Musculoskeletal Medicine

Evidence Update

2017

Rapid Critical Summary

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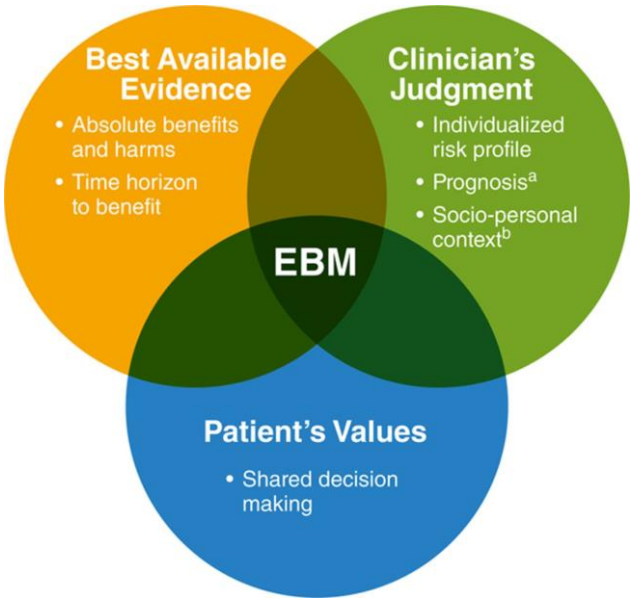

Evidence relevant to musculoskeletal medicine published between October 2016 and October 2017

The PCR - Improving MSK Medicine & Rheumatology

Keele University

Contents

Abbreviations

AE: Adverse effect.
BMI: Body mass index.
MA: Meta-analysis.
MD: Mean difference: the difference in the means between groups in a study.
NRS: Numeric rating scale: an outcome measure, using a numeric range of 0-10 or 0-100.
OA: Osteoarthritis
ODI: Oswestry Disability index: an outcome measure, specific to physical function of the back.
OR: Odds ratio: the ratio of odds in the groups in a study.
PICO: Population, Intervention (exposure), Comparator, Outcome.
RMDQ: Rolland Morris disability questionnaire, an outcome measure, specific to physical function of the back.
RCT: Randomised controlled trial.
RR: Risk ratio: the ratio of risks in the groups in a study.
SMD: Standardised mean difference: similar to MD, but it takes into account the variation at baseline (the standard deviation).
SR: Systematic review.
VAS: Visual analogue scale, similar to NRS, but uses a visual line from 0-10 or 0-100 rather than numbers.
WOMAC: The Western Ontario and McMaster Universities Arthritis Index: an outcome measure used in OA trials, and it is a composite of 3 components measuring pain, joint function and joint stiffness.

Osteoarthritis

The role of muscle strengthening in exercise therapy for knee osteoarthritis: A systematic review and meta-regression analysis of randomized trials. Bartholdy C. et al. Semin. Arthritis Rheum. 2017.

Study type: SR and meta-regression analysis.

Conclusion: Muscle strengthening exercises do not help improve pain or function in patients with knee OA, although they improve knee extensor muscle strength. An increase of at least 30% in knee extensor strength is required to be clinically beneficial in terms of pain and function.

P RCTs in patients with knee OA.
I American College of Sports Medicine (ACSM) interventions (exercises that aim at increasing muscle strength according to the ACSM guidelines)
C Not-ACSM interventions.
O Knee extensor muscle strength, pain and functional disability.

Definition of ACSM exercise: A voluntary contraction against an external resistance typically performed in especially designed equipment or with free weights. The external load should be above 40% of 1 repetition maximum (1RM) corresponding to very light to light intensity, and the exercises performed in 2–4 sets of 8-12 repetitions, preferably to contraction failure or muscular exhaustion. The exercise program should consist of at least 2–3 sessions per week.

Findings: 45 RCTs (n=4699). Age: average 64 years. 22 ACSM interventions and 34 non-ACSM interventions.
The 22 ACSM interventions had a median exercise period of 8 weeks (range: 4–120) with an average of 3 sessions per week (range: 2–7). The median number of exercise sets was 3 for each exercise with an average of 10 repetitions and a load of minimum 40% of 1RM.
The 34 non-ACSM interventions had an average exercise period of 8 weeks (range: 4–104) with a median of 3 sessions per week (range: 2–7).

- A statistically significant difference favouring ACSM interventions with respect to knee extensor strength [SMD: 0.448 (95% CI: 0.091 to 0.805)].
- No differences regarding pain and disability.
- The meta-regressions indicated that increases in knee extensor strength of 30–40% would be necessary for a likely concomitant beneficial effect on pain and disability, respectively.

Cautions

- Quality of included studies was poor, with particularly high risk of bias related to blinding, randomisation and concealment of allocation to treatment.
- Although the results showed benefit for muscle strengthening exercises on muscle strength, they didn't show clinical benefit in terms of pain and function, which are arguably more relevant to patients benefit.
- AEs not reported.

Notes and linking with current guidelines

- This is a well-conducted systematic review that included a relatively large number of studies.
- The review addressed a relevant question to test whether exercises that are recommended by the ACSM and that aim at muscle strength are superior to other types of exercises. The answer, notwithstanding the poor quality of included studies, was that they are not.
- NICE guidelines 2014 (Osteoarthritis: care and management) recommend exercise as a core non-pharmacological treatment and recommends that "exercise should include local muscle strengthening and general aerobic fitness." The specific mention of 'muscle strengthening' was not linked to a specific evidence.

Exercise for hand osteoarthritis. Osteras N. et al. Cochrane Database Syst.Rev., 2017

Study type: SR & MA of RCTs.

Conclusion: Low-quality evidence for small beneficial effects of exercise on hand pain, function and finger joint stiffness. The clinical relevance is not clear. Reporting on AE is poor.

