Pharmacotherapy Update in Rheumatoid Arthritis and Osteoarthritis

Tuesday, December 6, 2011
9:00 AM – 11:00 AM

Disclosures

The program chair and presenters for this continuing pharmacy education activity report no relevant financial relationships except:

Joseph Saseen
Consultant: Daiichi-Sankyo

Osteoarthritis: The Good, The Bad, and The Ugly

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Division Head of Adult Medicine

Learning Objectives

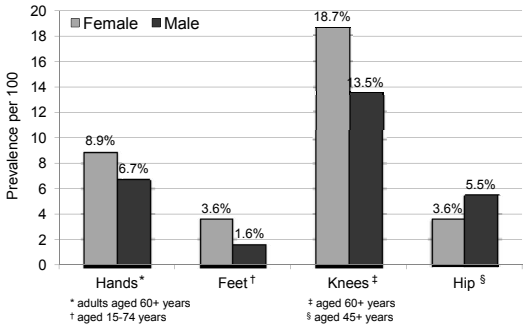
- Describe the effectiveness of available treatment options for management of osteoarthritis (OA).
- List at least two long-term toxicities associated with chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) and identify management strategies.

Osteoarthritis (OA) statistics

- Most common form of arthritis
- ~27 million Americans
- 13.9% of adults ≥ 25 years
  - 33.6% of those ≥ 60 years
- Prevalence underestimated
- More common in women
- Increases with age, levels off at ~80 years
- 7.1 million office visits

CDC Osteoarthritis. http://www.cdc.gov/arthritis/basics/osteoarthritis.htm#5

Prevalence of symptomatic OA



CDC Osteoarthritis. http://www.cdc.gov/arthritis/basics/osteoarthritis.htm#5

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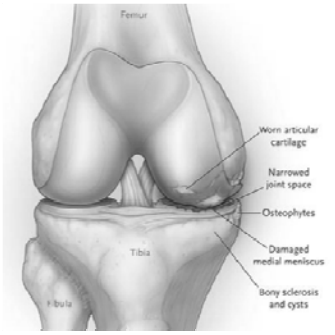
Pathophysiology of OA



Used with permission. Felson DT. New Engl J Med. 2006;354:841-848.
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Clinical presentation

- Pain
  - Usage related
  - Worse at end of day, relieved by rest
  - Mild morning pain/stiffness (<30 min)
  - Episodic or variable severity; slow to change
- Joint instability and misalignment
- Crepitus and restricted movement
- Bony enlargements
- Absent or moderate effusion
- Lack of inflammation

Zhang W. Ann Rheum Dis 2010;69:483–489.

The Good

Available guidelines

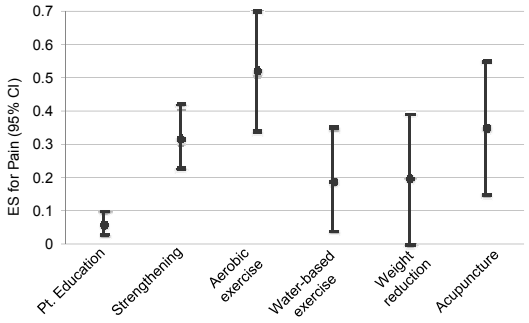
- American College of Rheumatology (ACR), 2000
- European League Against Rheumatism, (2003 knee, 2005 hip, 2009 hand)
- National Institute of Health and Clinical Excellence (NICE), 2008
- American Academy of Orthopaedic Surgeons (AAOS), 2008
- Agency for Healthcare Research and Quality (ARRQ), 2009
- Osteoarthritis Research Society International (OARSI), 2010

Nonpharmacological treatments

- Patient education
- Exercise
  - Strengthening
  - Aerobic (low impact)
  - Water-based
- Weight reduction
- Transcutaneous electrical nerve stimulation
- Assistive devices
- Acupuncture

Zhang W. OARSI Guidelines. Osteoarthritis Cartilage. 2010;18(4):476-499.

Effect Sizes (ES) for OA knee pain with nonpharmacological therapies*



* ES for both hip and knee

Zhang W. OARSI Guidelines. Osteoarthritis Cartilage. 2010;18(4):476-499.

