THE COLLEGE OF FAMILY PHYSICIANS OF CANADA

LE COLLÈGE DES MÉDECINS DE FAMILLE DU CANADA

Pick-N-Learn:

Rapid answers to chronic pain questions

November 17, 2020

Presenter Disclosures

Mike Allan, MD CCFP, FCFP

- CFPC and University of Alberta (salary);
- Receipt of honorarium - provincial chapters of the CFPC (Alberta, BC, NFL, ON), medical associations (Yukon, NW Territories), universities (Queens, UBC, Dalhousie, Calgary);
- Grants: Towards Optimized Practice, CIHR, PRIHS, Alberta Health, ON LHIN Grant, St. Paul's hospital;
- Clinical Trials: Bedmed, INR range

Samantha Moe, PharmD ACPR

- Employee of the CFPC
- No other conflicts of interest to declare

Joey Ton, PharmD

- Employee of the CFPC and Costco Pharmacy
- No other conflicts of interest to declare

This program has not received financial or in-kind support from any organization.

Learning Objectives

By the end of this activity, participants will be able to:

1. Describe what proportion of patients respond to different pain treatments.
2. Describe the evidence supporting common pharmacological and non-pharmacological treatments for chronic pain in primary care.
3. Identify practical take-away messages that can be used in family practice.

Deciding on Treatment for Pain

Research, what we've looked at

- Three Chronic Pain Conditions
  1. **Osteoarthritis Pain** (Knee and Hip)
  2. **Chronic Low Back Pain** (Radicular and Non-Radicular)
  3. **Neuropathic Pain** (Post Herpetic Neuralgia, Diabetic Neuropathy)

- A ton of studies on various interventions for each condition
  - **63,000+** RCTs titles/abstracts scanned.
  - **1400+** RCTs read in full.
  - **290** RCTs extracted and analyzed

- **Goal:** PEER Chronic Pain Guideline

Outcomes

1. **Continuous outcomes**
   - Generally consists of a measurement on a numerical scale.
     - Example: Visual analogue scale (VAS)
   - **Caveats:**
     - Can be difficult to summarize findings from all trials with these measurements as scales and baseline measurements vary from trial to trial.

2. **Responder (Dichotomous) outcomes**
   - Outcomes that lead to a Yes or a No response.
     - Example: Myocardial Infarctions
   - **Caveats:**
     - Easier to summarize findings from multiple trials but not all studies report these types of outcomes.

Responder (Dichotomous) Outcome

- Our team focuses on a “meaningful pain relief”

- Meaningful pain relief or meaningful improvement in pain
  - Mostly refers to a $\geq$ 30% decrease in pain.
  - Can also refer to achieving a certain threshold on a scale.

Time to pick your topic!

Game Board

NSAIDS & Acetaminophen	Antidepressants	Opioids	Steroids / Injections	Hodge Podge
Oral NSAIDs for OA	TCAs for NP	For LBP	Steroids for OA	Gabapentin for NP
Topical NSAIDs for OA	SNRIs for NP	For OA	Steroids for LBP	Cannabis for NP
Oral NSAIDS for LBP	SNRI for LBP	For NP	Viscosupplementation for OA	Capsaicin for LBP and OA
Acetaminophen for OA	SNRI for OA	Fun Slide!	PRP for OA	Exercise-induced OA
Glucosamine and chondroitin for OA	Spinal Manipulation for LBP	Acupuncture for LBP	Exercise for OA	Exercise for LBP

Sam’s Slides

SM

SNRIs for Neuropathic Pain

1 SR (8 RCTs, n=2746) for diabetic neuropathy

- Duloxetine 60-120mg/d (6 RCTs), venlafaxine75-225mg/d and desvenlafaxine 50-400mg/d
- Meaningful improvement in pain: 56% SNRI vs 41% placebo, NNT 7
- No difference btw agents; all industry funded studies; studies saw benefit at ≥12wks

Adverse effects (NNH):

- Gastrointestinal: nausea (7), constipation (17), anorexia (24), diarrhea (24), vomiting (28)
- CNS: somnolence (11), dizziness (16), asthenia (21), fatigue (21), insomnia (26)
- Miscellaneous: sweating (21), withdrawals due to AE (13)

Bottom Line: SNRIs can moderately decrease pain due to diabetic neuropathy, with 15% more patients achieving a 30% reduction in pain over the 41% on placebo. However, 1 in 7 experience nausea, and 1 in 13 withdrawing due to adverse effects.

PEER, Neuropathic Pain SR, In progress.

SM

Gabapentin/Pregabalin for Neuropathic Pain

Gabapentin

- 1 SR (18 RCTs, 4286 patients); duration 4-12 weeks
  - **Conditions include:** Postherpetic neuralgia (8), Diabetic neuropathy (7), mixed neuropathic pain (2), and nerve injury (1)
- Gabapentin 600-3600mg versus placebo.

Outcomes: meaningful improvement in pain

- 47% gabapentin versus 28%, **NNT 6**

Adverse Events:

- Dizziness: 19% versus 7% **NNH 8**
- Ataxia/Gait Disturbance: 14% versus 2% **NNH 9**
- Somnolence: 14% versus 5% **NNH 12**
- Withdrawal due to AE: 11% versus 8% **NNH 31**

Pregabalin

- 1 SR (45 RCTs, ~11,000 patients), 2-16 weeks.
  - **Conditions include:** PHN, DN, mixed, others
  - Pregabalin 150mg BID

Outcomes: meaningful improvement in pain

- PHN: 50% pregabalin vs 25%, **NNT 4**
- DN: 47% pregabalin vs 42%, **NNT 22**
- Higher doses produce greater response rates; 150mg/d ineffective except for PHN

Adverse Events:

- Dizziness: 29% versus 8% **NNH 5**
- Somnolence: 16% versus 6% **NNH 10**
- Withdrawal due to AE: 14% versus 5% **NNH 11**

1. www.pain-calculator.com
2. Derry, et al. Pregabalin for Neuropathic Pain in Adults. Cochrane Database, 2019.

SM

Gabapentin and pregabalin

Both gabapentin and pregabalin can moderately improve pain in about 1 in 4-6 patients.

Both have adverse effects and the incidence of AEs likely depends on the dosage used.

No head-to-head RCT evidence comparing efficacy/tolerability between the two medications.

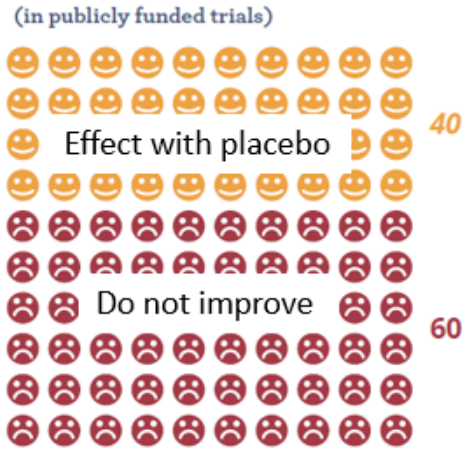
Do glucosamine and/or chondroitin improve pain for patients with osteoarthritis?

Glucosamine: 11 SR (2-25 RCTs, n=414-4963)

- 1500mg/d vs plb:
- Meaningful pain reduction:
  - Most recent (9 RCTs, n=1643). After 4-156 weeks:
    - 47% vs 37% placebo, NNT = 11

Chondroitin: 11 SR (6-18 RCTs, n=362-4044)

- 800-1200mg/day vs plb:
- Meaningful pain reduction:
  - Most recent analysis (9 RCTs, n=2477). After 12-48 weeks:
    - 57% vs 45% plb, NNT=9.



However, when analysis was restricted to publicly funded studies, no significant benefit was seen with glucosamine and chondroitin.