P RCTs on exercises for hand OA.
I Therapeutic exercise for hand OA
C No exercise or different exercise programmes for hand OA
O Hand pain (0-10 VAS) and hand function (various scales).

Findings: 7 RCTs (n=534).

- **Pain intensity:** Low-quality evidence (5 trials, n=381): pain reduced (SMD: -0.27, 95% CI -0.47 to -0.07). The absolute reduction in pain was 5% (1% to 9%). Significant.
- **Function:** Low quality evidence (4 trials, n=369): function improved (SMD -0.28, 95% CI -0.58 to 0.02). The absolute improvement 6% (0.4% worsening to 13% improvement). Not statistically significant.
- **Finger joint stiffness:** Low quality evidence (4 trials, n=369): stiffness reduced (SMD -0.36, 95% CI -0.58 to -0.15). The absolute reduction: 7% (3% to 10%).
- **AEs:** Low quality evidence (3 trials): intervention-related AEs and withdrawals due to AEs: increased finger joint inflammation and hand pain. An increased likelihood of AEs (risk ratio (RR) 4.55, 95% CI 0.53 to 39.31).

Cautions

- A small number of studies included.
- Quality of included studies low.
- Participants not blinded to treatment allocation, and although most studies reported blinded outcome assessors, main outcomes (pain, function, stiffness and quality of life) were self-reported.
- The exercise intervention varied in terms of dosage, content and number of supervised sessions.
- Reported adherence to the exercise programmes was poor.

Notes and linking with current guidelines

- This well conducted review illustrates the dearth of trials on hand OA, and in particular on exercise as a treatment. The question on the benefit of exercise for hand OA remains, therefore, unanswered.
- The NICE guidelines 2014 (Osteoarthritis: care and management) recommend exercise as a core treatment for OA, without a reference to a specific joint.

The Effectiveness of manual therapy for relieving pain, stiffness, and dysfunction in knee osteoarthritis: a systematic review and meta-analysis. Xu Q. et al. Pain Physician. 2017.

Study type: SR & MA of RCTs.

Conclusion: Evidence is not clear on whether manual therapy (MT) is an effective treatment for Knee OA, mainly due the wide varieties of this type of treatment. Reporting on AEs is poor.

P RCTs on MT in patients with knee OA.
I MT (massage, manipulation, joint mobilization, osteopathy, Maitlan joint mobilization, Swedish massage, Chinese tuina, self-massage, acupressure, manipulation, and manual stretching).
C Sham therapy
O WOMAC scale and AEs

Findings: 14 RCTs (n=841, 72% women). Duration of each treatment session ranged from 20 to 60 minutes, treatment frequency ranged from once a week to 7 times a week, and total treatment duration ranged from 2 to 12 weeks.
Quality of RCTs, moderate.
Effectiveness:
-MT had statistically significant effects, relieving pain, stiffness and function.
-In the subgroups, MT was only effective when more than 4 weeks overall duration.
-The long-term information for MT was insufficient.
AEs:
-Only 1 RCT reported that one participant felt increased discomfort and refused to complete the assessment. 7 studies (53.8%) did not report on AEs. The remaining 6 studies (46.2%) stated that no AEs occurred.

Cautions

- Heterogeneity in types of MT, which makes the overall conclusion unclear and difficult to apply in practice in which particular types of MT might be used.
- AEs poorly reported.

Notes and linking with current guidelines:
-This review conducted an extensive search of the literature on the subject to answer the relevant question of the benefit of manual therapy for knee OA.
- NICE guidelines 2014 (Osteoarthritis: care and management) recommend manual therapy ".. should be considered as an adjunct to core treatments, particularly for osteoarthritis of the hip." This, therefore, raises the question of whether manual therapy is not beneficial on its own, but only as an adjunct therapy.

Effect of physical activity and dietary restriction interventions on weight loss and the musculoskeletal function of overweight and obese older adults with knee osteoarthritis: a systematic review and mixed method data synthesis. Alrushud A. S. et al. BMJ Open, 2017

Study type: SR & Mixed method data synthesis

Conclusion: No sufficient or good quality evidence to answer the question.

P RCTs. Participants with BMI ≥25 kg/m2, age ≥55 years and with radiographic evidence of knee OA.
I Physical activity plus dietary restriction programmes.
C Usual care (including advice or physical activity alone or dietary restriction alone) or exercise
O Body weight, BMI, MSK function (self-reported or objective functional performance measures).

Findings: 1 pilot and 2 definitive RCTs.

- Meta-analysis was only possible to evaluate one outcome measure (mobility, 6 min walk test) at one time point (6 months) in 2 trials, and the pooled mean difference 15.05 (95% CI −11.77 to 41.87) was not statistically significant.

Cautions

- Meta-analysis was only possible on a secondary outcome and at one time point.
- Trials quality was not high.
- The outcome for which meta-analysis was done was not the primary outcome.
- The narrow and specific question this review tried to find evidence for should not be mixed with the question of the benefit weight loss on OA.

Notes and linking to current guidelines

- This is a well conducted systematic review, and the rationale for the apparently narrow focus on its target population (older overweight/obese adults) is that this population would be the most likely to benefit from such a low risk intervention, given their likely comorbidities.
- The evidence for the benefit of weight loss (among obese patients) on the progression and clinical symptoms of OA is strong.
- NICE guidelines 2014 (Osteoarthritis: care and management) recommend offering interventions to achieve weight loss in patients who are overweight or obese, but they do not specify the interventions or the approach.

Celecoxib for osteoarthritis. Puljak L. et al. Cochrane Database of Systematic Reviews 2017.

Study type: SR & MA of RCTs

Conclusion: No clinically important difference between celexocib and placebo and between it and other NSAIDs in reducing pain or improving function. Evidence on AEs is not clear.