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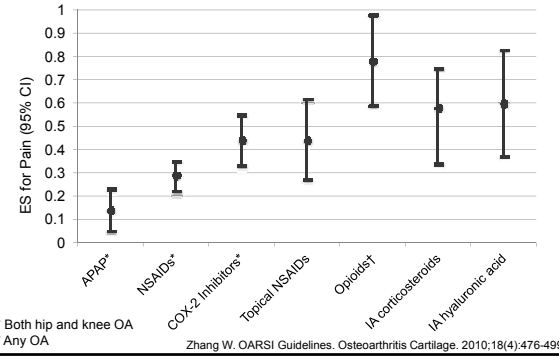
Pharmacological treatments

- Acetaminophen
- NSAIDs
  - Oral +/- gastroprotective agent
  - Topical
- Opioids
- Topical capsaicin
- Intra-articular (IA) corticosteroids
- IA hyaluronic acid

Effect Sizes (ES) for OA knee pain with pharmacological therapies*



* Both hip and knee OA
† Any OA

Zhang W. OARSI Guidelines. Osteoarthritis Cartilage. 2010;18(4):476-499.

Topical NSAIDs

Topical NSAIDs

- Act locally at application site
- Minimal systemic absorption
- Mild to moderate pain
- Superficial joints (e.g., knees and hands)
- Few joints affected
- Used *before* oral NSAIDs in EULAR and NICE guidelines
- Diclofenac 1% gel and 1.5% in 45.5% dimethylsulfoxide (DMSO) solution

Altman RD, et al. Drugs. 2011;71(10): 1259-1279.

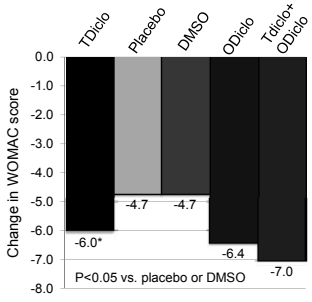
Topical vs. oral NSAID studies

Study	Methods	Results	Adverse Effects
Zacher et al., 2001	321 hand OA pts received diclofenac gel 4 times daily vs. PO ibuprofen 400 mg 3 times daily	Equally effective for pain at rest and on movement, stiffness, quality of life	Topical diclofenac fewer D/C due to treatment-related AE (1.25% vs. 8.3%) and GI AE (0.6% vs. 5.1%).
Tugwell et al., 2004	622 knee OA pts received diclofenac solution 3 times daily or PO diclofenac 50 mg 3 times daily	Improvement of 39-44% in WOMAC pain, function, stiffness and global assessment vs. 45-49% with PO	No serious AE with topical diclofenac. GI AE more frequent with PO (48% vs. 35%) Application site AE 27% vs. 1%.

Adapted from: Altman RD, et al. Drugs. 2011:71(10):1259-1279.

Efficacy and safety of topical diclofenac containing DMSO compared to placebo, DMSO vehicle and PO diclofenac for knee OA

- Randomized, placebo controlled trial
- 755 patients with knee OA
- Treatments:
  - Topical diclofenac 1.5% (TDiclo)
  - Placebo
  - DMSO
  - Oral Diclofenac 50 mg 3 times daily (ODiclo)
  - Topical + oral diclofenac (TDiclo+ODiclo)



Simon LS, et al. Pain. 2009:143(3):238-245.

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Topical diclofenac dosing and cost

- Dosing: 4 times daily
- 1% gel (Voltaren® gel)
  - Lower extremities: Apply 4 g to affected area
  - Upper extremities: Apply 2 g to affected area
  - Cost: $40.99 (1, 100 g tubes)
- 1.5% solution (Pennsaid®)
  - Apply 40 drops on each painful knee
  - Cost: $180.00 (150 mL)

Costs from: www.drugstore.com

The Bad

Acetaminophen (APAP) safety concerns

- APAP-induced liver injury due to toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI)
- Leading cause of acute liver failure 1998-2003
  - 48% of APAP-related acute liver failure cases associated with accidental overdose
- From 1990-1998 estimated:
  - 56,000 ER visits
  - 26,000 hospitalizations
  - 458 deaths

Fed Register. 2011;76(10):2691-2697.
FDA Safety Announcement: http://www.fda.gov/Drugs/DrugSafety/ucm239821.htm