	Glucosamine			Chondroitin		
Baseline pain	~52 on 100-pt scale			~56 on 100-pt scale		
	Placebo	Larger trials	Smaller trials	Placebo	Larger trials	Smaller trials
Pain reduced by	~13	Same as plb	~12 better than placebo	~19	~4 better than placebo	~12 better than placebo

SM

Do glucosamine and/or chondroitin improve pain for patients with osteoarthritis? (2)

Combination of glucosamine and chondroitin:

- 6 SRs: Only one SR examined meaningful pain reductions: effect similar to components alone.
  - Change in 100-point pain scale: not different from placebo.

Considerations

- Mostly knee osteoarthritis studied.
- Adverse events infrequently reported.

Bottom Line: Glucosamine and chondroitin do not appear to be effective in higher-quality, larger and/or publicly funded studies. If studies at high risk of bias are included, at best ~10% more people will have meaningful reduction in pain with either treatment over 35-45% of people with placebo. There is reason to doubt the effectiveness of either treatment.

SM

Topical NSAIDs for Osteoarthritis

One SR of 22 RCTs, n=7265:

- Meaningful pain relief: 61% topical NSAID vs 47% placebo group, NNT 8 over 1-12 wks
- All industry funded trials; benefit consistent over different time and in large/small trials
- Withdrawal due to adverse effects: 5.5% vs 3.5% placebo, NNH 50
  - Local site reactions (15% vs 13% placebo, NSS)
  - Gastrointestinal AE (3.4% vs 3.1% placebo, NSS)
- Data unavailable to support one formulation/conc'n over another

Bottom line: Topical NSAIDs are superior to placebo for the treatment of osteoarthritis pain.

CFP 2020; 66(3) e89-98.

SM

Exercise for Low Back Pain

SR of 18 RCTs (n=2561 patients) over 6-52 wks

- Meaningful pain response:
  - 50% exercise vs 35% control group; NNT 7
    - 4 weeks or more: associated with benefit
      - E.g. 4-12wk trials: NNT 21
    - 12-48 weeks beyond the intervention: 53% exercise vs 37% control; NNT 6

Adverse effects

- Reported in RCTS (increased back pain, joint pain): NSS.
- Withdrawal due to AE: not reported in any trial

Bottom Line:

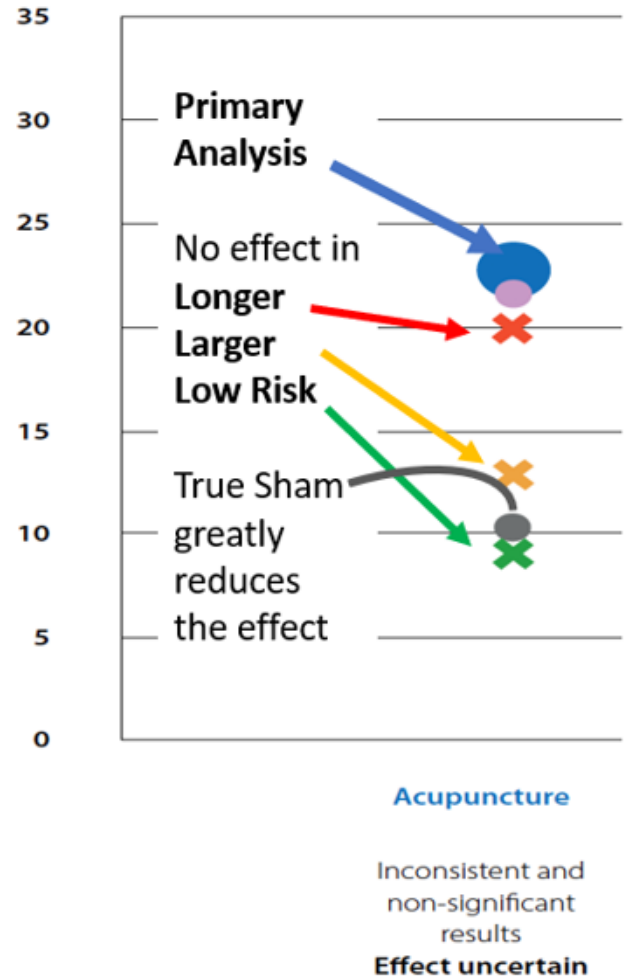
Exercise reduces low back pain when continued over 4 weeks and has low risk of adverse effects.

Type of exercise likely does not matter.

Peer SR Low Back Pain, in progress.

Acupuncture for Chronic Low Back Pain

- SR: 8 RCTs (4,618 pts), 4-24 weeks, 10-24 sessions
- Overall Outcomes: meaningful pain improvement
  - 54% acupuncture vs. 35% control, NNT 6
- Quality – No effect
  - Longer (≥12 weeks) or Larger (>150 pts) trials
  - Lower risk of bias
- Comparator (vs "sham")
  - 5/8 RCTs (1,676 pts)
  - 62% acupuncture vs. 57% control, NNT 20



PEER Chronic Low Back Pain
Systematic Review not yet published

SM

Acupuncture for Chronic Low Back Pain (2)

- **Bottom Line:**
  - Acupuncture for chronic low back pain may work but “how well” is still unclear.
    - Effects reduced (and non-significant) with multiple quality markers
  - When true sham used, improvement over placebo reduced
    - 62% acupuncture vs. 57% true sham

PEER Chronic Low Back Pain
Systematic Review not yet published

SM

Opioids for Osteoarthritis

- 1 SR (15 RCTs, n=6266, over 10d to 24 wks)
- Oxycodone, tapentadol, buprenorphine patch, tramadol
- Outcomes
  - Pain relief: 47% opioids vs 43% plb, NNT 32
  - <4 wks: 38% opioids vs 14% (NNT 14) while longer trials showed no advantage over placebo
  - All studies were industry funded
  - Smaller studies (n<150) favored opioids (RR 1.09); larger studies showed no difference
- Adverse events
  - Withdrawals due to AE: 21% opioids vs 7% placebo, NNH 8-10
  - GI: Constipation (NNH 9), nausea (NNT 6),
  - NCs: Drowsiness (NNH 9), dizziness (NNH 11), headache (NNH125)

Bottom Line: If opioids are associated with pain relief, appears to be in the short term only (ie. < 4 weeks). The confidence in these results are tempered since benefit seen only in industry funded and smaller studies. Harms likely exceeds benefits for opioids.

CFP March 2020, 66 (3) e89-e98.
CFP March 2020, 66(3): 191-3.
https://pain-calculator.com/

SM

TCAs for Neuropathic Pain

- 1 SR (2 RCTs, n=170)[1]: amitriptyline, PHN and DN
- Moderate pain improvement:
  - Diabetic neuropathy: 79% TCA vs 20% , NNT 2
  - Postherpetic neuralgia: 73% TCA vs 53%, NSS
  - Both trials: <150 patients, outcomes at 4-12wks
- Other SRs:
  - 10 RCTs[2], n=588: amitriptyline, DN or PHN
    - Moderate pain relief (30%): 64% TCA vs 32%, NNT 4
    - Similar results with desipramine and imipramine
  - 4 RCTs[3], n = 382: amitriptyline, DN/PHN/mixed neuropathy over 4-9wks
    - Moderate pain relief (inconsistently defined): 39% TCA vs 20%, NNT 6

1. PEER, Neuropathic Pain SR, In progress.
2. Saarto T, et al. Cochrane Database Syst Rev 2007, Issue 4. Art. No.: CD005454.
3. Moore RA, et al. Cochrane Database Syst Rev 2015, Issue 7. Art. NO.: CD008242.

TCAs for Neuropathic Pain, continued

Adverse Events (amitriptyline):

- Dry Mouth: 34% versus 6% **NNH 4**
- Sedation: 34% versus 9% **NNH 4**
- Withdrawal due to AE: 16% versus 7% **NNH 12**

Bottom Line:

Amitriptyline provides meaningful pain improvement for diabetic neuropathy and postherpetic neuralgia but may cause dry mouth and sedation in a similar number of patients. Trials were small and of short duration.

