Osteoarthritis management

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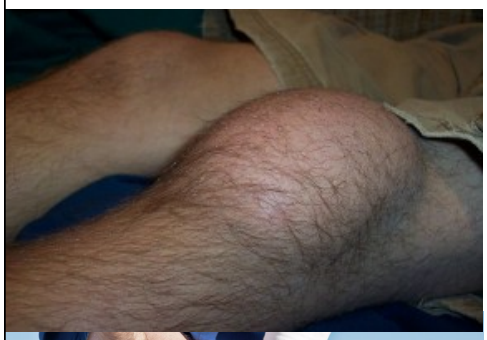
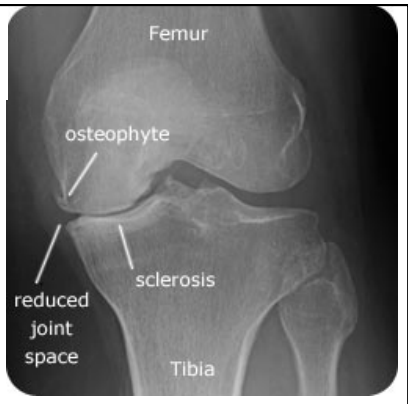
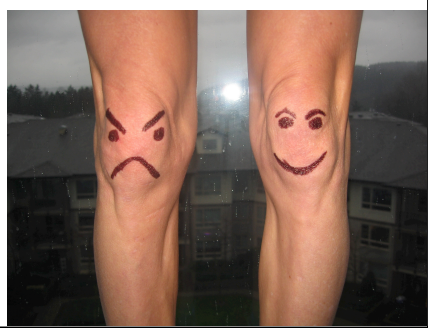
Objectives

1. Osteoarthritis
   - A. Non-Pharmaceutical Management
     - I. Exercise, etc
   - B. Pharmaceutical Management
     - i. Acetaminophen (Placebo or a little more)
     - ii. Topical NSAIDs
     - iii. Oral NSAIDs (including Cox-2's)
     - iv. Opioids
     - v. Glucosamine & Chondroitin
     - vi. Intra-articular injections (steroid or hylanuronan product)
2. Guidelines
3. NSAID risks (including Cox-2 anti-inflammatories)
   - A. GI risks
   - B. Cardiovascular risks

Diagnosis







OA Starting Point

- Mrs Phyte is a 64 year old complaining of prolonged bilateral knee pain (4 months).
- Her knees ache much of the day & get worse with activity. She has minimal morning stiffness or swelling.
- Exam reveals little swelling, crepitus, tenderness along the joint and some pain with movement. Ligaments & special test ok.
- Her X-ray reveals moderate OA in both knees.

Effect size Interpretations

- By convention, an effect size
- < 0.2 is usually considered as trivial;
- >0.2 - 0.5 as small;
- >0.5 - 0.8 as moderate;
- > 0.8 - 1.2 as important and
- >1.2 as very important

Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd edn. Hillsdale, NJ: Erlbaum 1988.

Activity

- >10 sys revs, focus on last 5 yrs & Cochrane
  - Largest 60 RCTs with 8218 patients[2]
  - Overall quality moderate

Knee Osteoarthritis

Outcome[2]	**Short-Term**		**Long term (2-6 months)**	
	SMD	Scores (0-100)	SMD	Scores
Pain	0.49 (0.39-0.59)	44 vs 36 (Ex)	0.24 (0.14-0.35)	6 pts better
Function	0.52 (0.39-0.64)	38 vs 28 (Ex)	0.15 (0.04-0.26)	3 pts better
Quality of Life	0.28 (0.15-0.40)	43 vs 47		

Hip similar: estimated NNT 6. Maybe slightly better long-term?[3]

1) Cochrane 2008; 4: CD004376. 2) with update 2015 Jan 9;1:CD004376. 3) Cochrane 2014; 4: CD007912. 4) BMJ 2013;347:f5555 doi: 10.1136/bmj.f5555. 5) Arthritis Rheumatol. 2014;66(3):622-36. 6) BMC Musculoskeletal Disorders2011,12:123. 7) Cochrane 2007; 4: CD005523. 8) Arch Phys Med Rehabil 2012;93:1269-85. 9) Clin Rehabil. 2013;27:1059-71. 10) J Rheumatol 2009;36:1109–17