TIME **Health**

FDA Advises Lower Dosage for Popular Painkiller

By ALICE PARK Wednesday, July 01, 2009

- June 30, 2009 FDA advisory panel recommended lowering maximum OTC APAP dose
- January 11, 2011 FDA limited Rx APAP dosing
  - Combination products ≥ 325 mg APAP
  - Maximum daily dose 4 g/day
  - Do not use ≥ 3 days for fever or 10 days for pain unless prescribed
  - Boxed Warning highlighting potential for severe liver injury and a warning highlighting potential for allergic reactions

http://www.time.com/time/health/article/0,8599,1908042,00.html
http://www.fda.gov/Drugs/DrugSafety/ucm239821.htm

Glucosamine and Chondroitin

Overview: glucosamine/chondroitin

- Glucosamine
  - Hexosamine sugar
  - Precursor in synthesis of connective tissue macromolecules
  - Sulfate or hydrochloride (HCl) salt
  - May stimulate chondrocytes
- Chondroitin
  - Glycosaminoglycan (GAG) found in articular cartilage
  - Hydrophilic properties
  - Allows articular cartilage to absorb water
  - Convey and absorb compressive forces

Miller KL, et al. Rheum Dis Clin N Am . 2011:37(1);103–118.

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Expenditures on glucosamine supplements

- Global sales $2 billion in 2008
- US sales $872 million
- Increased 62% since 2003
- Forecasted growth to 2013 of $2.3 billion
- US sales lag behind global sales

Heller L. www.nutraingredients-usa.com/Consumer-Trends/US-glucosaminegrows-slow-lags-global-sales.

Studies of glucosamine and chondroitin

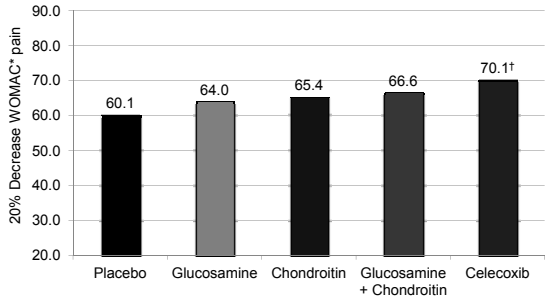
- Conflicting results
- Trials with positive results hampered
  - Poor study design
  - Small sample size
- Larger, methodologically sound trials often found no effect
- Publication bias?

Glucosamine, Chondroitin Sulfate, and the Two in Combination for Painful Knee OA (GAIT)

- Multicenter, double-blind, placebo- and celecoxib-controlled trial
- 1583 patients randomized to:
  - 1500 mg glucosamine daily
  - 1200 mg chondroitin daily
  - Combination
  - 200 mg celecoxib daily
  - Placebo
- 1 outcome: 20% ↓ pain baseline to week 24

Clegg DO, et al. N Engl J Med. 2006;354(8):795-808.

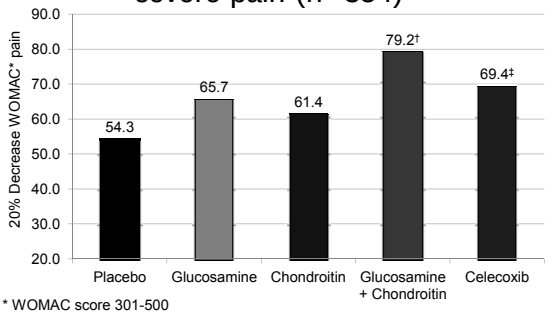
GAIT results: all patients



* Western Ontario and McMaster Universities Osteoarthritis Index
† p=0.008, Number needed to treat (NNT) = 10

Clegg DO, et al. N Engl J Med. 2006;354(8):795-808.

GAIT results: patients with moderate-to-severe pain (n=354)*



* WOMAC score 301-500
† p=0.002, NNT= 4
‡ p=0.06

Clegg DO, et al. N Engl J Med. 2006;354(8):795-808.

Effects of glucosamine, chondroitin, or placebo in patients with OA of hip or knee

- Network meta-analysis of large RCTs
- Trials with ≥ 200 patients with OA of hip or knee
- Received glucosamine, chondroitin, or both
- 10 trials with 3,803 patients included
- Primary outcome: pain intensity on 10 cm visual analogue scale (VAS)
  - Clinically significant difference -0.9 cm
- Secondary outcomes: joint space narrowing

Wandel S, et al. BMJ. 2010;341:c4675. doi:10.1136/bmj.c4675.

