Jeopardy for Pain

Rapid Answers to Pain Questions

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1

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2

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3

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  - Consulting fees, Patents, Others: N/A

4

JEOPARDY

5

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Osteoarthritis	Neuropathic Pain	Back Pain	Hodge Podge
Opioids	Opioids	Spinal Manipulation Techniques	Platelet Rich Plasma for Tendonitis
Acetaminophen	Gabapentin/ Pregabalin	Acetaminophen	CBD Ratios for Fibromyalgia
Glucosamine/ Chondroitin	Duloxetine/ Venlafaxine	Opioids vs Non-Opioids	Antihypertensives for Migraines
Visco-supplementation	Tricyclic Antidepressants	Cyclobenzaprine	Antidepressants for Migraine
Exercise	Cannabinoids	X-Rays	Pediatric MSK: Optimal Management?
NSAIDs	Capsaicin	Exercise	Opioid Use Disorder Risk and Opioids

End of Game

6

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Opioids for Osteoarthritis

- 1 SR (15 RCTs, n=6247);
- Oxycodone, tapentadol, oxycodone/naltrexone
- Outcomes
  - Pain relief: 47% opioids vs 43% plb, NNT 32
  - Quality: no effect if follow up after 4 weeks or in larger studies.
  - No publicly funded studies found.
- Adverse events
  - Pure opioids: dropout due to AE - RR 4.7 (3.5-6.2)
  - Tramadol: any AE (NNH 4), withdrawal due to AE (NNH 8), serious AE (NNH 39)
  - Tapentadol: any AE (NNH 7), study d/c due to AE (NNH 9)
- **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.**

7

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**
- **Other**: 8 SRs found a SMD 0.13-0.18 (MCID 0.37)
- **Bottom Line**:
  - Acetaminophen does not show benefit in patients with knee OA.

TFP #171, Herrero-Beaumont 2007, Miceli-Richard 2004

8

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Glucosamine for Osteoarthritis

- 1 SR (9 RCT, 1643 patients)
- Most common dosing: glucosamine 1500mg/d (divided TID)
- Outcome: Pain relief: 47% glucosamine vs 37% placebo, NNT 11
  - Industry funding:
    - Funded studies favored glucosamine: RR 1.62 (1.28-2.05)
  - Quality: Non-industry funded studies: glucosamine no different from placebo
  - Brand: benefit seen with Rotta brand formulations; non-Rotta brands do not show benefit
- Adverse events: composite of AE, GI AE – no different between groups

9

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Chondroitin for Osteoarthritis

- 1 SR (9 RCT, 2465 patients)
- Most common dosing: chondroitin 800-1200mg/day
- Outcome: Pain relief: 57% chondroitin vs. 45% placebo, NNT 9
  - Quality: RCTs not funded by industry have much smaller effect and not significant
    - Time of follow up has little effect. Larger trials have slightly less effect but still positive
- Adverse events: no difference between groups; placebo may have higher rates of serious/any AE

PEER. OA Syst Rev, in progress.

10

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Glucosamine and Chondroitin

Bottom line:

- **While glucosamine and chondroitin individually appear to provide greater pain relief vs placebo, industry funding and brand formulation may be driving most of the apparent benefit.**

11

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Viscosupplementation Injection for OA

- **SR**: 29 RCTs (5775 Patients), many 8-26 weeks, Mostly Knee OA, some hip OA
  - Hyaluronic Acid injections: single injection, 3x/weekly, 5x/weekly
- **Results:**
  - Patients with clinically meaningful response: 53% vs 44%
    - RR 1.22 (1.12, 1.33) **NNT 11**
  - Quality: trials without industry funding [RR 1.11 (0.73, 1.70)]
    - Smaller studies RR 1.65 (1.23, 2.22) vs large: RR 1.15 (1.07, 1.24)
    - Duration of follow up had no effect
- **Other:** 1 SR (89 RCTs) found pain reduction effect size: -0.37 (-0.46, -0.28)
  - MCID: -0.37 = 9/100mm
- **Bottom Line:**
  - Viscosupplementation injections did show benefit in patients with OA but higher quality and non-industry funded trials show none-less benefit.