P RCTs in participants with clinically or radiologically confirmed primary OA of the knee or hip, or both knee and hip.
I Celecoxib
C No intervention, placebo or another traditional NSAIDs.
O WOMAC scale for pain and function.

Findings:

- 36 RCTs (n=17,206: 9402: celecoxib 200 mg/day, and 7804: either NSAIDs (n = 1869) or placebo (n = 5935). Celecoxib vs placebo (32 trials), vs naproxen (6 trials) vs diclofenac (3 trials). Mean OA duration 7.9 years, mean age 62 (± 10) years; most participants women.
- **Celecoxib vs placebo**
    - **Pain** (4 studies, n=1622): slightly reduced: absolute improvement 3% (95% CI 2% to 5%), relative improvement 12% (95% CI 7% to 18%). This improvement is not clinically significant (high quality evidence).
    - **Function** (4 studies, n=1622): slightly improved: absolute improvement 4% (95% CI 2% to 6%), relative improvement 12% (95% CI 5% to 19%) This improvement is not clinically significant (high quality evidence).
    - **AEs:** very low quality evidence to draw any meaningful conclusions, due to serious imprecision and study limitations.
- **Celecoxib vs NSIADs**
    - **Pain:** Inconclusive results: absolute improvement 5% (95% CI 11% improvement to 2% worse), relative improvement 11% (95% CI 26% improvement to 4% worse) (2 studies, n=1180, moderate quality evidence due to publication bias).
    - **Function:** Celecoxib slightly improved physical function: absolute improvement 6% (95% CI 6% to 11% improvement) and relative improvement 16% (95% CI 2% to 30% improvement). *This improvement may not be clinically significant (low quality evidence due to missing data and few participants) (1 study, n=264).*
    - **AEs:** Results inconclusive for withdrawals due to AEs, gastro-intestinal events, and cardiovascular events.

Cautions

- Oral Celecoxib is not commonly used in the UK.
- Overall evidence quality is poor.
- Most trials had high attrition rates, with evidence of selective reporting in a third of the studies.
- The available evidence FOR AEs is poor and not all data was available from all relevant studies.
- Pharmaceutical industry involvement. Of 36 studies, 34 reported funding by drug manufacturers and in 34 studies one or more study authors were employees of the sponsor.
- Warning already published of increased risk of cardiovascular events with celecoxib.

Notes and linking with current guidelines

- This is a well conducted systematic review that although included a large number of trial, they were of poor quality and incomplete data.
- NICE guidelines 2014 (Osteoarthritis: care and management) recommend, under pharmacological interventions for OA, to offer "paracetamol and/or topical NSAIDs ahead of oral NSAIDs, cyclo-oxygenase 2 (COX-2) inhibitors or opioids."

The effect of vitamin D supplementation on keen osteoarthritis: A meta-analysis of randomized controlled trials.
Gao X. et al. Int.J.Surg. 2017.

Study type: SR & MA of RCTs.

Conclusion: No strong evidence that vitamin D supplementation is beneficial in treating knee OA.

P RCTs in patients with knee OA.
I Vitamin D supplementation
C Placebo
O WOMAC (pain, function, stiffness), tibial cartilage volume, serum vitamin D levels, and AEs.

Findings: 4 RCTs (n=1136). Daily dose of vitamin D varied greatly (800 IU to 60,000 IU).

- All 4 RCTs of low risk of bias (high quality).
- A daily supplement of > 2000 IU significantly reduced WOMAC pain & function (but not stiffness) than placebo, whereas the dose of < 2000 IU did not.
- No benefit regarding OA joint progression (2 RCTs).
- Only in 3 RCTs data on Vit D level were reported as an outcome.

Cautions

- A small number of studies, with significant heterogeneity in dosages used.
- It is not clear at which level supplementation is most beneficial.
- It is not clear how sustainable the effect of Vit D supplementation is.
- Hypercalcaemia was one of the common adverse effects of high doses of Vit D.
- Monitoring strategies are not clear.

Notes and linking with current guidelines

- This review is one of many that summarised the evidence for a link between Vit D (and its deficiency) and various MSK conditions (fibromyalgia, LBP, OA, CWP etc).
- The review is of good quality.
- NICE guidelines 2014 (Osteoarthritis: care and management) is silent on the role of Vit D in OA management.
- NICE guidelines 2014 (Vitamin D: supplement use in specific population groups) do not mention OA as a target population to consider for supplementation.

Cost-effectiveness of surgical interventions for the management of osteoarthritis: a systematic review of the literature. Kamaruzaman H. et al. BMC Musculoskelet.Disord. 2017

Study type: SR & MA of RCTs and observational studies.

Conclusion: Total knee arthroplasty (TKA) & total hip arthroplasty (THA) are cost-effective and lead to improvement in quality of life of patients.

P Clinical trials or cohort studies that assessed surgical, non-pharmacological and pharmacological interventions for knee or hip OA that included economic evaluations.
I Surgical interventions (TKA & THA).
C Any comparators (no interventions, usual care, and other surgical modalities)
O Any outcomes for economic evaluations (cost effectiveness, incremental cost-effectiveness ratio or ICER)

Findings: 23 studies (6 RCTs).

TKA

- **TKA vs non-operative/nonsurgical strategies:** 4 studies, all concluded that TKA is cost-effective.
- **TKA vs other treatments:** 1 study (over lifetime): TKA is cost-effective.
- **Early vs delayed TKA** (with and without a non-operative bridge): early TKA is more cost-effective than waiting for TKA without non-operative bridge.

