients > 60 years to 150/90

Antibiotics do NOT help acute bronchitis

ß-blockers in post-MI save lives

Pill splitters save BIG

NOW AVAILABLE ON THE GENERIC MARQUEE

Frova→frovatriptan
Voltaren gel→diclofenac Na 1% gel
Crestor→rosuvastatin
Nuvigil→armodafinil
Jalyn→dutasteride/tamsulosin
Ortho Tri-Cyclen Lo→Tri-Lo-Marzia, Tri-Lo-Sprintec, & others

The Prescriber's Letter (PL) (May 2017) offers 2 ½ pages of non-pharmacological interventions for a chronic low back pain before discussing any pharmacotherapy. Their take is that NSAIDs (their first line drugs) are more effective than acetaminophen for back pain, but that acetaminophen is a reasonable alternative for patients unable to take chronic NSAIDs. The PL lists antidepressants as second line pharmacotherapy (SNRIs) duloxetine 30mg to 60mg once daily. Avoid TCAs and SSRIs as there are no data supporting their efficacy. This guideline lumps gabapentin, skeletal muscle relaxants and opioids (including tramadol) into third line choices that should be avoided.

Chou et al concluded in a systematic review in the Annals of Internal Medicine 2017; 166:480-92 that *there is no significant clinical difference in pain control between opioids and NSAIDs for patients with chronic low back pain.*

My Take:
Φ Drugs, in general and NSAIDs in particular, are not very useful in limiting disability or managing pain in patients with chronic low back pain. Our focus should be on appropriately managing acute low back pain and identifying the 10% to 20% of patients at risk for progression to chronic back pain so that we can provide appropriate interventions earlier.

Φ Non-drug therapy that involves remaining active, weight loss, smoking cessation, exercise, acupuncture, mindfulness based stress reduction, chiropractic adjustments, yoga, massage, tai chi, and cognitive–behavioral therapy should be the heart of therapy for chronic low back pain.

2) Topical NSAIDs: What's their Role?

Topical NSAIDs are thought to be safer than oral NSAID products since they are only 5%–10% systemically absorbed. It is clear that topicals have fewer G.I. side effects, but the verdict is still out on whether they're safer from cardiovascular and renal standpoints.

Derry et al updated the Cochrane Database Syst Rev. 2016; 4:CD007400 that looked at the evidence from 39 randomized, double-blind controlled studies on the efficacy and safety of topically applied NSAIDs for chronic osteoarthritis pain in 10,631 adults. In studies lasting 6 to 12 weeks, topical diclofenac and topical ketoprofen were significantly more effective than their vehicle for reducing pain; about 60% of participants had significantly reduced pain. With topical diclofenac, the NNT for clinical success in six trials (2,343 participants) was 10. With topical ketoprofen, the NNT for clinical success in four trials (2,573 participants) was 7. The local side-effects were almost entirely mild skin reactions. Serious adverse events were infrequent and not different between topical NSAIDs and their vehicles. Few trials compared a topical NSAID to an oral NSAID.

My Take:
Φ Both direct and indirect comparisons of clinical success with oral placebo indicate that response rates with the vehicle (topical placebo) are about twice those seen with oral placebo. The hands on nature of rubbing the cream onto your knee 3 or 4 times a day apparently has some of the same mystique as the bright red B12 glowing in the syringe.

Φ Although these efficacy results were mostly derived from people with knee osteoarthritis, the literature also describes successes with using these products in patients with mild to moderate hand osteoarthritis.

Φ These products are pricey (branded diclofenac… Flector, Pennsaid, Voltaren Gel, Solaraze run $100 to $2,100 for 100mg), although generic topical diclofenac 1%, 100 grams is available for $27 (GoodRx, accessed 7/5/17)

3) Which, if any, NSAID to use in High CV risk patients? High risk patients for GI bleeding?

Two studies published in the last six months were directed toward answering these questions.

The CONCERN trial, (Lancet, vol. 389 June 17, 2017) enrolled 514 patients with arthritis and cardio thrombotic diseases (requiring 81mg of ASA per day) and acute upper G.I. bleeding. After ulcer healing, the patients were randomly assigned to receive oral celecoxib 100mg BID plus is esomeprazole 20mg per day or naproxen 500mg BID plus esomeprazole 20mg/day for 18 months. All patients resumed aspirin 81mg/day. Both patients and investigators were blinded to the treatments. The primary endpoint of the trial was re-current upper gastrointestinal bleeding within 18 months.

Results: The cumulative incidence of recurring bleeding in 18 months was 5.6% in the celecoxib group and 12.3% in the Naprosyn group. Serious cardiovascular events occurred in 4.4% of the celecoxib group and 5.5% in the naproxen group. The authors conclude, "In patients at high risk of both cardiovascular and gastrointestinal events, who require concomitant aspirin and NSAID, celecoxib plus proton pump inhibitor is the preferred treatment to reduce the risk for recurrent upper gastrointestinal bleeding."

My Take:
Φ Neither option seems very safe to me. If I had previously experienced a NSAID related G.I. bleed, I would not want to expose myself to even a 5.6% chance of bleeding again. Low-dose aspirin augments NSAID associated gastrointestinal bleeding risks. This trial does not address the risk estimate for aspirin use without a NSAID.