TFP #89, Herrero-Beaumont 2007, Miceli-Richard 2004

12

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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:**
    - Patients with a clinically meaningful response: 47% versus 21% with no intervention
      - RR 2.36 (1.79, 3.12) **NNT = 4**
    - All trials had no industry funding
  - **Adverse Events:**
    - Overall AE and Withdrawal due to AE: No Difference
  - **Bottom Line:**
    - Exercise for management of OA is on of the most effective options for patients.

13

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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 (short vs intermediate vs long term).
  - **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.

14

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Opioids for Neuropathic Pain

- 4 SRs (5-31 RCTs) with 236-1769 patients in diabetic neuropathy, phantom limb pain, post-herpetic neuralgia. All versus placebo, for 4-12 weeks:
  - Morphine and oxycodone (MEQ 90-180mg/day):
    - ≥30% improvement pain relief: 57% versus 34%, NNT=5
  - Oxycodone (MEQ 7.5-180mg/day) as monotherapy and/or add-on
    - Moderate pain relief or much/very much improved on PGIC: 44% versus 27%, NNT=6
  - Morphine or oxycodone (MEQ 60-240mg/day)
    - Meta-analysis (reanalyzed by authors): Reduce pain 1.2/10 more than placebo
- Quality of life poorly reported.
- Adverse Events (Opioids versus placebo): Withdrawal due to AE: NNH=11-12
  - GI: Constipation (NNH=4-5), nausea (6), vomiting (12); CNS: dizziness (8), drowsiness/somnolence (6-7)
- **Bottom Line:** Opioids moderately reduce pain for approximately 1 in every 5-8 people over placebo in studies using high doses with multiple adverse events (some 1 in every 4-5 people). Considered only in patients with refractory pain after multiple therapeutic (drug and non-drug) trials.

TFP #214 June 2018

15

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Gabapentin for Neuropathic Pain

- 1 SR (18 RCTs, 4286 patients); duration 4-12 weeks
  - **Conditions include:** Post herpetic neuralgia (8), Diabetic neuropathy (7), mixed neuropathic pain (2), and nerve injury (1)
  - Gabapentin 600-3600mg versus placebo.
- **Outcomes:**
  - 30% Pain Improvement: 47% versus 28%, **NNT 6**
  - At least moderate improvement on IMMPACT occurred more with gabapentin
    - IMMPACT includes pain, physical functioning, emotional functioning, patient improvement rating, and symptoms.
    - PHN - RR 1.75 (1.49-2.07), PDN - RR 1.86 (1.53-2.27)
- **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**

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16

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Pregabalin for Neuropathic Pain

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

Outcomes:

- 30% pain improvement with pregabalin 150mg BID
  - PHN: 50% vs 25%, **NNT 4**
  - DN: 47% vs 42%, **NNT 22**
  - Higher doses produce greater response rates; 150mg/d ineffective except for PHN
- 30% pain improvement with pregabalin 300mg BID
  - Mixed: 48% vs 36%, **NNT 9**
  - Low quality evidence suggests benefit for central neuropathic pain 44% vs 28%, **NNT 6**
- No effect on HIV neuropathy;

Adverse Events: pregabalin 150mg BID

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

Derry, et al. Pregabalin for Neuropathic Pain in Adults. Cochrane Database, 2019.

17

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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 available between the two medications.

18

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Duloxetine for Neuropathic Pain

- Clinical Question: How safe and effective is duloxetine for the treatment of neuropathic pain?
- Compared to placebo: meta-analysis[1] (5 RCTs, 2589 diabetic peripheral neuropathy patients over 12 weeks):
  - ≥50% improvement in pain: duloxetine 46% vs. placebo 30% , NNT 7
    - Mean pain scores improved 2.66 with duloxetine and 1.62 on placebo (on 0–10 scale).
  - Adverse events leading to d/c: duloxetine 60 mg/day 13.9% vs. placebo 8.3%, NNH 18
    - Adverse events: nausea (NNH 9), somnolence (NNH 14), dry mouth (NNH 17), dizziness (NNH 21).
  - Increasing dose no advantage: no difference in response but more adverse events.