THA

- **THA vs non-operative strategy:** 1 study: THA is cost-effective.
- **THA vs 'do nothing (over lifetime):** THA is cost-effective.
- **Early and delayed THA:** early THA is cost-effective across groups based on age and sex

Cautions

- Small number of studies included in each comparison subgroup.
- The majority of studies are observational studies, not clinical trials. Although this is not uncommon in conducting cost analysis, it is problematic in comparing interventions.
- Heterogeneity in methods estimating cost effectiveness.
- Cost-effectiveness of interventions depends on the population that is considered and the interventions that were compared with, and both of these areas varied among included studies.

Notes and linking with current guidelines

- NICE guidelines 2014 (Osteoarthritis: care and management) recommend referring for surgery patients with OA that has significant impact on their daily life, but before there is prolonged and established functional limitation and severe pain.

Knee arthroscopy versus conservative management in patients with degenerative knee disease: a systematic review. Brignardello-Petersen R. et al. BMJ Open. 2017.

Study type: SR of RCTs and observational studies (An update of previously published review).

Conclusion: Compared with conservative management, knee arthroscopy does not provide significant benefits in pain or function, especially in the long term. Evidence for AEs is not clear.

P For effects: RCTs; for complications: RCTs and observational studies, in patients with degenerative knee disease.
I Arthroscopic surgery
C Conservative management strategy (including sham surgery)
O Pain (0-100 VAS), function (0-100 VAS), AEs.

Findings: 13 RCTs and 12 observational studies included (n > 1.8 million!)

- **Pain:** high quality evidence that knee arthroscopy results in a very small reduction in pain up to 3 months (mean difference =5.4, 95% CI 2.0 to 8.8) and very small or no pain reduction up to 2 years (mean difference =3.1, 95% CI −0.2 to 6.4) when compared with conservative management.
- **Function:** moderate quality evidence that knee arthroscopy results in a very small improvement in the short term (mean difference =4.9, 95% CI 1.5 to 8.4) and very small or no improved function up to 2 years (mean difference =3.2, 95% CI −0.5 to 6.8).
- **AEs:** low-quality evidence suggested a very low probability of serious complications after knee arthroscopy.

Cautions:

- Reduction of 5 points on a 0-100 scale for pain and function is very small and not clinically meaningful.
- Evidence for AEs is based only on observational studies, and not RCTs, which raises the risk of bias due to possible confounding and uncertainty on of causality and direction.

Notes and linking with current guidelines

- This is a well-conducted systematic review that included a large number of studies to answer the question.
- This review should provide a sufficient, strong and final evidence that arthroscopic surgery should not be offered for knee OA.
- NICE guidelines 2014 (Osteoarthritis: care and management) states: “Do not refer for arthroscopic lavage and debridement as part of treatment for osteoarthritis, unless the person has knee osteoarthritis with a clear history of mechanical locking (as opposed to morning joint stiffness, 'giving way' or X-ray evidence of loose bodies).

The association of recreational and competitive running with hip and knee osteoarthritis: a systematic review and meta-analysis. Alentorn-Geli E. et al. J.Orthop.Sports Phys.Ther. 2017

Study type: SR & MA of observational studies

Conclusion: Based on observational studies, recreational runners had a lower occurrence of OA compared with competitive runners and sedentary individuals.

P Observational studies investigating the occurrence of OA of the hip and/or knee among runners.
I Runners: “Competitive”: professional/elite athletes or participated in international competitions; “Recreational”: running in a nonprofessional (amateur) context.
C Sedentary, non-running individuals
O Prevalence rate and odds ratio (OR) (with 95% CI) for OA between runners (at competitive and recreational levels) and controls.

Findings: 25 studies (n = 125 810) included, 17 (n = 114 829) meta-analysed.
Overall prevalence of hip and knee OA:

- 13.3% (95% CI: 11.6%, 15.2%) in competitive runners,
- 3.5% (95% CI: 3.4%, 3.6%) in recreational runners,
- 10.2% (95% CI: 9.9%, 10.6%) in controls.

OR for hip and/or knee OA in competitive runners > OR in recreational runners (OR 1.34; 95% CI: 0.97, 1.86 and 0.86; 95% CI: 0.69, 1.07, respectively; controls as reference group; P<.001).
Exposure to running of less than 15 years was associated with a lower association with hip and/or knee OA compared with controls (OR = 0.6; 95% CI: 0.49, 0.73).

Cautions

- The evidence is on association. Causation and direction couldn't be established.
- Studies included were heterogonous in their methodology, including longitudinal cohorts, case-controls and cross sectional studies.
- Not all studies included control comparisons.
- Not all potential confounders were accounted for, such as previous injury.
- 'Exposure to running' was not reported in all studies. This is important and considered as the 'dose' of running.

Notes and linking to current guidelines

- This is a well-conducted systematic review that included a large number of observational studies.
- Although the evidence is for association not causation, this is the right study design for this type of evidence.
- The finding of high prevalence of OA among sedentary controls compared with recreational runners is interesting, as it raised questions about the role of mechanical loading and inflammation in OA pathogenesis.

Prevalence of neuropathic pain in knee or hip osteoarthritis: A systematic review and meta-analysis. French H.P. et al. Semin. Arthritis Rheum. 2017.

Study type: SR & MA of observational studies.

Conclusion: 23% of patients with hip/knee OA also have neuropathic pain. But, estimate should be interpreted with caution and is likely considered as an over-estimate in this population.

P Observational studies which measured neuropathic pain in people aged 18 years and older with hip or knee OA.
O Prevalence estimates.

Findings: 9 studies (n=3032), 8 knee OA, 1 hip OA. Setting: general population, hospital and community settings. Identification of neuropathic pain based on self-report questionnaires, the Pain DETECT questionnaire (PDQ).

- Overall prevalence estimate: 23 % (95%CI: 10–39%).
- Considerable heterogeneity (I^2 = 97.9%).
- This estimate was largely unchanged with subgroup analyses based on index joint, questionnaire type, setting and consideration of other potential causes of neuropathic pain.