Mike’s Slides

You get what you pay for,...

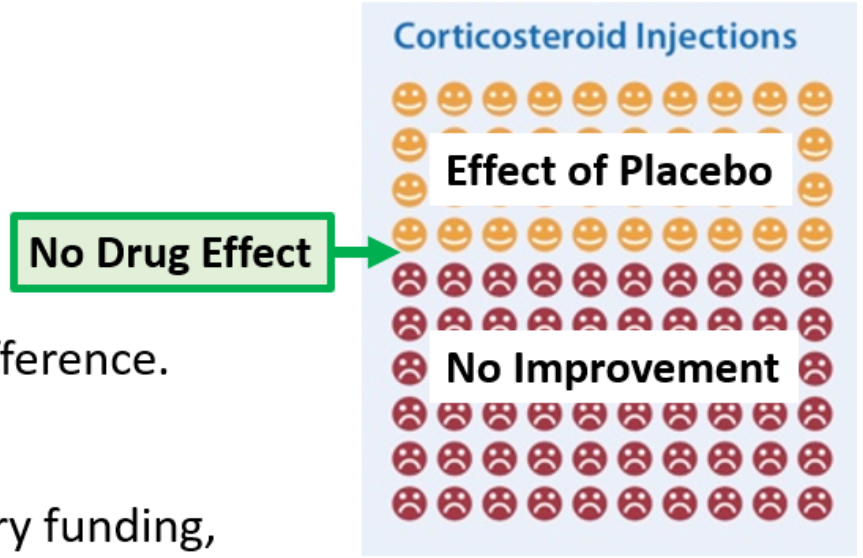
- 82 people, electric shock pain RCT.
  - Group 1: pain pill worth $2.50 (similar to codeine) but faster etc.
  - Group 2: Pain pill worth $0.10, discounted medicine.
- All were placebos
- Outcome: High cost = better mean pain ~12mm
  - 85% high cost got better vs 61% of discounted
- **Bottom-Line**: If it's expensive, it's better. (May explain some of patient complaints around generics).

JAMA. 2008 Mar 5;299(9):1016-7.

Corticosteroids for Low Back Pain

- SR: 10 RCTs (1,152 pts), 4-104 weeks
  - Methods varied greatly
- Outcomes:
  - 44% corticosteroids vs. 43% placebo, No Difference.
- Quality - no effect in:
  - Large studies, longer studies, or non-industry funding,
  - Lower risk of bias studies.
- Harms
  - Withdrawals due to AE not reported

Bottom Line: Corticosteroids for low back pain appear to be no more effective than placebo.



PEER Chronic Low Back Pain Systematic Review not yet published

MA

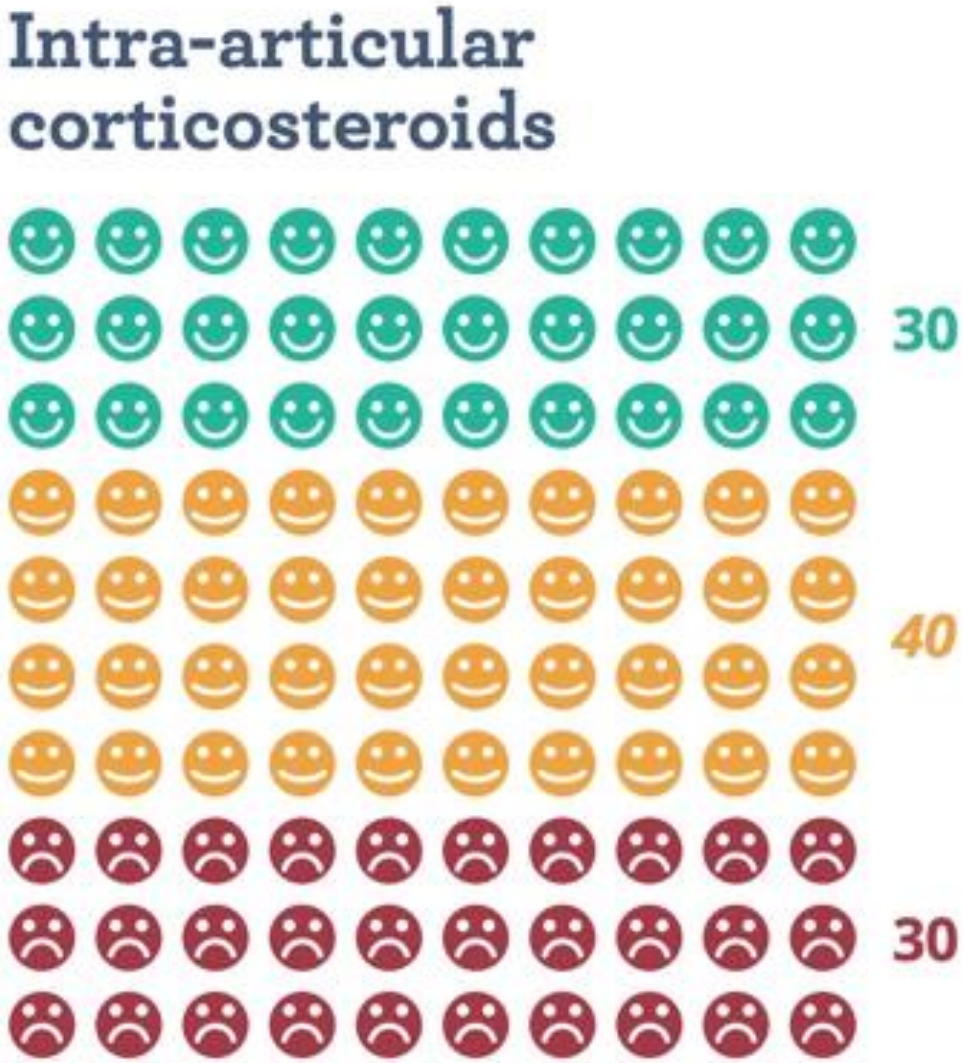
Intra-Articular Corticosteroids for OA

- SR: 7 RCTs (706 pts), Hip and knee injections, 4-24 weeks
  - methylprednisolone (40mg, 120mg), triamcinolone (40mg), cortivazol (3.75mg) vs. saline
- Outcomes (meaningful pain relief):
  - 50% corticosteroids vs. 31% placebo, NNT = 6
- Duration
  - Trials divided into ≤4 weeks, 4-12 weeks and ≥12 weeks
  - Effects diminished over time, NSS at ≥12 weeks
- Harms
  - 2/7 studies even mentioned AEs, with no difference in steroids & placebo
  - Risk of joint infection likely one in 14,000-77,000 (TFP #135)

Can Fam Physician . 2020 Mar;66(3):e89-e98

Bottom Line

- Appear to be effective for OA pain management
- Effects for knee osteoarthritis peak between 1-2 weeks
- May inject up to 4 times per year