1. TFP #103: January 2018.

19

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What about venlafaxine?

- One Syst rev (6 RCTs, 460 patients):[1]
  - 80% participants had diabetic neuropathy
  - 4 of 6 studies reported some positive benefit for venlafaxine
  - Largest study (n=245)[2]
    - 50% pain reduction, 56% vs 34%, NNT 5 but selection bias limits confidence in results
  - Adverse effects similar between groups
- Limitations: small sample size(n=15-245), small number of studies, short duration (≤ 8 wk)
- **Bottom Line: Compared to placebo, duloxetine improves pain by ≥50% for one in seven people. One in 20 people over placebo will have to quit due to adverse events. There appears to be insufficient evidence to support routine use of venlafaxine for neuropathic pain at this time.**

1. Gallagher HC et al. Cochrane Database Syst Rev 2015; CD 011091.
2. Rowbotham MC et al. Pain 2004; 110(3): 697-706.

20

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Amitriptyline for Neuropathic Pain

- 3 systematic reviews, 2-15 RCTs, 58-948 patients 4-9 weeks.
  - Conditions include: PHN, DN, Mixed Neuropathy, Post-stroke
  - Amitriptyline 12.5mg-150mg versus placebo
- **Outcomes:**
  - Moderate (30%) Pain Improvement: ~40% vs 20% **NNT 6**
  - Global Impression - Moderate Improvement 64% vs 32% **NNT 4**
- **Adverse Events :**
  - Dry Mouth: 34% versus 6% **NNH 4**
  - Sedation: 34% versus 9% **NNH 4**
  - Withdrawal: 16% versus 7% **NNH 12**

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21

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Bottom Line

- Amitriptyline is effective for treating neuropathic pain.
- Side effects include dry mouth or sedation, occurring with 1 in 4 patients.
- Nortriptyline, imipramine and desipramine seem equally effective to amitriptyline.
- One small study suggests a trend towards less intolerable side effects with nortriptyline compared to amitriptyline.

23

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What about other TCAs?

- 1 crossover RCT (33 patients with post-herpetic neuralgia)
- Amitriptyline 10mg vs Nortriptyline 10mg
  - 5 weeks of medication, 2 week wash out, 5 weeks of other medication.
- **Results:** No statistical difference for pain, depression, sleep. Amitriptyline trended towards more intolerable AE (mostly dry mouth)
- Desipramine and imipramine found similar effectiveness to amitriptyline, however no head to head trials (differences in adverse events unknown)

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22

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Cannabinoids and Neuropathic Pain:
Pain Outcomes: 30% pain reduction & others

Type of Pain	Risk Ratio	Cannabis	Placebo	NNT
Chronic Pain	1.23 (0.98-1.56)	37%	31%	~19
Smoked, Neuropathic	1.62 (1.24-2.12)	47%	29%	6
Neuropathic	1.34 (1.04-1.74)	38%	30%	14
Cancer	1.35 (0.63-2.09)	NR	NR	NR
Palliative	1.34 (0.96-1.86)	30%	23%	~15
Chronic Pain	**1.37 (1.14- 1.64)**	**39%**	**30%**	**11**

- On a 0-10 point scale:
- Baseline ~6/10.
  - Placebo reduces things ~0.8
  - Cannabinoids:
    - 0.2 to 0.8

Can Fam Physician 2018 (submitted); 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.