Activity

- Types of exercise: Generally no diff
  - Example effect on Pain: Quad strengthening (SMD 0.29); Lower limb strengthening (0.53); strength & aerobic (0.40); walking (0.48); Other (0.32).[1]
  - Subtle diff not consistent[5,9] (e.g. Quad > lower limb[5])
- Aquatic exercise: 0.26- 0.68 pain,[7,4] 0.34 function[4]
  - 10 RCTs, aquatic vs Land: No diff in any outcome[6]
- Likely Supervised & more often better (e.g 3/wk)[5]
- No more research required (had enough by 2002)[4]

1) Cochrane 2008; 4: CD004376. 2) with update 2015 Jan 9;1:CD004376. 3) Cochrane 2014; 4: CD007912. 4) BMJ 2013;347:f5555 doi: 10.1136/bmj.f5555. 5) Arthritis Rheumatol. 2014;66(3):622-36. 6) BMC Musculoskeletal Disorders2011,12:123. 7) Cochrane 2007; 4: CD005523. 8) Arch Phys Med Rehabil 2012;93:1269-85. 9) Clin Rehabil. 2013;27:1059-71. 10) J Rheumatol 2009;36:1109–17

Acetaminophen: First do no harm

- Acetaminophen (≤10 RCTs, 1712 pts)[1,2]
  - Pain, Effect Size= 0.2 (0.02-0.41) or less
  - Pain NNT=16 (any pain relief)[2]
  - But mean pain score diff=3 (from 54/100)[4]
  - Toxicity overall & withdrawal not stat sign
- Effect Size small and NNT poor for a pain
  - In most comparative studies, acetaminophen the least effective[3-5] & may not be meaningful[4]
- BUT, harm similar to placebo.

1. Ann Rheum Dis. 2004;63(8):901-7. 2. Cochrane 2006 (1):CD004257. 3. Ann Intern Med. 2015;162:46-54. 4) Euro J Pain 2007; 11:125–138. 5. Osteoarthritis Cartilage. 2010;18(4):476-99.

Oral NSAIDs: The Balancing Act

- Traditional NSAIDs vs Cox-2 selective
  - No efficacy difference Cox-2 & traditional NSAIDs[1]
- Meta-analysis[2]: 23 RCTs, 10,845 pts
  - VA improved 10.1mm or 15.6%. SMD 0.32.
  - Exclude run-in bias trials (10 left), SMD 0.23.
- Sys Rev[5]: 25 RCTs, 9964 pts
  - 10.2 better out of 100 (from baseline of 64)
- Network Meta-analysis[6]: 0.33 (celecoxib)- 0.52 (diclofenac)

1. NICE OA Guideline (http://www.rcplondon.ac.uk/pubs/contents/d87b4537-b333-4b8a-a2d8-5e96b7f4b65a.pdf) 2. BMJ 2004; 329 (7478):1317. 3 Cochrane 2006 (1):CD004257. 4. Ann Rheum Dis. 2004;63(8):901-7. 5. Euro J Pain 2007; 11: 125-38. 6. Ann Intern Med. 2015;162:46-54.

Oral NSAIDs: The Balancing Act

- NSAID vs Acetaminophen[3]
  - Pain -0.31 (-0.4, -0.2) standard mean diff
    - for comparison, Effect size = 0.2 (0.1-0.3) from a similar study[4]
  - Global improvement (by patient) = 57% NSAID vs 39% Acet, NNT 6
  - Toxicity: overall and withdrawal, no diff
  - GI adverse
    - Trad NSAID, 19% vs 13%, NNH=12 (Cox-2 no diff from acetaminophen)
    - Withdrawal due to GI AE, 8% vs 4%, NNT 25.

1. NICE OA Guideline (http://www.rcplondon.ac.uk/pubs/contents/d87b4537-b333-4b8a-a2d8-5e96b7f4b65a.pdf) 2. BMJ 2004; 329 (7478):1317. 3 Cochrane 2006 (1):CD004257. 4. Ann Rheum Dis. 2004;63(8):901-7.