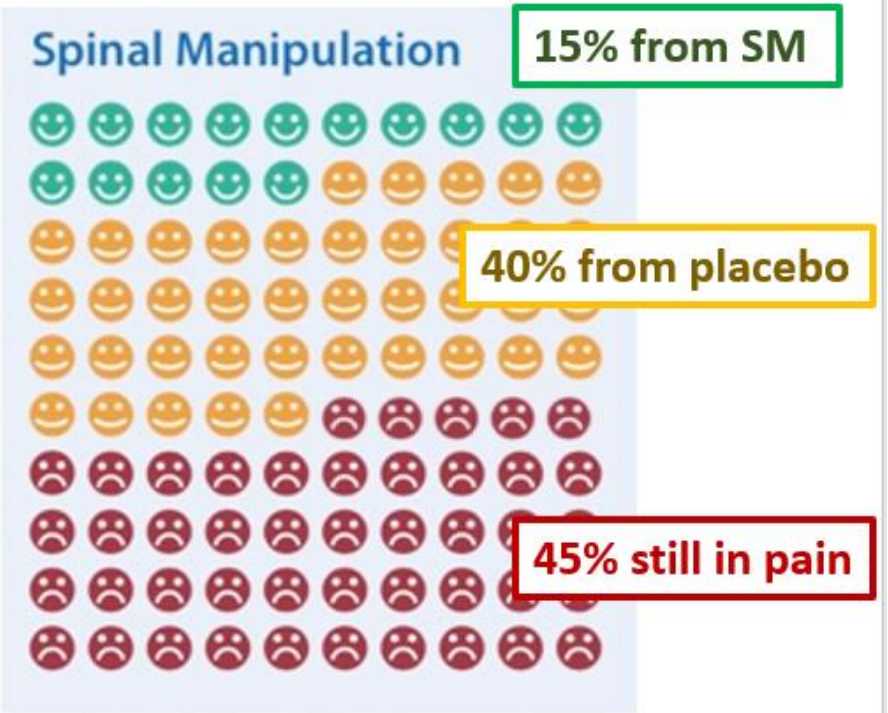


Can Fam Physician . 2020 Mar;66(3):e89-e98

Spinal Manipulation for Low Back Pain

- SR: 5 RCTs (686 pts)
  - Duration: “not reported” - 176 weeks
- Overall Outcomes:
  - 57% spinal manipulation vs 39% control, NNT=6
- Quality - In studies that were
  - Larger, lower risk of bias, or sham-controlled
    - Relative benefit reduced from 1.54 to ~1.35
    - That means the estimated benefit (if control rate 40%)
      - 22% overall drops to 15% in good quality (sham) studies

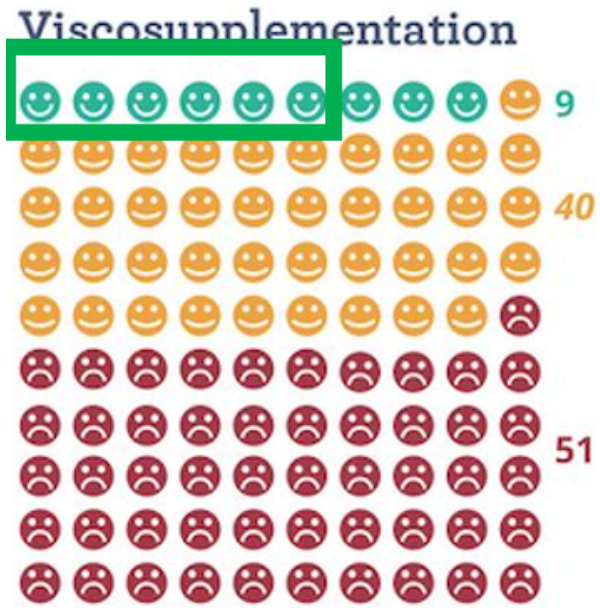
Bottom Line: Spinal Manipulation may be effective for chronic low back pain. Patients should be advised re: potential harms associated with neck manipulation.



PEER Chronic Low Back Pain Systematic Review not yet published
Nielsen et al. Systematic Reviews (2017) 6:64

Viscosupplementation injection for OA

- **SR**: 31 RCTs (6254 Patients), many 8-26 wks, Mostly Knee OA, some hip OA
  - Hyaluronic Acid injections: single injection, 3x/weekly, 5x/weekly
- **Results:** ≥30% improvement, RR 1.22 (1.12, 1.33): 53% vs 44%.
  - No difference between <4, 4-12 or >12 weeks
  - No difference in Non-profit RCT RR 1.11 (0.73,1.70)]
  - Smaller (<150) RR=1.65 vs large studies (>150) RR=1.15
    - Estimated benefit goes from ~26% to 6%)

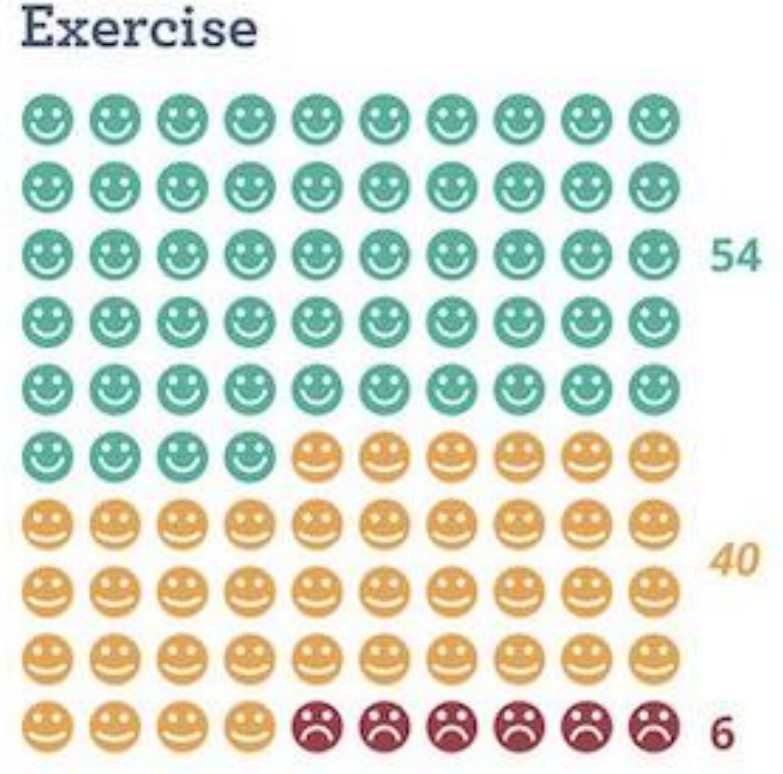


Bottom Line: Viscosupplementation injections did show benefit in patients with OA but higher quality and non-industry funded trials show none-less benefit.

Can Fam Phys March 2020, 66 (3) e89-e98. TFP #89, Herrero-Beaumont 2007, Miceli-Richard 2004

Exercise for Osteoarthritis

- 11 RCTs (1367 patients), knee or hip OA, many trials 8-12 weeks
  - **Includes**: Hip strengthening exercise, PT delivered exercise, Hydrotherapy, Tai chi, Aquatic physical therapy, quadricep strengthening exercise.
- **Results:** ≥ 30% improve - RR 2.36 (1.79, 3.12), meta-graph 47% vs 21%



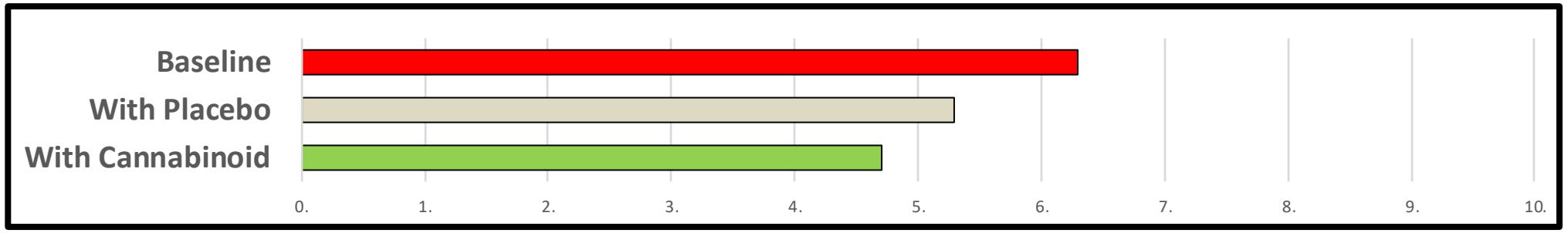
- All trials non-profit funding & Smaller trials (<150) showed better effect
- Adverse Events: No Difference

- **Bottom Line:** Exercise for management of OA is on of the most effective options for patients.