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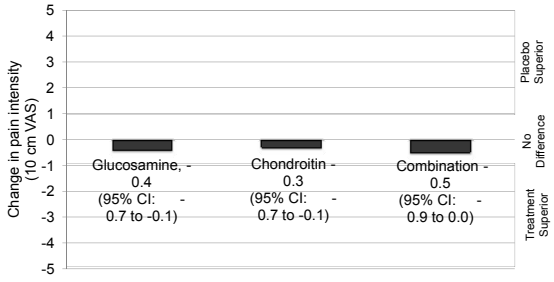
Change in pain intensity compared to placebo



Wandel S, et al. BMJ. 2010;341:c4675. doi:10.1136/bmj.c4675.

Additional results

- No difference in joint space narrowing
  - Glucosamine -0.2 mm (-0.3 to 0.0 mm)
  - Chondroitin -0.1 mm (-0.3 mm to 0.1 mm)
  - Combination 0.0 mm (-0.2 to 0.2 mm)
- Glucosamine/chondroitin safe
  - Adverse effects similar to placebo
  - No differences in drop outs

Wandel S, et al. BMJ. 2010;341:c4675. doi:10.1136/bmj.c4675.

Glucosamine and/or Chondroitin Bottom Line

- Not recommended
- Data lacking demonstrating benefit
- Costly
- Products are safe
- If patients choose to start:
  - Use glucosamine sulfate rather than HCl
  - Choose reputable manufacturer
  - Discontinue after 3 months if no benefit

The Ugly

NSAID adverse effects and safety considerations

- Worsening hypertension
- Heart failure exacerbations
- Avoid in cirrhosis
- Renal dysfunction
- Concomitant ACE inhibitor or ARB
- Concomitant anticoagulant or ASA use
- *Upper gastrointestinal (GI) events*
- *Cardiovascular disease (CVD)*

Risser A. et al. *Am Fam Physician.* 2009;80(12):1371-1378.

Medication Guide for NSAIDs

- "May increase the chance of a heart attack or stroke that can lead to death. This chance increases:"
  - with longer use of NSAID medicines
  - in people who have heart disease
- "Should never be used right before or after a heart surgery called a 'coronary artery bypass graft (CABG).'"
- "Can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:"
  - can happen without warning symptoms
  - may cause death

www.fda.gov/downloads/Drugs/DrugSafety/ucm085919.pdf

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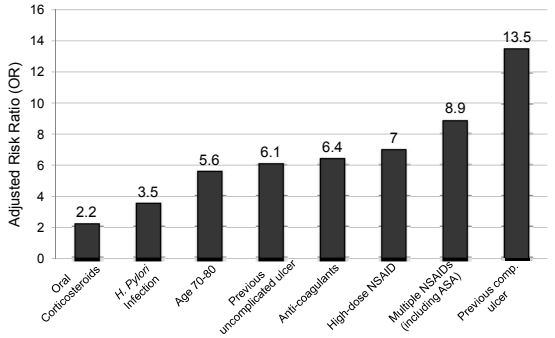
Upper GI events (UGIE) and NSAIDs

- 1:20 NSAID users develop UGIE (symptomatic or complicated ulcers)
  - 1:7 for elderly
- 30% may result in hospitalizations and/or death
- Among patients with arthritis:
  - 107,000 hospitalizations
  - 16,500 deaths

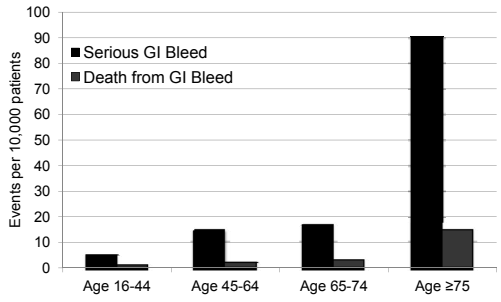
Bhatt DL, et al. J Am Coll Cardiol. 2008;52(18):1507-1517.