Oral NSAIDs: The Balancing Act

- NSAID preferred by pts (RR 2.34) but more GI AE[4] AND actual numbers preferring low,…
- E.g. 12 wk randomized, n-of-1, (mean age 65, 63% ♀), Celecoxib vs Acetaminophen[5]
  - 80% no preference in 2 Tx;
  - 17% picked Celebrex (5% sure it was better)
  - 3% picked Acetaminophen
- Harms: see end of presentation

1. NICE OA Guideline (http://www.rcplondon.ac.uk/pubs/contents/d87b4537-b333-4b8a-a2d8-5e96b7f4b65a.pdf) 2. BMJ 2004; 329 (7478):1317. 3 Cochrane 2006 (1):CD004257. 4. Ann Rheum Dis. 2004;63(8):901-7. 5 Rheumatology 2007;46:135-140

Topical NSAIDs: benefit over risk

- ≥5 Sys Rev, Most recent from Cochrane
  - 34 RCTs (7688 pts). RCT quality moderate-good

Duration	% better on Topical NSAID	% better on Placebo	RR (95% CI)	NNT
2-3 weeks	37%	19%	1.9 (1.6-2.4)	5-6
4-6 weeks	42%	24%	1.7 (1.4-2.1)	6
8-12 weeks	60%	50%	1.2 (1.1-1.3)	10

- Adverse events
  - No diff between Topical NSAID & placebo in systemic or GI
  - Local AE: Topical 12.6%vs placebo 7.8%, NNH 21
  - Withdrawal due to AE: Topical 5.4% vs Placebo 3.8%, NNH 63
  - Withdrawal due to lack of effect: 4.7% vs 8.5%, NNT 27

1. BMJ 2004;329(7461):324. 2. J Rheumatol 2006;33:1841–4. 3. www.Bandolier.com March 05. 4. NICE OA Guideline (http://www.rcplondon.ac.uk/pubs/contents/d87b4537-b333-4b8a-a2d8-5e96b7f4b65a.pdf) 5. J Rheumatolo 2004;31(10): 2002-12. 6. Tools for Practice #40, Jan 24, 2011. Cochrane 2012; 9: CD007400.

Topical NSAIDs: benefit over risk

- Others[1-3,6] (≤14 RCTs, ≤1983pts)
  - At 2 wks ES=0.40 & at 4-12 wks, ES = 0.28
  - NNT for clinical effect overall= 4.6 (3.8 – 5.9)
- Compared to oral NSAID
  - Equal therapeutic level in joint but 15% level in circulation[4]
  - Pain: Topical=Oral , RR 1.1 (0.9-1.3) to 1.02 (0.94-1.11)[3,4,6,7]
  - Adverse Events primarily topical (vs oral which are GI)[5,7]
    - Local AE: 21.5% (topical) - 5.8% (oral), NNH 7
    - GI AE: 16.5% (topical) - 26.1% (oral), NNT 11
    - Drop-out: 12% (topical) – 14.7% (oral), NNH 37 (but not ss)

1. BMJ 2004;329(7461):324. 2. J Rheumatol 2006;33:1841–4. 3. www.Bandolier.com March 05. 4. NICE OA Guideline (http://www.rcplondon.ac.uk/pubs/contents/d87b4537-b333-4b8a-a2d8-5e96b7f4b65a.pdf) 5. J Rheumatolo 2004;31(10): 2002-12. 6. Tools for Practice #40, Jan 24, 2011. 7. Cochrane 2012; 9: CD007400.

Glucosamine: Harm=0 (? Benefit)

- >20 sys rev glucosamine in OA (mostly knee, mostly vs placebo). Focus 6 last 5 yrs + Cochrane
  - 7 Sys rev with 2-25 RCTs (414-4963 pts). Most use SMD
- Pain: Widely variable results, SMD -0.16 (ns) to -0.51 (sign)
  - Some subgroups higher:[1-4,7] Rotta brand SMD -1.11 (sign).[7]
  - In larger studies:[1] Change in pain scale 0.4 / 10 (Sign).
    - Clinically meaningful change=0.9
- Function: Results vary with trial duration and assessment tool, SMD -0.08 (NS) to -0.54 (sign).[2,7]

1) BMJ. 2010; 341:c4675. 2) Int J Clin Pract. 2013; 67:585-94. 3) Arthritis Care Res (Hoboken). 2014 Jun 6. 4) Osteoarthritis Cartilage. 2010; 18(4):476-99. 5) Rheumatol Int. 2010; 30(3):357-63. 6) Am J Sports Med. 2014 May 27. [Epub ahead of print] 7) Cochrane 2005; (2):CD002946.