The PRECISION trial is a multinational, double-blind study of adults (mean age 63 years; 64% female) with rheumatoid arthritis (10%) or osteoarthritis (90%) requiring daily NSAID therapy who also had elevated cardiovascular risk. Patients were randomized to celecoxib (n=8072), naproxen (n=7969) and ibuprofen (n=8040). The primary endpoint was non-inferiority of celecoxib for the composite outcome of cardiovascular mortality, nonfatal myocardial infarction and nonfatal stroke.

Results: The mean duration of treatment was 20 months and the mean follow-up was 34 months. A resounding 69% of patients discontinued their study drug and 27% dropped out. The primary event occurred in 2.3% percent of celecoxib patients, 2.5% of naproxen patients and 2.7% of ibuprofen patients. Celecoxib was associated with significantly fewer serious gastrointestinal events than either comparator. (0.7% vs 1.4% and 1.4%)

My Take:
Φ At first glance, this study would make you want to abandon prescribing all NSAIDs except celecoxib. PRECISION's strengths are its multicenter nature, large "N" and Cleveland Clinic's Steve Nissen as its first author. The potential and real limitations of this study are its sponsorship by Pfizer (manufacturer of branded Celebrex) and its high discontinuation and dropout rates. A resounding 69% of patients discontinued their study drug and 27% dropped out. Further the patients in this study were taking mean daily doses of celecoxib 209mg, naproxen 852mg and ibuprofen 2045mg. The celecoxib dose in the study is not real world. Below see the Rocky Mountain Health Plans data

for the first six months of 2017. Sixty-one percent of Rocky patients are taking 400mg of celecoxib. PRECISION's use of a low celecoxib dose biases the CV complication rate to favor Pfizer's celecoxib.

Celebrex/celecoxib Dosage per day	Number of RMHP members January – June 2017
50 mg	1
100mg	36
200mg	258
400mg	467
600mg	1
800mg	1
Total members	764

4) NSAIDs and Aspirin in Chemoprevention of Colorectal Cancer (CRC)

A large body of research has shown that aspirin and NSAIDs inhibit colorectal carcinogenesis. The evidence collected over the last 20+ years is diverse.

The Prevention of Colorectal Sporadic Adenomatous Polyps trial (N Engl J Med. 2006; 355(9) 885.) was a randomized placebo-controlled, double-blind study of the COX-2 inhibitor celecoxib given daily in a single 400-mg dose at 107 centers in 32 countries, 1561 subjects who had had colonic adenomas removed were randomly assigned to receive celecoxib (933 subjects) or placebo (628 subjects). The primary outcome was detection of adenomas at either year 1 or year 3 by colonoscopy.

Results: The cumulative rate of **all adenomas** detected through year 3 was 33.6% in the celecoxib group and 49.3% in the placebo group (**NNT = 6**). The cumulative rate of **advanced adenomas** detected through year 3 was 5.3% in the celecoxib group and 10.4% in the placebo group (**NNT = 19**). Serious cardiovascular events occurred in 2.5% of subjects in the celecoxib group and 1.9% of those in the placebo group (**NNH = 167**).

Recently, (2016) the USPSTF has released the following guidelines regarding **aspirin** and **primary** chemoprevention of both cardiovascular and colorectal cancer.

Population	Recommendation	Grade (What's This?)
Adults aged 50 to 59 years with a ≥10% 10-year CVD risk	The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.	B

Dulai et al (BMJ 355:i6188. Dec 5, 2016) performed a network analysis of 14 randomized controlled trials of 10 different strategies for chemoprevention of colorectal cancer in a total of 12,234 adults with previous colorectal neoplasia. They compared low-dose and high-dose aspirin, non-aspirin NSAIDs, calcium, vitamin D, folic acid and combinations compared with another agent or placebo. The primary outcome was prevention of advanced neoplasia detected by colonoscopy within 3 – 5 years, and the primary safety outcome was serious adverse events including death.

Results: Among individuals with previous colorectal neoplasia, non-aspirin NSAIDs (celecoxib and sulindac) are the most effective agents for the prevention of advanced neoplasia, whereas low dose aspirin has the most favorable risk:benefit profile.

Anticipated Absolute Risk Difference over 3-5 years per1000 Treated Individuals

Risk Group	Advanced Neoplasia	Serious Adverse Effects
Non-aspirin NSAIDs		
Low Risk	-47 (NNT=21)	+34 (NNH=29)
High Risk	-96 (NNT=10)	+34 (NNH=29)
Low Dose Aspirin		
Low Risk Risk	-20 (NNT=50)	-35 (NNT=29)
High Risk	-42 (NNT=24)	-35 (NNT=29)

My Take:

Φ A number needed to treat (NNT) of 6 or10 for anything in medicine is a thing of wonder!

Φ The authors argue, and I would agree, that although low-dose aspirin was ranked second in preventing recurrent advanced adenomas, it has the most favorable safety profile and the excess benefit over risk might be favorable for all patients with previous colonic neoplasia.

Addendum (July 12, 2017)

Today I was able to look at the raw data of the Dulai study. One of the issues that concerned me with this study was the failure of the authors to carefully define "colonic neoplasia."

When looking at only the frank colon cancers prevented, the number needed to treat (NNT) in this study to prevent one recurrent colon cancer with an NSAID over 3-5 years was >13,000. Certainly, a lot can go wrong for the 12,999 patients who do not reap a benefit. The NNT to prevent one recurrent colon cancer with low-dose aspirin was ~500. When something in medicine appears to be, "too good to be true," it often is.

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