Cautions

- OA diagnosis: a range of diagnostic methods used, most commonly self-reported pain and stiffness, only 1 study reported using standardised ACR OA diagnostic criteria.
- Neuropathic pain diagnosis: self-reported in 8 studies (using the PDQ) (& the clinician administered Douleur Neuro- pathique (DN4)).
- Studies quality: moderate to high risk of bias, i.e. poor quality.

Notes

- This is a well conducted systematic review, and included studies of the correct design to answer this question of association.
- Notwithstanding the important cautions mentioned above, this evidence should raise awareness of the co-existence of neuropathic pain in patients with OA, as this might have important implications.
- NICE guidelines 2014 (Osteoarthritis: care and management) does not include under pharmacological interventions any recommendations on the use of medications that are used for neuropathic pain.

Is body mass index associated with patellofemoral pain and patellofemoral osteoarthritis? A systematic review and meta-regression analysis. Hart H.F. et al. Br.J.Sports Med. 2017.

Study type: SR & Meta-regression analysis of observational studies.

Conclusion: Higher BMI is associated with PFP and PFOA in adults, but not in adolescents with PFP.

P Cross-sectional, observational and interventional studies reporting BMI in individuals (adults & adolescents) with PFP or PFOA compared with healthy controls.
O BMI in patients with PFP & PFOA

Findings: 52 studies (39 case–control, 10 prospective, 3 intervention).

- Greater BMI in adults with PFP compared with healthy controls (33 studies) (SMD: 0.24, 95% CI 0.12 to 0.36, small effect), and PFOA (0.73, 0.46 to 0.99, moderate effect), but not in adolescents with PFP (2 studies only) (−0.19, −0.56 to 0.18).
- No significant link between BMI and intervention outcomes in adults with PFP (3 studies).

Cautions:
This evidence is based mainly on observational studies and therefore subject to the influence of possible confounders and lack of directional clarity, i.e. which is leading to the other? PFP/PFO to higher BMI or vice versa?

Notes and linking with current guidelines:

- The rationale for the question behind this review is that increase in BMI might be particularly damaging to the PF joint leading to PFP and later to PFOA. The evidence summarised by the review, however, did not support this rationale.
- Evidence, mainly based on observational studies, pointing to weight as a risk factor for weight bearing joint OA.
- NICE guidelines 2014 (Osteoarthritis: care and management) do not specify PFP or PFOA as a specific category.

Efficacy of tailored exercise therapy on physical functioning in patients with knee osteoarthritis and comorbidity: a randomized controlled trial. de Rooij M. et al. Arthritis Care.Res. 2017.

Study type: RCT – USA - secondary outpatient rehabilitation centre.

Conclusion: Tailored exercise is efficacious and safe in patients with knee OA and severe comorbidities.

P Patients with a clinical diagnosis of knee OA (n-126, 63 in each arm), with at least 1 comorbidity: coronary disease, heart failure, type 2 DM, COPD, or obesity (BMI =>30 kg/m2), with severity score =>2 on the Cumulative Illness Rating Scale (impact on daily activities and patient receiving regular care for the comorbid disease).

I - **20-week individualized knee OA exercise**, with 2 sessions of 30–60 minutes per week under the supervision of a PT; consisted of muscle-strength training of the lower extremity, aerobic training, and training of daily activities.

- **Comorbidity-related adaptations** were made by applying restrictions to duration, frequency and intensity of exercises. During every training session, comorbidity-related symptoms and clinical parameters were monitored, and exercise adapted.
- **Education on knee OA** was provided, and participants were encouraged to perform exercises at home at least 5 times a week.

C Usual care, and placed on a waiting list for a period of 32 weeks for the active intervention.
O WOMAC, subscale physical functioning (WOMAC-pf), and the 6-minute walk test (6MWT): (baseline, after 20 weeks (directly post-treatment), and at 3 months post-treatment).

Findings

Directly after treatment:

- **WOMAC –**pf: statistically significant differences in favour of the intervention, mean difference 7.43 95% CI 9.99, 4.87, P< 0.001.
- **6MWT:** statistically significant differences in favour of the intervention, mean difference 34.16, 95% CI 17.68, 50.64, P< 0.001.

At 3 months:

- Mean improvements in the intervention were 33% on the WOMAC scale and 15% on the 6MWT.
- **These improvements are of clinical relevance.**

No serious AEs.

Cautions

- OA diagnosis at entry clinical only, might bring doubt into its accuracy? However this should be the same in both arms of the RCT and might not cause bias but might affect applicability of the results.
- Most participants had mild OA (0/1 OA radiological severity than 4).
- Confirmation of the medical diagnosis was obtained by history and medication prescription.
- Obesity was the most common co-morbidity.
- Drop out at end of study: 19% in intervention, 11% control – some imbalance.
- Cost? This was not studied and is important.
- Applicability of the intervention in clinical practice?

Notes and linking with current guidelines

- NICE guidelines 2014 qualify their recommendations for exercise that *".. the clinician needs to make a judgement in each case on how to effectively ensure participation. This will depend upon the person's individual needs and circumstances ...".*

Post-acute rehabilitation after total knee replacement: a multicenter randomized clinical trial comparing long-term outcomes. Fransen M. et al. Arthritis Care.Res. 2017.

Study type: RCT – Australia - 12 public and private hospital centres.

Conclusion: Post-acute group exercise program did not result in greater reductions in long-term knee pain or activity limitations than usual care. Patients undergoing primary TKR retain marked physical performance deficits 12 months after surgery.

15% of patients report ongoing moderate-to-severe pain in the operated knee for many years after TKR.
25% of patients fail to achieve a minimum clinically important improvement in function 6 or more months after TKR.
20% of patients still report moderate-to-severe activity limitations 2 years after TKR.
Early or acute rehabilitation: during the admission period or in the first 1 or 2 months after TKR:
Late or post-acute: commencing after 2 months.