24

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Type of AE	Cannabinoid Event Rate	Placebo Event Rate	NNH
Overall	81%	62%	6
Withdrawal	11%	~3%	14
Ataxia/Muscle Twitching	30%	11%	6
Blurred Vision/ Visual Hallucination	6%	0%	17
Central Nervous System	60%	27%	4
Disorientation/Confusion	9%	2%	15
Dissociation/ Acute Psychosis	5%	0%	20
Disturbance attention/ disconnected thought	17%	2%	7
Dizziness	32%	11%	5
Dysphoria	13%	0.3%	8
Euphoria	15%	2%	9
"Feeling High"	35%	3%	4
Hypotension	25%	11%	8
Impaired Memory	11%	2%	NS (12)**
Numbness	21%	4%	6
Psychiatric	17%	5%	9
Sedation	50%	30%	5
Speech Disorders	32%	7%	5

25

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Cannabinoids

- Bottom-line:
  - **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.
  - It is very unclear if one type medical cannabinoids is better but the best research is on nabiximol.
  - Lots of harms

26

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Capsaicin for Neuropathic Pain

- SR (7 RCTs, 1600 patients with various neuropathic pain conditions)
  - 0.075% topical capsaicin versus placebo
  - **Results at 6-12 weeks:** Clinical improvement not statistically different (42% vs 28% placebo)
- SR (6 RCTs, 656 patients):
  - **Results:** ≥50% pain improvement: **NNT 7**
- 1 RCT (33 patients with diabetic neuropathy): 0.025% vs placebo:
  - **Results:** No difference in patients achieving 30% pain reduction or pain score change
- **Adverse Events:** Burning, stinging or erythema **(NNH 3)**, Withdrawal due to AE **(NNH 8-9)**
- **Bottom Line:**
  - Evidence for topical capsaicin in neuropathic pain is highly inconsistent, with some studies showing clinical benefit while other studies show no benefit.
  - Local adverse effects (burning, stinging) in up to 60% of patients lead to one in 8-9 more stopping therapy.

TFP #225, Dec 2018

27

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Manipulating Spinal Manipulative Research

- >20 SRs of RCTs: If SMT authored: lower quality, but more positive
- RCT issues: low quality, SMT added to other interventions (exercise, meds), multiple analysis (91 in 1 SR!)[1]
- Acute LBP: examples of syst rev
  - 20 RCTs, ~2600 pts: 3/17 comparisons SS (One ↓ pain 0.6 in 1 month), No diff in recovery
  - 24 RCTs: 10mm pain improvement (100mm scale) but many limitations: non-blinded, absence of sham arm; multiple co-administered txs, authored by SMT providers[2]
- Chronic LBP: 26 RCTs, ~6,000 pts
  - 11/29 comparisons SS (↓ pain ~0.3-0.9 in 1 month)
  - Possibly ↑ recovery (best NNT: 11 @ 1 month)
- Function: minority comparisons benefit, ? clinically meaningful
- Bottom-Line: Research around SMT is poor, consistently inconsistent, and almost impossible to interpret. No reliable effects in acute LBP. Possible small effects in chronic LBP: pain (≤0.9 points out of 10) and recovery (1 in ~11 patients at one month) but two thirds of comparisons found no effect.

1. TFP # 181 Feb 2017
2. Paige NM, et al. JAMA 2017;317(14):1451-1460

28

SM

Can acetaminophen improve acute back pain?

- One high quality RCT: 1652 pts with acute back pain; ≈4000mg/d vs ≤4000mg/d PRN vs placebo
  - Mean age 45y, 53% men, baseline pain 6.3, days since onset of pain 10d
  - 4 wks: No effect on any outcome (Recovery, function, pain, sleep, etc.)
- 6 SR (3-10 RCTs, ≤1825 patients): acetaminophen
  - Vs placebo: no effect in acute back pain
  - Vs other treatments: (on 100 point scale)
    - NSAIDS better (~7.5 points) for pain
    - Amitriptyline or heat wraps better (~13 points) for pain
- Risk of Elevated Liver Enzymes (>1.5x normal): NNH 21
- **Bottom-line: Acetaminophen is not effective for back pain.**

#171 September 26, 2016.