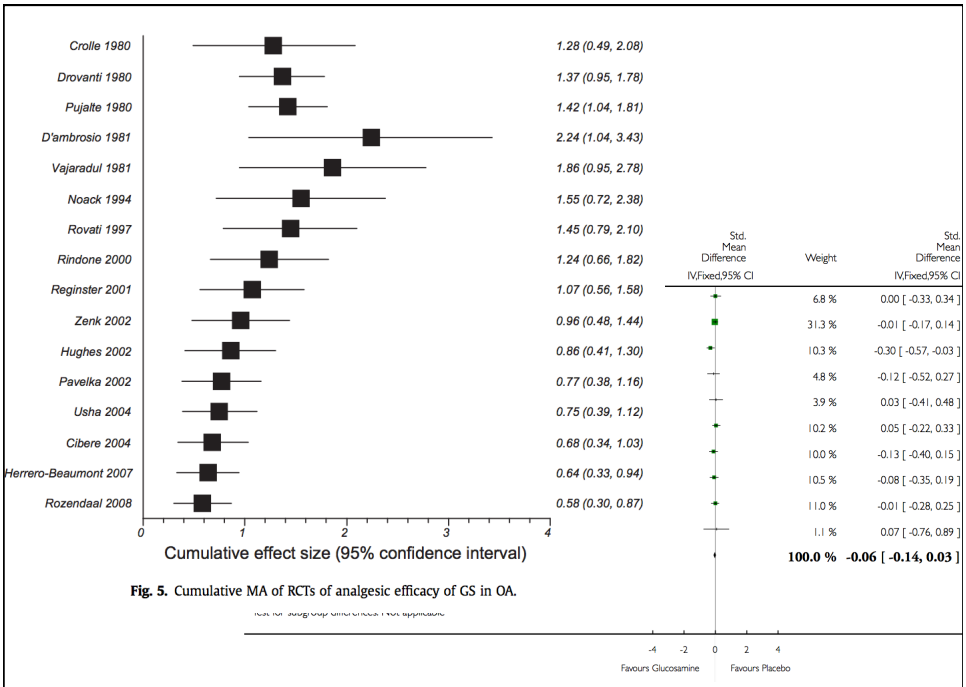


Fig. 5. Cumulative MA of RCTs of analgesic efficacy of GS in OA.

Osteoarthritis Cartilage. 2010; 18(4):476-99. Cochrane 2005; (2):CD002946.

Glucosamine: Harm=0 (? Benefit)

- Joint Space Narrowing:[1,4-7] Results vary
  - One reached "clinical significance" (>0.5mm)[5] at 0.51mm less narrowing vs Placebo[6] but it's a surrogate marker.
- Adverse effects: None.[7]
- Issues with evidence: Industry funding significantly inflated effects,[1,3,4] negative studies likely unpublished,[3,4] inconsistent results,[2,3,4] higher quality studies or newer or longer show little/no effect,[2-4,7] only certain brands/compounds are effective.[3,4,7]
- Approximate yearly cost is $60 at 500mg TID.

1) BMJ. 2010; 341:c4675. 2) Int J Clin Pract. 2013; 67:585-94. 3) Arthritis Care Res (Hoboken). 2014 Jun 6. 4) Osteoarthritis Cartilage. 2010; 18(4):476-99. 5) Rheumatol Int. 2010; 30(3):357-63. 6) Am J Sports Med. 2014 May 27. [Epub ahead of print] 7) Cochrane 2005; (2):CD002946.

Chondroitin: More of the Same

- Sys Rev[2]: 43 RCTs, 9110 pts (9 low risk of bias)
  - 20% improvement on WOMAC: NNT 17,
  - Pain NNT 4-5 (but my calculation is 10-12)
- Heavily dependent on quality markers

PAIN

Sensitivity	Variable 1	Outcome 1	Variable 2	Outcome 2
RCT Size	n<100	**0.59 (0.31, 0.88)**	n≥100	**0.14 (-0.17, 0.45)**
Drug Co	Yes	**0.52 (0.24, 0.80)**	No	**0.0 (-0.16, 0.15)**
Study year	1990-99	**0.89 (0.66, 1.13)**	≥2010	**0.06 (-0.13, 0.25)**
Allocation Concealment	Unclear	**0.67 (0.40, 0.93)**	Yes	**0.06 (-0.24, 0.37)**

Ann Intern Med. 2007;146:580-90. Cochrane 2015; 1: CD005614.