Canadian Family Physician March 2020, 66 (3) e89-e98

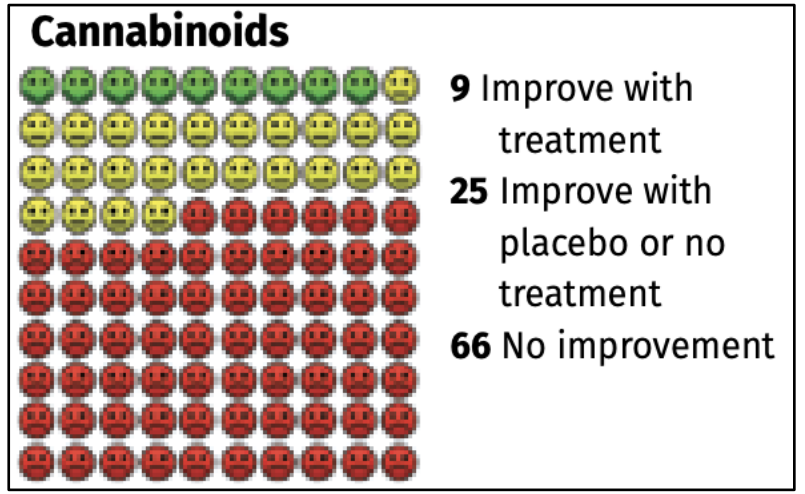
MA

Cannabinoids and Neuropathic Pain:



Pain Outcomes: 30% pain reduction & others

Type of Pain	Risk Ratio	Cannabinoid	Placebo	NNT
Neuropathic	1.34 (1.04-1.74)	38%	30%	14
Palliative	1.34 (0.96-1.86)	30%	23%	~15
Chronic Pain	**1.37 (1.14- 1.64)**	**39%**	**30%**	**11**

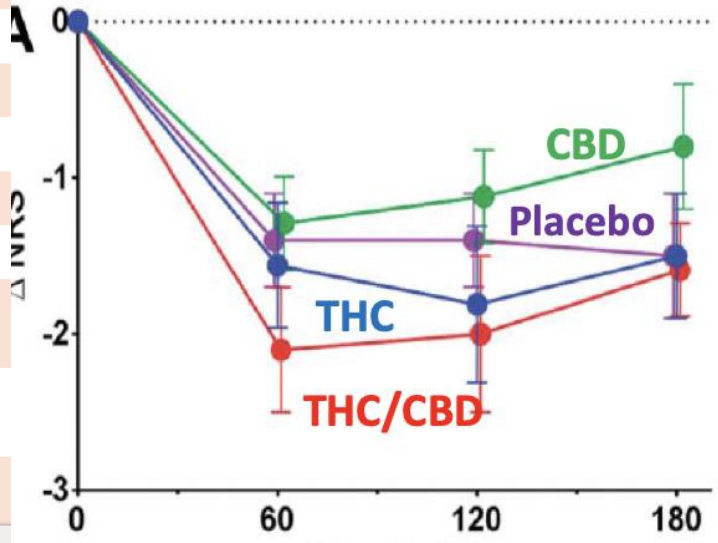


Can Fam Physician 2018, 64 (2) e78-e94;. JAMA. 2015;313:2456-73. J Pain 2015;16:1221-32. Schmerz 2016; 30: 62-88. Medwave 2016;16 Suppl 3:e6539. Curr Med Res Opin 2007;23:17-24. Der Schmerz 2016;30:25-36.

TYPE OF ADVERSE EVENT	CANNABINOID EVENT RATE, %	PLACEBO EVENT RATE, %	NNH
Overall	81	62	6
Withdrawal due to adverse events	11	Approximately 3%	14
Serious adverse events	NS	NS	NS
Central nervous system effects	60	27	4
“Feeling high”	35	3	4
Sedation	50	30	5
Speech disorders	32	7	5
Dizziness	32	11	5
Ataxia or muscle twitching	30	11	6
Numbness	21	4	6
Disturbance in attention or disconnected thoughts	17	2	7
Hypotension	25	11	8
Dysphoria	13	0.3	8
Psychiatric	17	5	9
Euphoria	15	2	9
Impaired memory	11	2	12*
Disorientation or confusion	9	2	15
Blurred vision or visual hallucination	6	0	17
Dissociation or acute psychosis	5	0	20

Cannabinoids

20 Fibromyalgia pts
≥30% response in,
90% THC/CBD
65% THC
55% placebo
40% CBD



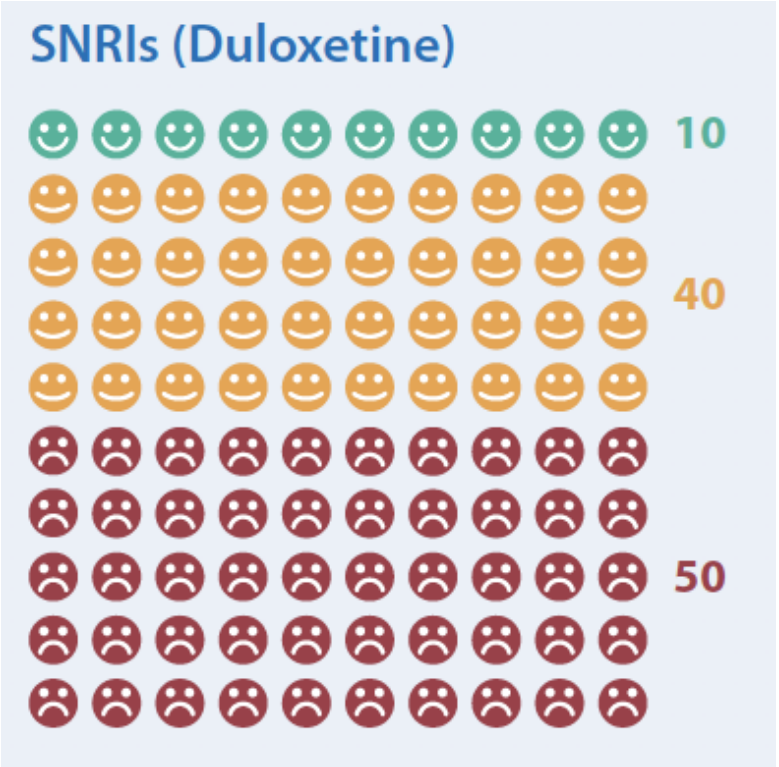
- Bottom-line: there are lots of AE.
  - At best, medical cannabinoids reduce pain ≥30% for one in 11 patients suffering from neuropathic pain (vs placebo).
  - This includes highly biased research, meaning the effect is likely exaggerated
    - Mostly in less common neuropathic pain,
    - No benefit in larger (≥150)or longer studies (≥9 weeks).

Can Fam Phys 2018, 64: e78-e94.
Pain. 2019 Apr;160(4):860-869

MA

SNRI for Low Back Pain

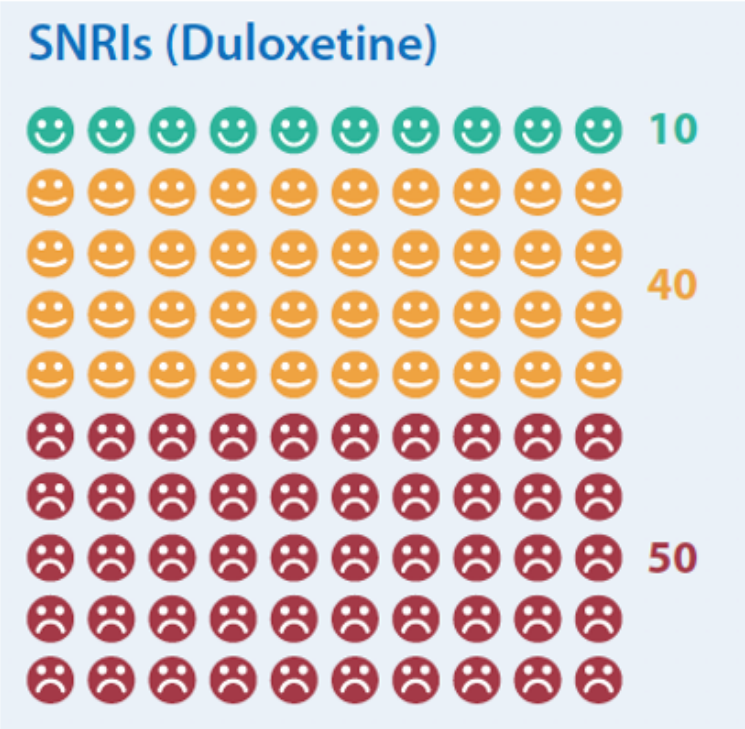
- SNRI (Duloxetine) was 4 RCTs with 1499 pts followed 12-13 weeks.
- Results: Attain ≥30% improvement RR = 1.25 (1.13, 1.38)
  - Quality assessment (larger, longer and low risk of bias studies) found similar