29

SM

Chronic Back or OA Pain: Opioid vs Other

- RCT: 240 pts (mean 58y; 87% male), 1 yr, unblinded.
  - Opioids vs non-opioid (Aceta, NSAID; TCA, gabapentin, topical lidocaine/capsaicin; pregabalin/duloxetine, +/- tramadol). 65% back, 35% OA
- Primary Outcome: Function (scale or ≥30%) – No diff
  - Pain: start 5.4, down to 4 (opioid) vs 3.5 (SS). ≥30%= 41% vs 54% (NNT8)
  - QoL, visits, ED use, most measures = no difference.
  - Opioid: ≤15% pts on ≥50mg MEQ. Tramadol in 11% non-opioid.
  - AE: 2 vs 1 out of 19 score (SS). Discontinue med 19% vs 8%
- Bottom-Line: Comapred to opioids, non-opioid meds have similar or greater effectiveness, with less adverse events and better tolerability.

JAMA. 2018;319(9):872-882.

30

MA

Does Cyclobenzaprine improve improve Back Pain?

- Muscle relaxants vs placebo: 4 sys rev (9-46 RCTs, 820-5401 pts)[1,2]
  - Pain: ~12 points on 100 VAS at 10 d;
  - Pain target: NNT 4-7 at 2-7 days
  - Global efficacy improves (NNT 4 at days 2-4) but no meaningful effect on function[1]
- Cyclobenzaprine vs Placebo:
  - 1 Sys rev (14 RCTs, 3023 pts): Global improve, NNT 3 at ~14 days
  - 2 RCTs on Dosing: 1384 patients at 7 days
    - Backache: 50% 5mg TID vs 38% placebo, NNT 9 (No diff: 5mg vs 10mg)
  - 2 RCTs Extended or Immediate Release: 504 patients at 4 days
    - Global improve: NNT 7 (No diff: ER 30mg OD vs IR 10mg TID)
- Somnolence: 10% placebo, 29% for 5mg TID, 38% for 10mg TID
- No added benefit when cyclobenzaprine added to naproxen at 1 week follow up[3]
- Bottom-line: Cyclobenzaprine provides reduced pain and global improvement over placebo for one in every 3-9 patients in the first week. Cyclobenzaprine is as good or better than diazepam. Cyclobenzaprine 5mg TID is as effective as 10mg TID with less somnolence.

1. Shaheed CA et al. European J Pain 2017; 21: 228-37.
2. TFP #143. July 20, 2015.
3. Friedman BW et al. JAMA 2015; 314 (15): 1572-80.

31

MA

X-Rays for non-specific lower back pain

- Meta-Analysis (6 RCTs; 1804 pts; 0-44% with sciatica; 2 trials MRI/CT, 4 trials X-ray)
  - Good trials but high heterogeneity (except pain)
  - Short- and long-term outcomes of pain, function, QOL, mental health and patient satisfaction did not differ significantly
  - Pain @ 3 mos slightly worse with X-ray
- RCT (421 pts; low back pain ≥6 wks; followed 3 mos)
  - Pts. still in pain: 74% X-ray versus 65% placebo NNH 12
  - Pts. requiring follow-up with physician: 53% versus 30% NNH 5
  - Self-rated health: 5% worse in X-ray
  - ≥ 80% of both groups want X-ray; receiving X-ray = more satisfied
- Bottom-Line: In non-specific low back pain, X-rays do nothing to improve outcomes and may worsen some (such as pain).

TFP #17: July 13, 2016.

32

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Will exercise improve acute back pain?

- **Acute (<6 weeks):** Advice stay active vs bed-rest (4 RCTs):
  - Improved function 6/100 and reduced sick leave (mean 3.4 days).
  - Adding exercise to advice provided no additional benefit.
- **Chronic (>12 weeks):** Motor control exercises (strength/stability, often via physiotherapy) versus nothing
  - Reduces pain 10-13 points out of 100
  - Reduced recurrent back pain episodes by 50% over ½-2 years. NNT=4-8
  - Reduced the use of sick-leave over one year. NNT=6
  - Motor control ? better than other exercises, differences small (~4-8 points).
  - Others report: Aerobic activity (like running or walking) effective
- **Others:** Aquatic Exercise and Yoga are also effective
- **Bottom-line:** For acute back pain, exercise does not improve pain, but giving advice to stay active will improve function slightly and reduce sick days (by ~3 days). For chronic back pain, exercise (probably strength and stability with physiotherapy) reduces pain 10-13 points and prevents pain recurrence for 1 in 4 per year.