Chondroitin: More of the Same

- Sys Rev[1]: 22 RCTs, 4056 pt; median age 61, 62% ♀
- Again, quality (& trial size) matter
  - 3 high quality trials (1553), ES= −0.03 (−0.13 to 0.07)
  - 17 low quality trials (2293), ES= - 0.88 (−1.13 to −0.64)
- Note: lower quality also ++ heterogeneous.

- Bottom-Line: Impressive but all driven by studies at high risk of bias. The best studies indicate no effect.

Ann Intern Med. 2007;146:580-90. Cochrane 2015; 1: CD005614.

Viscosupplementation:

- ≥7 sys revs. Best = Rutjes 2012:[1] 89 RCTs
  - 12,667 patients (mean age 63), ~16 weeks.
- Pain reduced (at 3 months) SMD -0.37 (-0.46, -0.28)
  - MCID benefit (-0.37 = 9mm on 100mm pain scale).
- BUT many issues,
  - High quality RCTs (>100 pts, proper randomization, blind outcome assessor): no meaningful effect on pain/function
  - Publication bias: Negative trials less likely to be published. 5/6 unpublished studies showed no effect.
- Adverse Events increased. Example, Dropouts due to adverse events, RR1.33 (1.01, 1.74)

1) Ann Intern Med. 2012; 157:180-91. 2) CMAJ 2005;172:1039-43. 3) JAMA 2003; 290:3115-21 4) Cochrane 2006 CD005321. 5) J Fam Pract 2006; 55:669-75. 6) J Fam Pract 2005; 54: 758-67. 7) J Bone Joint Surg 2004; 86:538-

Viscosupplementation:

- 6 others[2-7] (7-76 RCTs) found
  - Similar results[2,3]
  - No difference in patients reporting global improvement[4]
  - Placebo injections similar to viscosupplementation[5]
  - MCID not discussed or rarely attained[2-7]
  - Higher quality studies showed smaller benefit[2,6]
  - Pts >65 yrs with more advanced OA < likely to benefit.[7]
- Hylan vs hyaluronic acid: no difference (hylan may > AE).[9]
- Sys rev: examined timing of effect[8]
  - Peak at 8 wks: SMD 0.34 (0.02-0.67), in high quality.
- Viscosupplementation (1-3 injections) ~$285-500.

1) Ann Intern Med. 2012; 157:180-91. 2) CMAJ 2005;172:1039-43. 3) JAMA 2003; 290:3115-21 4) Cochrane 2006; 2: CD005321. 5) J Fam Pract 2006; 55:669-75. 6) J Fam Pract 2005; 54: 758-67. 7) J Bone Joint Surg 2004; 86:538-45. 8) Osteoarthritis and Cartilage 2011; 19: 611-9 9) Arthritis & Rheumatism 2007; 57(8): 1410-8.

Steroid Injection (knee) for OA

- 6 Systematic Reviews: 5-13 RCTs with 207-648 patients.
  - Corticosteroid (triamcinolone 20-40mg mostly, then methylprednisolone 40-120mg & others) vs placebo injections.
- Pain: Using 100 point Visual analog scale, ~54 baseline,[4] Steroids reduced pain more than placebo:
  - 21-22 points lower at one week,[1,2] 16.5 points lower at two weeks,[3] 7.4 points at 3-4 weeks[1]
    - Average ~15 points better between 1-4 weeks[4]
    - Maximal effect may occur at 1.5 weeks[4]
  - At later time points, difference is non-statistically significant[1]
  - Compared to baseline, pain was reduced 29 points at 3 months.[5]

1. *Can Fam Physician. 2004;50:241-8. 2. Cochrane. 2006;2:CD005328. 3. BMJ. 2004;328:869. 4. Eur J Pain. 2007;11:125-38. 5. Ann Intern Med. 2015;162:46-54. 6. J Am Acad Orthop Surg. 2009;17:638-46.*