- Adverse Events: 18% withdrawal due to AE vs 9% in control.
  - Dizziness (NNH 23) and nausea (NNH 11) most common AE over placebo.
- **Bottom-Line**: Duloxetine (60-120mg) can improve low back pain more than placebo but will cause a similar number to withdrawal due to adverse events.

SNRI for Low Back Pain (2)

- SNRI (Duloxetine) was 4 RCTs with 1499 pts followed 12-13 weeks.
- Results: Attain ≥30% improvement RR = 1.25 (1.13, 1.38)
  - Quality assessment (larger, longer and low risk of bias studies) found similar



- Adverse Events: 18% withdrawal due to AE vs 9% in control.
  - Dizziness (NNH 23) and nausea (NNH 11) most common AE over placebo.
- **Bottom-Line**: Duloxetine (60-120mg) can improve low back pain more than placebo but will cause a similar number to withdrawal due to adverse events.

Rubefacients for OA and Back Pain

- **OA*:*** 1 RCT (113 patients), 0.025% capsaicin vs vehicle placebo no statistical difference at 4, 8, or 12 weeks.
- **Back Pain**: 3 RCTs (611 patients) followed ≤3 weeks.
  - ≥30% pain relief RR 1.39 (1.20, 1.61).
  - Estimated benefit is 40% with placebo and 56% with rubefacients.
  - Withdrawals due to adverse events were not reported.
- **Bottom-Line**: Rubefacients possibly have no effect in OA but data limited. In Chronic Back Pain, there is a positive short term effect but no data >3 weeks so questionable for chronic use.

CFP March 2020, 66 (3) e89-e98. Forthcoming Sys Rev.

Joey’s Slides

How effective are SNRIs for Osteoarthritis?

- 6 RCTs (2060 patients with Knee OA), mean age ~63yo, duration 12-16 weeks
  - **Intervention:** Duloxetine 60-120mg QD
    - **Titration:** 60mg over 1-2weeks or 120mg over 3-7 weeks
  - **Comparator:** Matching Placebo

- **Results:**
  - Meaningful pain relief: 64% vs 43% with placebo
    - RR 1.53 (1.25, 1.87) NNT 5
  - Adverse Events:
    - **Overall AE:** 55% vs 37% placebo
    - **Discontinuation due to AE:** 12.4% vs 5.5% with placebo (RR 2.17 (1.57,3.01)
    - **GI AEs**: 35.5% vs 7.7% (RR 4.43(3.45, 5.69)

JT

How effective are SNRIs for Osteoarthritis? (2)

- **Other Details:**
  - All studies were industry sponsored
  - Majority of quality assessment low risk for all studies (eg. blinding, allocation concealment)
  - No studies looked at venlafaxine for osteoarthritis pain.

- **Bottom Line:**
  - Duloxetine have found to be effective for knee osteoarthritis versus placebo.
    - 64% vs 43% with placebo
  - Still comes with side effects with 55% having an AE versus 37% with placebo.

JT

How effective are Opioids for Low Back Pain?

- 6 RCTs (2708 patients), mean age ~55yo, duration 4-12 weeks,
  - **Interventions**: Opioid alone (3 trials), tramadol/acetaminophen combination (3 trials)
  - **Comparator**: Matching placebo

- **Results:**
  - **Meaningful pain relief:** 39% vs 32% with placebo **(NNT 15)**

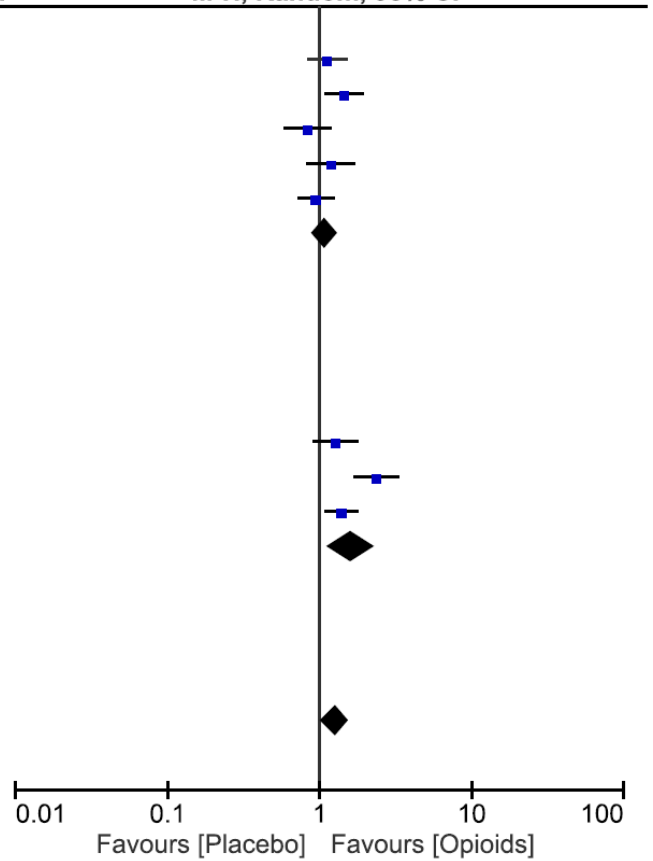
  - **Adverse Events:**
    - Withdrawals due to AE: 27% vs 5% with placebo
    - To name a few: Nausea (NNH 6), dizziness (NNH 7), somnolence (NNH 8), constipation (NNH 9)

Peer SR on Low Back Pain, in progress.

JT

How effective are Opioids for Low Back Pain? (2)

Study or Subgroup	Opioids Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Opioid Only						
Buynak 2010 (Oxycodone)	99	328	43	160	12.8%	1.12 [0.83, 1.52]
Buynak 2010 (Tapentadol)	125	318	43	159	13.1%	1.45 [1.09, 1.94]
Cristoph 2017 (Cebranopadol)	117	385	23	63	11.5%	0.83 [0.58, 1.19]
Cristoph 2017 (Tapentadol)	57	126	24	63	11.3%	1.19 [0.82, 1.72]
Uberall 2012	52	116	57	120	13.4%	0.94 [0.72, 1.24]
Subtotal (95% CI)		**1273**		**565**	**62.2%**	**1.09 [0.90, 1.32]**
Total events	450		190			
Heterogeneity: Tau² = 0.02; Chi² = 7.32, df = 4 (P = 0.12); I² = 45%						
Test for overall effect: Z = 0.92 (P = 0.36)						
1.1.2 Opioid Acetaminophen Combination						
Lee 2013	49	125	37	120	11.8%	1.27 [0.90, 1.80]
Peloso 2004	79	163	34	165	12.0%	2.35 [1.68, 3.30]
Ruoff 2003	82	151	57	146	14.0%	1.39 [1.08, 1.79]
Subtotal (95% CI)		**439**		**431**	**37.8%**	**1.60 [1.12, 2.28]**
Total events	210		128			
Heterogeneity: Tau² = 0.07; Chi² = 7.90, df = 2 (P = 0.02); I² = 75%						
Test for overall effect: Z = 2.59 (P = 0.010)						
Total (95% CI)		**1712**		**996**	**100.0%**	**1.26 [1.02, 1.55]**
Total events	660		318			
Heterogeneity: Tau² = 0.06; Chi² = 24.72, df = 7 (P = 0.0008); I² = 72%						
Test for overall effect: Z = 2.19 (P = 0.03)						
Test for subgroup differences: Chi² = 3.38, df = 1 (P = 0.07), I² = 70.4%						



Peer SR on Low Back Pain, in progress.