P =422 (I: 210, C: 212), age 45–75 years, underwent primary TKR (uni-or bilateral). Wound healed, full weight-bearing on the operated leg, ambulating independently outdoors for more than 50 meters, and not requiring daily opioid based analgesics for pain.
I Exercise: Twice-weekly, 1-hour group exercise classes for at least 8 weeks. Each class consisted of a short warm-up and cool-down component, progressive functional and strengthening exercises, and a 20-minute monitored aerobic exercise session on a stationary bicycle
C Usual care
O WOMAC (pain and activity limitations) at 12 months after surgery.

Findings: at 12 months:

- No significant differences in treatment-responders between groups: 69% and 72% of participants in post-acute exercise and usual acute care arms, respectively.
- Marked deficits in physical performance measures remained.

Cautions

- Inclusion criteria are rather strict. However, even with such strict criteria the intervention was not found to be effective!
- Only approximately 50% of participants attended the full program of 16 classes. Still, a subgroup "per protocol" analysis restricted to the 140 participants attending at least 12 of the post-acute exercise classes did not detect a significant benefit compared with usual acute care for any of the outcome measures.

Notes

- This is a good quality large RCT that showed no benefit for immediate post TKR rehabilitation.
- The area of the timing of rehabilitation following TKR is challenging as there is no evidence for the optimum timing and therefore currently no agreed guidelines, but rather a wide variety of approaches adopted by various providers.

Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. McAlindon T.E. et al. JAMA, 2017.

Study type: RCT – USA - Patients recruited through clinics and local advertisements.

Conclusion: In patients with symptomatic knee OA, 2 years of intra-articular triamcinolone (every 3 months), compared with intra-articular saline, resulted in significantly greater cartilage volume loss and no significant difference in pain.

P n=140 (70 in each arm) (mean age, 58 years, 54% women), with symptomatic knee OA, Kellgren-Lawrence grades 2 or 3 and with USS features of synovitis.
I Ultrasound guidance: 1 mL intra-articular triamcinolone every 12 weeks for 2 years. No local anaesthetic.
C Ultrasound guidance: 1 mL intra-articular saline every 12 weeks for 2 years. No local anaesthetic.
O Annual knee MRI (quantitative evaluation of cartilage volume), and WOMAC.

Findings: n= 119 (85%) completed the study.

- Cartilage thickness: significantly greater cartilage volume loss with triamcinolone than saline: mean difference: −0.11 mm; 95%CI, −0.20 to −0.03 mm, which corresponds to a moderate effect size of 0.46 mm.
- Pain: no significant difference: −1.2 vs −1.9; mean difference, −0.6; 95% CI, −1.6 to 0.3.
- AEs: the triamcinolone group had 5 treatment-related AEs compared with 3 in the saline group and had a larger increase in HbA1c levels (between-group difference, 0.2%; 95%CI, 0.5% to 0.007%).

Cautions

- This is a 'proof-of-concept' study, i.e. it assesses a fact which is the effect of steroid on cartilage.
- The results is for 3 monthly injections. But it is not clear how it applies to injections that are not this frequent?

Notes and linking to current guidelines:

- Evidence from this study echoes in-vivo and clinical evidence that indicates the general catabolic effects of corticosteroids.
- The hypothesis that intra-articular corticosteroids might reduce the rate of cartilage loss and other structural manifestations of OA is based on the role of inflammation in its pathogenesis, and reduced structural progression observed in-vivo.
- However, the results of this study show intra-articular corticosteroid injection led to greater progression of knee cartilage volume loss and no sustained effect on intra-articular inflammation.
- The results raise questions about the role of inflammation in OA progression.
- Cartilage loss was not associated with worsening of symptoms.

- NICE guidelines 2014 recommend that "Intra-articular corticosteroid injections should be considered as an adjunct to core treatments for the relief of moderate to severe pain in people with OA". They are silent on the number or frequency of repeat injections.

Platelet-rich plasma injections for advanced knee osteoarthritis: a prospective, randomized, double-blinded clinical trial. Jubert N. et al. Orthop.J.Sports Med., 2017.

Study type: RCT – Spain – secondary care.

Conclusion: A single intra-articular injection of PRP has similar effects to 1 injection of corticosteroid for patients who are 67 years or older and with late-stage knee OA.

P n= 65 (30-53 in each arm) already on the waiting list for knee replacement. Age 40-80 years and with pain intensity of > 60 on 0-100 VAS.
I 4 mL autologous PRP
C 4 mL (2 mL betamethasone: 6 mg betamethasone sodium phosphate + betamethasone acetate 6 mg and 2 mL bupivacaine 0.25%).
O Pain intensity at 1 month.

Findings

- No statistically significant difference in pain intensity outcomes between groups at any time point.
- No differences in the use of painkillers and nonsteroidal anti-inflammatories or dose or frequency between groups at any time point.
- At 6 months, no statistically significant differences in patient satisfaction between the groups.
- No AEs at injection time or follow-up.

Cautions

- Small sample size. It is interesting, as small trials tend to over-estimate effect size, i.e. usually finds a significant difference between interventions, yet this was not the case in this small trial!
- Cost effectiveness was not measured, this is particularly relevant here given the difference in the procedure between injecting PRP and corticosteroid.
- Patient satisfaction: although this was found similar in the 2 groups, it is important to be clear as to what was the 'satisfaction' about? Was it about pain/symptoms? Or was it including the whole experience with the intervention, including the actual procedure? This is not clear. Furthermore, and linked with small sample size point above: the study was powered based on the primary outcome measure of pain intensity, and might not be powered to provide clear answers for satisfaction, which was a secondary outcome.
- Applicability/implementing the procedure of injection PRP in clinical practice?