Steroid Injection (knee) for OA

- Pain: Reaching pain target or global improvement
  - 74-78% steroid vs 45-54% placebo:[1-3] NNT 3-5, at 1-4 weeks.[1-3]
  - Results at >4weeks inconsistent: 2 no effect,[1,2] one reports NNT 5 at 16-24 weeks.[3]
- Function and stiffness not reliably changed.[5]
- Sensitivity mostly unclear (e.g. if steroids vary[7]) but maybe
  - Worse radiographic severity ≈ reduced effectiveness[8]
  - Higher clinical severity ≈ improve effectiveness[8]
- Joint infection 1/14,000-77,000 with intra-articular injection[9]

1. *Can Fam Physician. 2004;50:241-8. 2. Cochrane. 2006;(2):CD005328. 3. BMJ. 2004;328(7444):869. 4. Eur J Pain. 2007;11:125-38. 5. Ann Intern Med. 2015;162:46-54. 6. J Am Acad Orthop Surg. 2009;17:638-46. 7. Clin Rheumatol. 2014;33:1695-706. 8. Rheumatology. 2013;52:1022-32. 9. Am Fam Physician. 2014;90:115-6.*

Opioids

- Sys Rev: 22 RCTs (8275 pts).
  - Moderate quality but publication bias seen
  - Pain: SMD 0.28 (0.20-0.35), 0.7 better out of 10
  - Function: SMD 0.26 (0.17-0.35), 0.6 better out of 10
    - Estimated NNT's for these 10-12.
  - Adverse pooled by group: for oxycodone
    - Any AE: 87% vs 52%, NNH 3
    - Withdrawal due to AE: 32% vs 6%, NNH 4
  - No diff with opioid type, analgesic potency, route of administration, daily dose, quality of trials, or funding.

Cochrane 2014; 9: CD003115.

Opioids

- Other Sys Revs:
- 18 RCT, 4856 pts, (12 wks), SMD 0.58 (0.52-0.64)
  - Opioid sub-groups: Strong 0.69 vs weak 0.52
  - Function SMD 0.31 (0.24-0.39)
  - Withdrawal rates = 7% Placebo, 19% weak opioids (NNH=9), 31% strong opioids (NNH 5)
- 6 RCTs (1057 pts),[2] 10.5 better out of 100
  - Benefit similar to NSAID
  - High withdrawal rates may inflate opioid benefit[2]

1 OsteoArthritis & Cartilage 2007;15:957-965 2. European J of Pain 2007; 11:125–138

Opioids (Tramadol)

- Tramadol, Sys rev: 11 RCTs, (1939 pts)
  - Pain Scale: 8.5 better out of 100.
  - Pain (% ≥Mod Improve): RR 1.37 (1.22-1.55), 71%% vs 51%, NNT 5
  - Adverse Events: minor 20% vs 8%, NNH 9
    - Withdrawal due to AE: 28% vs 12%, NNH 7
- Bottom-Line: Opioids work, NNT ~5-10 but it's similar to NSAID and lots of adverse events (NNH 5-10)

Cochrane 2006; 3: CD005522.

Miscellaneous 1

- Acupuncture: 16 RCTs (3498 pts), For pain,
  - Vs Sham: SMD 0.28 (0.11-0.45) ≈ 0.45 better out of 10.
  - Better trials (e.g. good blinding): even less effect
- Ultrasound: 5 RCTs (341 pts), For Pain
  - SMD 0.49 (0.23-0.76) ≈ 1.2 better out of 10
  - Unreliable: poor quality RCTs (Mean score 0.8 / 8)
- Thermal Therapy: 3 RCTs (179 pts)
  - Unreliable: poor, small, diff outcomes (?quad strength)

Cochrane 2010;1:CD001977. Cochrane 2010;1:CD003132. Cochrane 2003;4:CD004522.