JT

How effective are Opioids for Low Back Pain? (3)

- **Other Details:**
  - All studies were industry sponsored
  - Quality of evidence was a bit all over.

- **Bottom Line:**
  - Opioids seemed to provide a small benefit over placebo with patients achieving a meaningful pain relief.
    - (39% vs 32% with placebo)
  - Comparing this benefit with the adverse events, it's a toss up.

JT

NSAIDs for Osteoarthritis

- 39 RCTs (26,359 patients), Knee or Hip OA, mostly 6-12 weeks
  - **Includes:** Etorcoxib 30-60mg QD, Celecoxib 200mg QD, Naproxen 500mg BID, Ibuprofen 800mg TID
  - **Results:**
    - Patients with clinically meaningful change: 57% versus 40% with placebo.
      - RR 1.43 (1.35, 1.51) **NNT 6**
    - COX-2 vs Traditional NSAIDs: **NNT 7 vs NNT 6**
    - Effect on pain stayed fairly consistent throughout various time frames.
  - **Adverse Events:**
    - **Celecoxib:** Withdrawal due to AE (5.6% vs 5.7% placebo), GI Ulcer or Bleed (0.1% vs 0.1% placebo)
    - **Traditional NSAIDs**: Dyspepsia (5.8% vs 1.8% placebo), Upper Abdominal Pain (3.2% vs 1.5% placebo), NSAID related GI Symptom (32% vs 28% placebo)
  - **Bottom Line:**
    - COX-2 and Traditional NSAIDs are similarly effective.
    - In general, NSAIDs are a good treatment option for patients with OA.
    - AE data in the OA population is lacking, however reasonable to extrapolate NSAID use in other conditions.

JT

Oral NSAIDs for Low Back Pain

- 4 RCTs (1637 patients with Chronic Low Back Pain, ~12yrs), mean age ~50yo, duration 4-16 weeks.
  - **Intervention**: Oral NSAIDs
    - Included: Naproxen (1000mg/day), Rofecoxib (25-50mg), Valdecoxib (40mg)
  - **Comparator:** Placebo

- **Results:**
  - **Meaningful pain Relief:** 55% versus 37% in control **(NNT 6)**
  - **Withdrawal due to AE, Edema, Headache: %** Similar in both groups

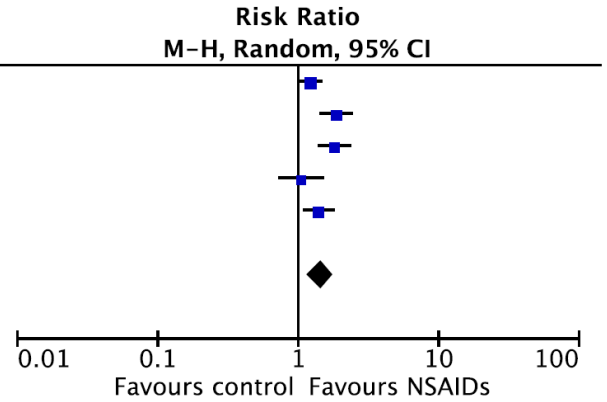
JT

Oral NSAIDs for Low Back Pain (2)

Study or Subgroup	NSAIDs Events	NSAIDs Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Coats 2004	96	148	77	145	24.1%	1.22 [1.01, 1.48]
Katz 2003a	149	233	39	114	20.0%	1.87 [1.42, 2.45]
Katz 2003b	142	229	39	114	19.9%	1.81 [1.38, 2.38]
Katz 2011	45	88	20	41	15.3%	1.05 [0.72, 1.52]
Kivitz 2013	111	295	62	230	20.7%	1.40 [1.08, 1.81]
Total (95% CI)		**993**		**644**	**100.0%**	**1.44 [1.17, 1.78]**
Total events	543		237			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 12.16$, df = 4 (P = 0.02); $I^2 = 67\%$

Test for overall effect: Z = 3.47 (P = 0.0005)



- Bottom Line:
  - NSAIDs are effective in terms of having patients achieving a meaningful pain relief (55% vs 37%, NNT 6).
  - No significant adverse events in the studies included, however studies exclude patients who are at a high risk of AE with an oral NSAID.

JT

Opioids For Neuropathic Pain

- 6 RCTs (1149 patients with postherpetic or diabetic neuropathy), mean age ~60yo, duration 5-12 weeks,
  - Intervention: Opioids
    - 3 studies Oxycodone, 1 study tramadol/acetaminophen, 1 study tapentadol, 1 study buprenorphine
  - Comparator: Placebo

- **Results:**
  - **Meaningful Pain Relief:** 49% vs 36% with placebo
    - RR 1.37 (1.19, 1.57) **NNT 8**
  - **Adverse Events:**
    - **Withdrawal due to AE:** 14% vs 6% with placebo, NNH 13
    - Somnolence (NNH 7), Nausea (NNH 6), Vomiting (NNH 11), Constipation (NNH 6), Dizziness (NNH 10)

Peer SR on Neuropathic Pain, in progress.

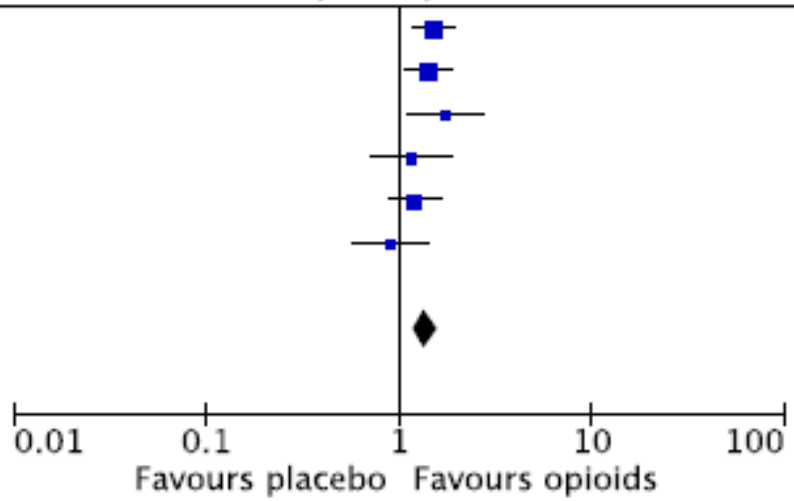
JT

Opioids For Neuropathic Pain (2)

Study or Subgroup	Opioids Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Freeman 2007	90	160	57	153	28.7%	1.51 [1.18, 1.93]
Hanna 2008	72	169	51	169	25.1%	1.41 [1.06, 1.88]
Jensen 2006	37	82	20	77	10.2%	1.74 [1.11, 2.71]
NCT01124617 2010	29	60	13	31	8.5%	1.15 [0.71, 1.88]
Simpson 2016	46	93	38	93	18.7%	1.21 [0.88, 1.67]
Zin 2010	15	29	19	33	8.8%	0.90 [0.57, 1.42]
Total (95% CI)		**593**		**556**	**100.0%**	**1.37 [1.19, 1.57]**
Total events	289		198			

Heterogeneity: $Chi^2 = 6.04$, $df = 5$ ($P = 0.30$); $I^2 = 17\%$

Test for overall effect: $Z = 4.43$ ($P < 0.00001$)



Peer SR on Neuropathic Pain, in progress.