Notes and current guidelines

- NICE guidelines 2014 do not include any recommendations for using PRP for OA.

Treatment of knee osteoarthritis: platelet-derived growth factors vs. hyaluronic acid. A randomized controlled trial. Lisi C. et al. Clin. Rehabil. 2017.

Study type: RCT – Italy - Outpatient rehabilitation service.

Conclusion: Compared with hyaluronic acid, activated PRP reduces articular damage as evident on MRI, as soon as six months after treatment; it reduces pain and improves patient's function and overall quality of life.

P n=58 (30-28 in each arm) with knee OA grade 2–3 on MRI (See table), with no previous OA treatment with local hyaluronic acid or steroid injections.
I Ultrasound guidance: 3 autologous PRP intra-articular injections (2mL each) at 4-week intervals.
C Ultrasound guidance: 3 intraarticular hyaluronic acid (20 mg/2 mL) injections at the same intervals by the same study staff.
O Proportion of patients with >1 MRI grade improvement at six months from last injection.

Findings

- Patients with at least 1 grade improvement at repeat MRI were 14 (48.3%) in the intervention and 2 (8%) in the control group ($P < 0.003$).
- Improvement in symptoms and functional scales was consistently higher in the intervention group.
- No side-effects were observed in either group.

Cautions

- Small sample size. There is evidence that treatment effects sizes tend to be overestimated in small trials.
- Clinicians who provided the injections were not blinded and there is a risk, therefore, that a placebo effect might have been introduced?
- Although the paper states patients were blinded, it doesn't report how that was done, this is particularly relevant with the difference in the procedures.

Notes and current guidelines

- NICE guidelines 2014 do not include any recommendations on PRP for OA.
- The guidelines recommend the clinicians "Do not offer intra-articular hyaluronan injections for the management of osteoarthritis.".

SPINAL PAIN

Non-steroidal anti-inflammatory drugs for spinal pain: a systematic review and meta-analysis. Machado G.C. et al. Ann. Rheum.Dis. 2017.

Study type: SR & MA of RCTs.

Conclusion: The size of the difference in benefit between NSAIDs and placebo is ***not clinically significant.***

P RCTs in patients with acute or chronic neck or LBP of any intensity, with or without radicular pain.
I NSAIDs any class, formulation or route of administration (topical, oral or injection).
C Matching placebo
O Pain intensity (VAS), functional disability (RMDQ), quality of life and AEs. A between-group difference of 10 points (on a 0–100 scale) was used for pain and disability as the smallest clinically significant difference. A follow-up period <2 weeks as immediate-term, and between 2 weeks and 3 months as short-term.

Findings: 35 RCTs. Medial duration of follow up 7 days.

- **Pain:** Moderate-quality evidence: pain reduced in the immediate term (MD −9.2, 95% CI −11.1 to −7.3) and short-term (MD −7.7, 95% CI −11.4 to −4.1) compared with placebo.
- **RMDQ:** effects smaller than for pain: (MD at immediate-term −8.1, 95% CI −11.6 to −4.6), and short-term (−6.1, 95% CI −9.5 to −2.8)

The size of reduction in pain and improvement in function were not clinical important.

- **AEs:** NSAIDs increased the risk of gastrointestinal reactions by 2.5 times.
- **Studies quality:** Nearly all trials were therapist and assessor-blind, but 20% of trials had high dropout rates (>15%). Seven trials did not report relevant outcomes or failed to report results previously described in their methods and were judged at high risk of reporting bias.

Cautions

- Small trials, with short follow up.
- Evidence quality not very good.
- High drop-out rate in RCTs.
- Selective reporting of outcomes in included trials.

Notes and linking with current guidelines

- This is a well-conducted systematic review that included a large number of studies.
- At present, there are no simple analgesics that provide clinically important effects for spinal pain over placebo.
- However, in practice these analgesics are rarely provided alone as treatment, but often combined with other analgesics, exercise or physiotherapy. Most of the studies that test the effect of analgesics tend to test them on their own.
- NICE guidelines, 2016, recommend that clinicians “consider oral NSAIDs for managing LBP, taking into account potential differences in gastrointestinal, liver and cardio-renal toxicity, and the person’s risk factors, including age. Prescribe oral NSAIDs at the lowest effective dose for the shortest possible period of time”.

Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials. Shanthanna H. et al PLoS Med. 2017.

Study type: SR & MA of RCTs.

Conclusion: There is a significant risk of AEs with gabapentinoids without any demonstrated benefit for cLBP. Their use for cLBP is, therefore, not recommended.

P RCTs reporting the use of gabapentinoids for the treatment of cLBP of >3 months duration, in adult patients.
I Gabapentinoids
C Placebo or other analgesic treatments
O Pain intensity (0-10 VAS).

Findings: 8 RCTs included:

Pain intensity:

- Gabapentin compared with placebo: 3 studies, n = 185: minimal improvement in pain (MD = 0.22 units, 95% CI −0.5 to 0.07; GRADE: very low).
- Pregabalin compared with other types of analgesic medication: 3 studies (n = 332): greater improvement in the other analgesic group (MD = 0.42 units, 95% CI 0.20 to 0.64; GRADE: very low).
- Pregabalin as an adjuvant (n = 423): studies were not pooled due to heterogeneity, but the largest of them showed no benefit of adding pregabalin to tapentadol.

AEs:

- No deaths or hospitalizations reported.
- Compared with placebo, the following AEs were more common with gabapentin: dizziness- (RR = 1.99, 95% CI 1.17 to 3.37); fatigue (RR = 1.85, 95% CI 1.12 to 3.05); difficulties with mentation (RR = 3.34, 95% CI 1.54 to 7.25); and visual disturbances (RR = 5.72, 95% CI 1.94 to 16.91).