Risk factors for upper GI bleeding associated with NSAIDs



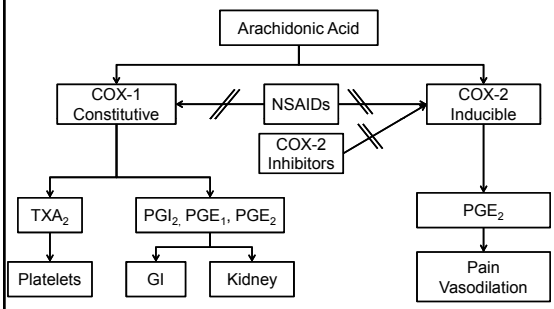
Adapted from: Lanas A. Rheumatology (Oxford). 2010;49(supp 2):ii3-ii10.

Age and NSAID induced GI toxicity



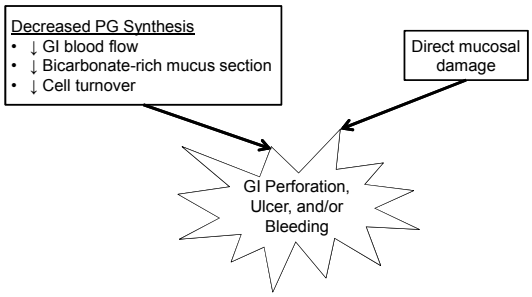
AHRQ. J Pain Palliat Care Pharmacother. 2009;23(4):433-457

NSAIDs and Cyclo-oxygenase (COX) inhibition



Naesh O. et al. N Z Med J. 2006;119(1242):U2170.

Mechanism of NSAID-induced GI mucosal damage



Bhatt DL, et al. J Am Coll Cardiol. 2008;52(18):1502-1517.

ACCF/ACG/AHA 2008 Expert Consensus on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use

- PPIs preferred for therapy and prophylaxis of NSAID- and ASA-associated GI injury
- Test for and eradicate H. pylori in patients with history of ulcer before starting chronic antiplatelet therapy

Bhatt DL, et al. J Am Coll Cardiol. 2008;52(18):1502-1517

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NSAIDs and risk of CVD

- Increase BP and edema
- COX-2 inhibition ↓ prostacyclin (PGI_2)
  - ↓ smooth muscle cell relaxation and vasodilation
  - ↓ inhibition of platelet aggregation
- Meta-analyses indicate:
  - COX-2 selective NSAIDs ↑ risk of CV events
  - Non selective NSAIDs also ↑ risk
  - Exception naproxen (?)

Antman EM, et al. Circulation. 2007;115(120):1634-1642.

NSAIDs and CVD versus placebo

Type of Study	Outcome	RR	95% CI
Naproxen			
Meta-analysis of RCTs*	Vascular events	0.92	0.67-1.26
Meta-analysis of OSs†	CV events, mostly MI	0.97	0.87-1.07
Ibuprofen			
Meta-analysis of RCTs	Vascular events	1.51	0.96-2.37
Meta-analysis of OSs	CV events, mostly MI	1.07	0.97-1.18
Registry	Recurrent MI	1.25	1.07-1.46
Registry	Mortality	1.50	1.36-1.67
Diclofenac			
Meta-analysis of RCTs	Vascular events	1.63	1.12-2.37
Meta-analysis of OSs	CV events, mostly MI	1.40	1.16-1.70
Registry	Recurrent MI	1.54	1.23-1.93
Registry	Mortality	2.40	2.09-2.80

* Randomized controlled trials
† Observational studies

Adapted from: Antman EM, et al. Circulation. 2007;115(120):1634-1642.

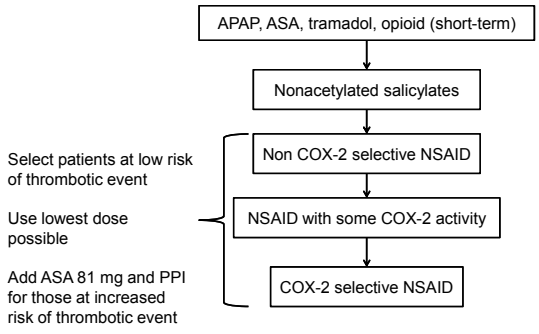
NSAIDs and CVD versus selective COX-2 inhibitor

Type of Study	Outcome	RR	95% CI
Naproxen			
Meta-analysis of RCTs	Vascular events	0.64	0.49-0.83
Any non-naproxen NSAID*			
Meta-analysis of RCT	Vascular events	1.14	0.89-1.45

* Primarily diclofenac or ibuprofen

Adapted from: Antman EM, et al. Circulation. 2007;115(120):1634-1642.