JT

Opioids For Neuropathic Pain (3)

- **Other:**
  - 5/6 studies funded by industry

- **Bottom Line:**
  - Opioids were found to be effective for post herpetic and diabetic neuropathy but expect side effects.
  - Limited evidence on combination opioid products, tapentadol and buprenorphine.

Acetaminophen for Osteoarthritis

- **Systematic Review**: 2 RCTs (991 patients), 6-24 weeks, Knee OA
  - Acetaminophen 1000mg TID-QID
  - **Results:**
    - Patients with a OARSI-A Response: 47% vs 43% with Placebo
      - RR 1.17 (0.83, 1.64) **NSS**
    - Duration 4-12 weeks and >12 weeks: **NSS**
  - **Side Effects:**
    - Any AE, Serious AE, Withdrawal due to AE: **NSS**
    - Abnormal Liver Function (1.5x UL): **NNH 21**
- **Aside:** Could not find any RCTs with acetaminophen and chronic low back pain with responder analyses.
- **Bottom Line**:
  - Acetaminophen does not show benefit in patients with knee OA.

What's the evidence for Exercise induced OA?

- 1 SR (17 Observational Studies) 114,829 patients
  - Competitive runners compared to controls
  - **Includes:** professional runners, recreational runners, elite runners that represent their countries at competitions.

- **Results:**
  - **Overall Prevalence of Knee/hip OA:** 4% vs 10% Control
  - **Hip OA:** No difference
  - **Knee OA:** 32% in runners vs 38% with control

- Largest Study (16,961 patients) followed for 11 years
  - **Results:**
    - No association with exercise and OA
    - Exception: Men <50yo who run or walk >30km/week had increased risk of self reported Knee/Hip OA.

JT

What's the evidence for Exercise induced OA? (2)

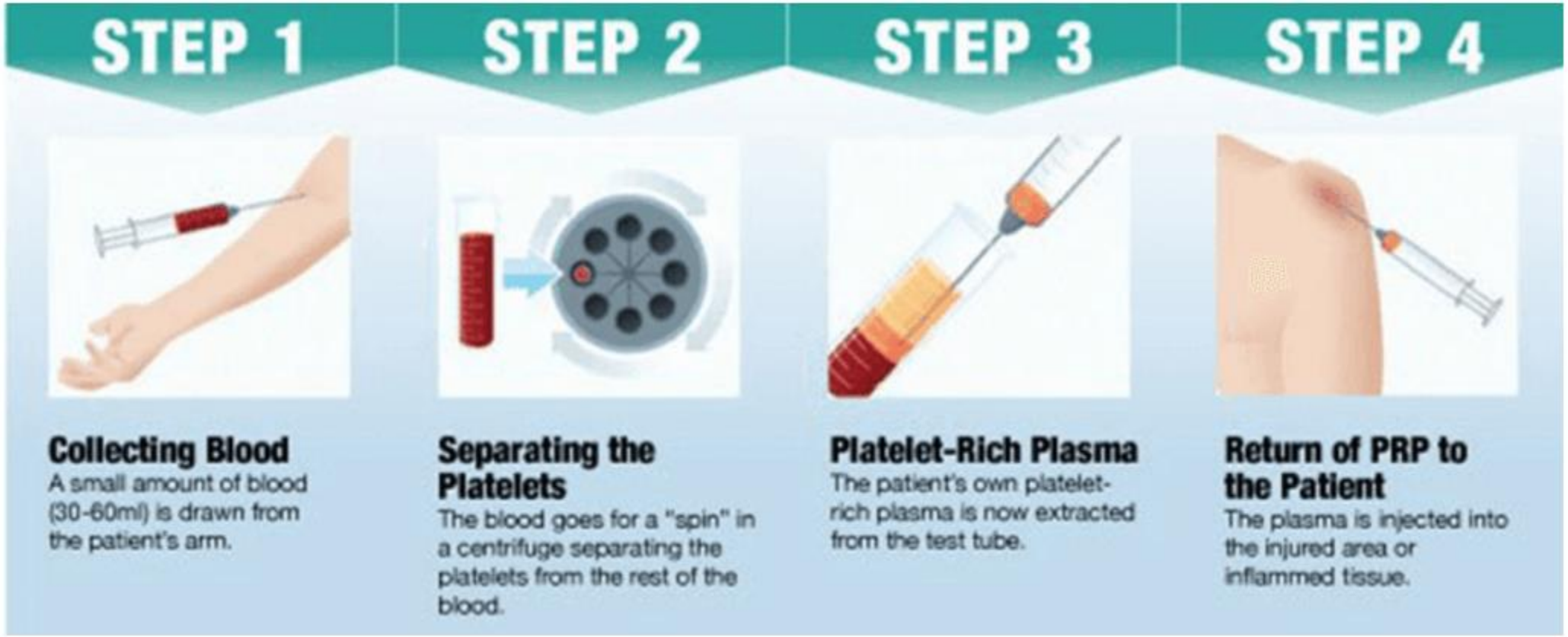
- **Context:**
  - Weak correlation between xray findings and OA symptoms.
  - Some evidence that suggests knee injuries are associated with development of knee OA.
  - Our OA Systematic review found exercise being the most effective treatment options.

- **Bottom Line:**
  - Observational evidence suggests running does not increase the risk of developing OA. Rather, runners may be at a lower risk of OA.
  - Exercise is an effective treatment for OA.

JT

How effective is PRP for Osteoarthritis?

- Refresher



JT

How effective is PRP for Osteoarthritis? (2)

5 RCTs (PRP vs Saline Injections for Knee OA)

- **1 RCT (123 patients, mean ~54yo, mostly early OA) [1]**
  - Groups (three injections total): PRP x3, PRP x1, Saline
  - Results at 6 months:
    - EQ-VAS (100-point scale) – Baseline ~50pts:
      - PRPx3 (71pts) versus PRP x1 (62pts) versus Saline (48pts)
      - Mean EQ VAS for Canada = 80

- **1 RCT (114 patients with Knee OA) [2]**
  - 3 weekly injections: PRP versus Saline
  - Results at 12 months:
    - WOMAC-Pain score (20-point scale) – Baseline ~10points
      - PRP (2 points) versus saline (9 points)

1. Gormeli 2017 2. Smith 2016 3. Patel 2015

JT

How effective is PRP for Osteoarthritis? (3)

- **1 RCT (78 patients with bilateral OA, broke up groups by knees)** [3]
  - PRP x2 injections (q3weeks) versus PRP x1 versus single saline injection
  - Results at 6 months:
    - WOMAC-Pain – Baseline ~10points:
    - PRP x2 (5pts) vs PRP x1 (6pts) vs Saline (10pts)

- **2 RCTs (both 3 weekly injections) :**
  - **One found PRP reduced pain on movement from (7.1 -> 2.8) vs saline (7.7 -> 5.2)**[4]
  - **Another found PRP reduced WOMAC-overall more than saline.**[5]

- **Adverse Effects:**
  - One study reported dizziness, nausea and pain/stiffness with injected knee.

1. Gormeli 2017 2. Smith 2016 3. Patel 2015 4. Elik 2019 5. Lin 2019

How effective is PRP for Osteoarthritis? (4)

- **Limitations:**
  - All single center studies (Two in Turkey, one in US, India and Taiwan)
  - Each author is known for PRP injections

- **Bottom Line:**
  - Current evidence suggests PRP reduces pain compared to saline injections.
  - Would like to see broader OA population studied.
  - Price likely a limiting factor for most.

Upcoming Webinars

Practical Talks for Family Docs

Tuesdays at 12:00 p.m. (ET)

- December 15, 2020– Deprescribing with Dr. Barb Farrell and Team
- January 19, 2021 – Diabetes Management with Dr. Mike Allan and Dr. Tina Korownyk
- February 23, 2021 – Eye Disorders in Primary Care with Dr. Simon MOore and Dr. Christine Richardson