#170 September 12, 2016.

33

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PRP for Tendonitis

- **Chronic Lateral Epicondylitis**
  - 2 RCTs (28-60 patients): No difference in pain/function.
- **Adverse Events:** None reported in studies

- **Bottom Line:**
  - Best evidence shows no difference in pain, function or return to sport between PRP, dry needling, or saline for patients with Achilles tendinopathy, lateral epicondylitis, or rotator cuff tendinopathy.

35

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PRP for Tendonitis

- **Chronic Achilles Tendinopathy**
  - 3 RCTs looked at PRP injection vs saline injection
    - 1 RCT: Best RCT, 54 patients randomized to single injection PRP or saline
      - **Results at 6, 12 and 24 weeks:** No significant difference in pain, function, return to sport or patient satisfaction.
    - 2 RCTs: unblinded, 24-38 patients
      - Results:
        - Single injection PRP or saline: No difference in pain at 12 weeks
        - Four injections (q2weeks) PRP or saline: PRP improved pain on 100-pt scale at 6,12 and 24 weeks.
- **Rotator Cuff Tendinopathy:**
  - 2 RCTs, PRP vs saline or dry needling: No difference in pain or disability scores.

34

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CBD Ratios for Pain

4 RCTs (THC, CBD or combined versus each other or placebo)

- RCT (n=243, terminal cancer and weight loss)[1]
  - Results: No difference in appetite or adverse events
- RCT (n=177, refractory cancer pain on ~270mg morphine)[2]
  - Results: ≥30% pain reduction: 38% THC/CBD vs 21% THC, (NNT 6)
    - AEs not significantly different between THC/CBD and THC.
- RCT (n=48, brachial nerve injury with baseline pain ~7.5/10)[3]
  - Results: Both THC/CBD & THC pain ~1.3 better vs 0.6 placebo
    - AEs not significantly different between THC/CBD and THC.
- RCT (N of 1) n=24, chronic pain who benefits from THC/CBD[4]
  - Results: Patients with ≥ pain control vs THC/CBD (given before trial)
    - 38% THC/CBD vs 33% THC vs 17% CBD.

36

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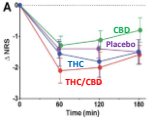
CBD Ratios for Pain

20 fibromyalgia – single doses 2 wks apart, x 4 products (cross-over)

1. 22% THC and <1%CBD: Received 100 mg with 22.4-mg THC + ≤1-mg CBD.
2. 6.3% THC and 8% CBD: Received 200 mg with 13.4-mg THC + 17.8-mg CBD.
3. 9% CBD and <1% THC. Received 200 mg with <1-mg THC + 18.4-mg CBD
4. Placebo

Results:

- Who got a ≥30% response,...
- 90% THC/CBD, 65% THC, 55% placebo, 40% CBD
- Drug High correlated with pain response
- THC had more "psychedelic" effects,
- Paranoid/anxiety and some AE (e.g. nausea) less with CBD



Bottom-Line: The effects are often not much over placebo, associated with being high & may depend on THC. CBD does have some less negative effects.

Pain. 2019 Apr;160(4):860-869.

37

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Anti-hypertensives for Migraine Prevention

- Sys Rev (58 RCTs, 5072 pts)
- Propranolol vs Placebo
  - 50% reduction: 57.1% vs 29.7% NNT 4
  - Stopping due to AEs: 4.1% vs 1.6% NNH 40
- Propranolol vs other beta-blockers or calcium-channel blockers
  - No consistent differences
- RCT (55 pts; Lisinopril 20mg/d vs placebo): reduced migraine days/mo, rescue meds, and headache severity
- RCT (57 pts; Candesartan 16 mg/d vs placebo): reduced frequency, use of sick leave, and rescue meds.
- Bottom-line: A number of hypertensive meds are effective in migraine prophylaxis. The best data are for propranolol, which will benefit 1 in 4, over placebo.