2007 AHA Stepped Care Approach with Known CV Risk factors for IHD



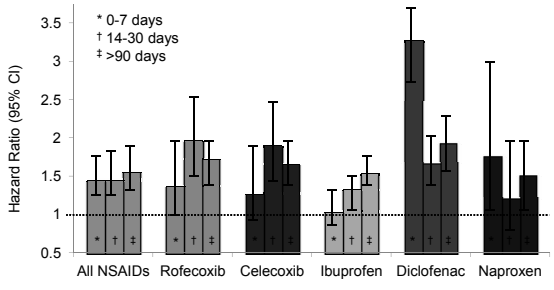
Adapted from: Antman EM, et al. Circulation. 2007;115(120):1634-1642.

Duration of treatment with NSAIDs and impact on risk of death and recurrent myocardial infarction (MI)

- Population-based Danish registry study
- 83,677 patients >30 years admitted for first MI between 1997-2006
- NSAID use evaluated at various time frames from pharmacy database
- Primary outcome: risk of death and recurrent MI according to:
  - NSAID
  - Time frame

Schjering Olsen AM, et al. Circulation. 2011;123(10):2226-2235.

Risk of death/RE-MI associated with NSAIDs



Schjering Olsen AM, et al. Circulation. 2011;123(10):2226-2235.

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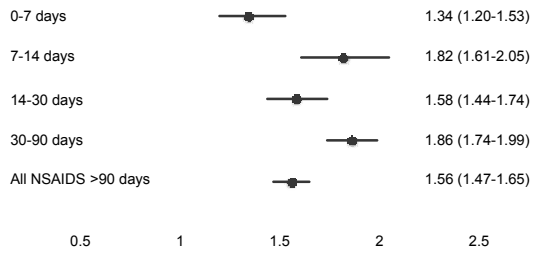
Risk of death associated with all NSAIDs



Adapted from: Schjering Olsen AM, et al. Circulation. 2011;123(10):2226-2235.

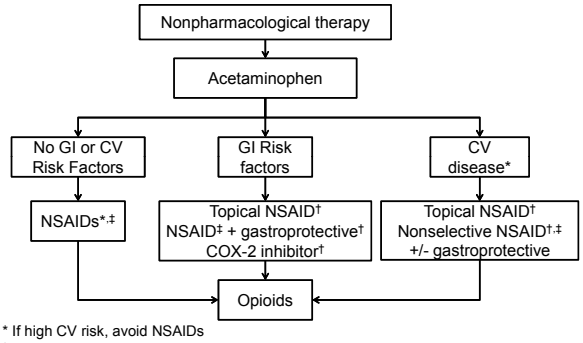
Recommendations for prevention of NSIAD-related ulcer complications

	Gastrointestinal Risk*		
	Low	**Moderate**	**High**
Low CV risk	NSAID alone (least ulcerogenic)	NSAID + PPI/misoprostol	Alternative therapy if possible or COX-2 inhibitor + PPI/misoprostol
High CV risk (low-dose ASA required	Naproxen + PPI/misoprostol	Naproxen + PPI/misoprostol	Avoid NSAIDs or COX-2 inhibitors. Use alternative therapy

* Stratification by low risk (no risk factors), moderate risk (1-2 risk factors include age (>65), high dose NSAID, previous history of uncomplicated ulcer, concurrent ASA, corticosteroids, or anticoagulants, or high risk (previous complicated ulcer or >2 risk factors).

Lanza FL. Am J Gastroenterol. 2009;104(3):728-738.

Summary of treatment of OA



* If high CV risk, avoid NSAIDs
† Add additional therapies (e.g., capsacian, intraarticular injections) as appropriate
‡ Naproxen preferred initial NSAID

Conclusions

- Effective drug treatments for OA
- Always use with nonpharmacological modalities
- Data support use of topical NSAIDs
- Glucosamine/chondroitin appear ineffective
- Carefully weigh GI and CV risks/benefits before using oral NSAIDs

Questions?

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