Miscellaneous 2

- Transcutaneous electrostimulation:18 RCT (813 pts)
  - Pain SMD 0.86 (0.49-1.23); 2.1 better out of 10
    - In 4 RCTs the effect better than with jt replacement!
  - Poor quality (mean 1.4 / 8), 80% heterogeneity, pub bias
  - In bigger studies, SMD = 0.07 (meaningless)
- Electromagnetic Field Therapy: 9 RCTs (636pts)
  - Pain: 15.1 better out of 100
  - Function and Quality of Life (& AE): No difference
  - Mean score: 5.8 (but poor evaluation; ? not understood)
    - No sensitivity analysis (if better trials also good)

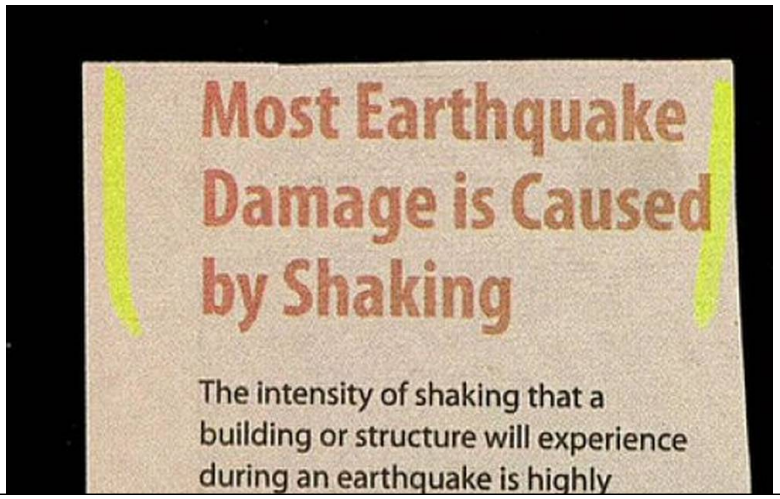
Cochrane 2009; 4: CD002823. Cochrane 2013; 12: CD003523

Miscellaneous 3

- Braces & Orthoses: 5 RCTs (589 pts)
  - Insoles x 3 & 2 braces: Not combined:
  - Real Mix with most non-significant
  - Authors report “silver evidence” that a brace and a lateral wedge insole have small effect.
  - Mean quality score 5.5 out of 10.
  -
- **Bottom-Line: Acupuncture: No. Ultrasound, thermal and TENS: very unlikely. Maybe brace/ orthoses & (?) electromagnetic field therapy.**

Cochrane 2005; 1: CD004020.

Looking to experts for wisdom



American Academy of Orthopedic Surgeons CPG

Strong recommendations For	**Moderate Recommendations For**
Activity.	Weight loss (if BMI >25)*
NSAIDs & Tramadol	
Inconclusive Recommendation	
Electrotherapeutic modalities	Manual Therapy
Unloader type braces.	Acetaminophen, Opioids, Patches
Intra-articular corticosteroids	Articular growth factor/plasma-rich protein
Strong Recommendations Against	**Moderate Recommendations Against**
Acupuncture.	Lateral Wedge Insoles
Glucosamine or Chondroitin	Needle Lavage
Hyaluronic	

* Insufficient evidence to support: Open Rheumatol J. 2014;8:89-95.

American College of Rheumatology CPG

Table 4. Pharmacologic recommendations for the initial management of knee OA*

We conditionally recommend that patients with knee OA should use one of the following:
- Acetaminophen
- Oral NSAIDs
- Topical NSAIDs
- Tramadol
- Intraarticular corticosteroid injections

We conditionally recommend that patients with knee OA should not use the following:
- Chondroitin sulfate
- Glucosamine
- Topical capsaicin

We have no recommendations regarding the use of intraarticular hyaluronates, duloxetine, and opioid analgesics

* No strong recommendations were made for the initial pharmacologic management of knee osteoarthritis (OA). For patients who have an inadequate response to initial pharmacologic management, please see the Results for alternative strategies. NSAIDs = nonsteroidal antiinflammatory drugs.

Ortho CPG: J Bone Joint Surg Am. 2013;95:1885-6
Rheum CPG: Arthritis Care Res (Hoboken). 2012;64(4):465-74.

NSAIDs: Between a Rock and Hard Place

NSAID: Non-selective & Cox-2

- Adverse Events
- First: No difference in effectiveness between NSAID and Cox-2 selective NSAID
- Both effect renal function (not discussed further).
- That leaves GI outcomes & Cardiovascular disease.