TFP #52: May 11, 2015.

38

MA

Antidepressants for Migraines

- 37 trials: 17 tension, 13 migraine, rest mixed, 3176 pts, mean age 40):
- Daily tricyclic antidepressants (TCAs) vs placebo:
  - 'Burden of headache' reduced (SMD -0.96 95% CI -1.39, -0.53)
  - 50% reduction in headaches: 38% vs 25% NNT 8
  - Both migraine/tension improved; benefit increased with time
  - Adverse events higher with TCAs (NNH 5); no diff. in withdrawal
- TCAs vs SSRI: TCAs superior
  - Another Meta found TCAs similar to SSRI in reducing headache frequency but TCA better tolerated.
- TCAs vs other agents: Limited data, however, direct comparison suggests TCAs>topiramate (2 trials) or beta blockers (3 trials)
- SSRIs/SNRIs: no evidence to support (11 trials, 585 pts)
- **Bottom Line:** Daily TCAs, particularly elavil, reduce headache severity and frequency for 1 in 8, vs placebo. They are effective regardless of headache type and benefit improves with time.

TFP #51: April 30, 2015.

39

MA

Pediatric MSK: Optimal pain management?

- Single Agents
  - 336 children (MSK injury; 54% fx), 60 minutes, pain scale: ibuprofen sig. better (-2.4) vs acetaminophen (-1.2) or codeine (-1.1)
    - 30% pain reduction: ibuprofen > acetaminophen (NNT 7) or codeine (NNT 9)
  - 134 children (uncomplicated fx), 24 hours, morphine versus ibuprofen: no difference in pain; less nausea with ibuprofen (NNT 5)
- Combinations: 2 RCTs (arm fracture or limb trauma)
  - 336 children, 3 days: acetaminophen + codeine vs. ibuprofen- no diff but ibuprofen less functional limitation and less AEs (NNT 5)
  - 81 children, 120 min: ibuprofen + codeine vs ibuprofen- no diff
- **Bottom Line:** Current evidence suggests that ibuprofen provides better single-agent relief than acetaminophen or codeine, and is at least equivalent to both acetaminophen with codeine and morphine for acute injury related pediatric pain, with fewer adverse events.

TFP #14: July 13, 2016.

40

SM

The Incidence of Iatrogenic OUD

- Clinical Question: What is the risk of developing OUD when taking prescription opioids?
- Syst rev (12 studies, n=310,408): pain patients prescribed opioid therapy (≥7d and 97% had ≥3mo)
  - Incidence of opioid dependence or "abuse": 3.1% in higher quality studies
    - 4.7%, if all studies included
  - Diagnostic criteria matter: incidence varies (1-11%) with diagnostic criteria
- Syst rev (24 studies, n=2507): chronic pain patients prescribed opioid therapy, avg exposure 26 mo (range: 2-240)
  - Incidence of opioid addiction was 3.3%
    - 0.2% in patients without a history of "substance abuse/addiction" versus 5% with positive history
  - Limitations: Addiction definitions; quality of trials included: retrospective (71%), prospective and/or randomized (29%); unclear pooling technique
- Two syst revs: incidence 0.3%-0.5% but generally lower risk patients

41

SM

The Incidence of Iatrogenic OUD

Context:

- Prevalence of OUD ranges: 0.05%-23%
- Wide variation: study quality, diagnostic criteria/terminol, inconsistent reporting, populations

- Most studies (using terms like "addiction" or "substance abuse") published before DSM-V criteria
- **Bottom Line: Incidence of OUD with prescribed opioids among chronic pain patients is ~3% (over ~2 years) but causation uncertain. Patients with no history of SUD - lower risk (<1%).**

42

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43