Endoscopic (non-clinical) ulcers

	Endoscopic Gastric Ulcer		Endoscopic Duodenal Ulcer	
	NSAID	Cox-2	NSAID	Cox-2
Event rates	18.7%	3.8%	5.3%	1.6%

Clin Gastro Hep 2007;5:818–828

Clinical Important GI Events

	Perforation, obstruction, bleed, & symptomatic ulcer		Perforation, obstruction & bleed	
	NSAID	Cox-2	NSAID	Cox-2
Event rates	1.43%	0.58%	0.63%	0.20%
NNT	118		233	

NNT = Number needed to treat to benefit 1 patient Clin Gastro Hep 2007;5:818–828

NSAID GI events

- Based on GI benefits, US Study[1] show COX-2 QALY = $275,000
  - not cost effective,
  - Maybe in high risk (QALY = $55,000) BUT,…
- Adding ASA to a Cox-2 inhibitor appears to remove its GI advantage[2]
  - so no longer cost effective.

1. Ann Intern Med. 2003 May 20;138(10):795-806. 2. Clin Gastro Hep 2007;5:818-28

NSAID GI events: GI protection

- H. Pylori eradication[1]:
  - Reduces Ulcer rates (risk ratio 0.35 (0.20 – 0.61)
  - Cost effective (>50) even if H pylori rates as low as 5%.
- Misoprostol (200mcg QID) reduces important clinical GI events but adverse events (cramping, diarrhea, etc).[2]
- H2 blockers: limited data.[1]
- PPI: Clinically important event (GI bleeds) reduced with PPI added to Cox-2 vs Cox-2 alone (0 vs 9%)[3]

1. Am J Gastroenterol 2009; 104:728 – 738. 2. Ann Intern Med 1995 ; 123 : 241 – 9 .
3. Lancet. 2007;369(9573):1621-6

NSAID GI events

- It had been estimated that only 15% of endoscopic ulcers will become clinically important.
- Note: Although the relative risks and endoscopic ulcers rates are impressive, it is important to focus on absolute rates of clinically important outcomes.

Clin Gastro Hep 2007;5:818–828

NSAID: CVS risk

- Meta-analysis 754 RCTs (~350,000 pts)
  - Mixed population, CV event rate ~1% per year).
  - COX-2 inhibitors vs placebo, increased:
    - All-cause mortality, RR 1.22 (1.04–1.44).
    - Major CVD, RR 1.37 (1.14 – 1.66).
  - Diclofenac (150 mg/day): similar to COX-2s for mortality & CVD.
  - Naproxen (1000 mg/day): <CVD & mortality vs COX-2 inhibitors and similar to placebo
  - Low dose ibuprofen (≤1200 mg/day) low risk also.

Can Fam Physician. 2014;60(3):e166.

Conclusion

- Based on the above evidence,
- Two reasonable approaches from recent publications (relatively reputable groups)

Management Approach 2

Table 2. Summary of recommendations for prevention of NSAID-related ulcer complications

	Gastrointestinal risk[a]		
	Low	Moderate	High
Low CV risk	NSAID alone (the least ulcerogenic NSAID at the lowest effective dose)	NSAID+PPI/misoprostol	Alternative therapy if possible or COX-2 inhibitor+PPI/misoprostol
High CV risk[b] (low-dose aspirin required)	Naproxen + PPI/misoprostol	Naproxen + PPI/misoprostol	Avoid NSAIDs or COX-2 inhibitors. Use alternative therapy

[a]Gastrointestinal risk is stratified into low (no risk factors), moderate (presence of one or two risk factors), and high (multiple risk factors, or previous ulcer complications or concomitant use of corticosteroids or anticoagulants). [b]High CV risk is arbitrarily defined as the requirement for low-dose aspirin for prevention of serious CV events. Patients with a history of ulcers who require NSAIDs should be tested for *H. pylori*, and if the infection is present, eradication therapy should be given.

Am J Gastroenterol 2009; 104:728 – 738.

Who is High GI risk?

Table 1. Patients at increased risk for NSAID GI toxicity

High risk
1. History of a previously complicated ulcer, especially recent
2. Multiple (>2) risk factors
Moderate risk (1–2 risk factors)
1. Age >65 years
2. High dose NSAID therapy
3. A previous history of uncomplicated ulcer
4. Concurrent use of aspirin (including low dose) corticosteroids or anticoagulants
Low risk
1. No risk factors
H. pylori is an independent and additive risk factor and needs to be addressed separately (see text and recommendations).

Am J Gastroenterol 2009; 104:728 – 738.

The End

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