Cautions

- Included RCTs of poor quality.
- Heterogeneity in medications dosages, comparator treatments and outcome measures, which pauses a problem in interpreting the results.
- Inconsistent reporting of AEs in included studies.

Notes and current guidelines

- This is a well conducted systematic review, notwithstanding the important methodological issues in the included studies.
- NICE guidelines, 2016, recommends that clinicians "Do not offer anticonvulsants for managing LBP".
- Those guidelines were based on evidence from one RCT (2001). This systematic review identified 7 more recent RCTs which were not included in the NICE evidence, but still did not change the thrust of the recommendations in the NICE guidelines.

Efficacy and safety of etanercept in the treatment of sciatica: A systematic review and meta-analysis. Jing S. et al. J. Clin. Neurosci. 2017.

Study type: SR & MA or RCTs and non-RCTs.

Conclusion: Evidence is inconclusive for the benefit of etanercept for sciatica.

P RCTs and non-RCTs in patients with sciatica (lumbar disc herniation or spinal stenosis).
I Etanercept
C Steroids or placebo
O Leg pain scores (VAS score or numeric rating scale NRS).

Findings: 5 studies (4RCTs, 1non-RCT) (n=184, range 12 to 54). Dosage of etanercept varied, best dose in each trial was selected for analysis. Trials quality: moderate.

- Compared with placebo: etanercept could significantly reduce leg pain
- Compared with steroids: no significant difference in the relief of leg and back pain.
- Etanercept showed no improvement in ODI compared with placebo and steroids.
- No serious AEs related to etanercept.

Cautions

- Small number of very small trials
- Moderate trials quality
- Not all included trials are randomised or blinded.
- Heterogeneity: setting, population, doses of interventions.

Notes and linking with current guidelines

- This is a well conducted review, although the quality of included studies and their heterogeneity limit the review's benefit.
- The rationale for testing etanerecept for LBP is related to its anticipated benefit as it blocks the action of inflammatory mediators found at the site of disc herniation associated with LBP symptoms.
- NICE guidelines 2016 do not include any recommendations regarding the use of etanerecept fro LBP.

Most red flags for malignancy in low back pain guidelines lack empirical support; a systematic review. Verhagen A.P. et al. Pain, 2017.

Study type: SR of observational studies.

Conclusion: The evidence for most red flags recommended in LBP clinical guidelines is very weak.

P 33 studies (2 Systematic and narrative reviews, 7 prospective cohorts, 10 retrospective cohorts, and 8 case series). 13 red flags for malignancies (excluding elevated ESR) endorsed in 16 guidelines for LBP.
O Sensitivity, specificity, and likelihood ratio (LRs).

Red flags: *signs or symptoms collected in the clinical assessment signalling underlying serious pathology that requires attention).*

Findings

Prevalence of spinal malignancy

- The prevalence of spinal malignancies in patients with LBP seemed to be influenced by setting.
    - In prospective primary care cohort studies: 0% and 0.6%-0.7%.
    - In cohorts of radiographic reports of patients referred from primary care: 0.2% and 7.0%.
    - In 1 retrospective cohort study in tertiary care: 5.9%.
- Inclusion of specific red flags in various guidelines vary widely.

Diagnostic accuracy

- Very limited diagnostic accuracy evidence was available for most guideline-endorsed red flags.
- Two red flags (“*history of malignancy*” and *“strong clinical suspicion”)* show potential in identifying patients with a higher likelihood of malignancy as they have sufficiently high LR+.
- Five other red flags (“*unexplained/unintentional weight loss*,” “*atypical pain*,” “*older age*,” “*failure to improve with treatment*,” and “*duration of complaint > 1 month*”) have quite modest LR+ and so would not assist clinical decision making, given the low prevalence of malignancy in primary care.
- “Atypical pain” endorsed in 12 guidelines, has very varied and unclear definitions!

Cautions

- ESR not included as a red flag sign.
- Setting of studies include primary, secondary and tertiary, and specificity and sensitivity therefore will vary greatly, as it depends on the prevalence in these settings.

Notes

- This is a well-conducted systematic review of observational studies which are of the correct design to answering the question of risk factors.
- The findings echo those from similar previously published Cochrane reviews.

Comparison with previous studies on the prevalence of ‘Red flags’ in LBP patients:

- A primary care cohort of 1172 patients with LBP: 80.4% had at least 1 red flag.
- A study among physiotherapists: 7 of 11 red flags were documented in 98% of patients.
- A web-based survey among adults with LBP: 68.2% reported at least 1 red flag.

Combination red flags – a prognostic model

An alternative strategy could be to focus on a combination of red flags to identify patients with a higher likelihood of malignancy (ruling people in).

- A combination of “ESR>20 mm/h” and “a history of cancer” was tested and found to provide high false negative results (in about half the patients tested).
- A strategy to refer for MRI all people who had one or more of the following clinical findings (“history of cancer,” “age >50 years,” “weight loss,” and “failure to improve with treatment”) in combination with “an ESR >50 mm/h” or “a positive X-ray” Was also tested and still included high false negative results.

Physiotherapists' beliefs and attitudes influence clinical practice in chronic low back pain: a systematic review of quantitative and qualitative studies. Gardner T. et al. J.Physiother. 2017.

Study type: SR & MA of quantitative and qualitative studies.

Conclusion: Physiotherapists’ beliefs and attitudes about LBP influence their management of patients and the clinical advice they provide.

P Quantitative (cross-sectional) and qualitative studies in physiotherapists managing LBP and investigated an association between physiotherapists' attitudes/ beliefs about LBP and their clinical management.
O Any outcomes to measure beliefs and attitudes

Findings: 5 quantitative and 5 qualitative studies. Quality: moderate to high.
Quantitative studies (UK, Netherlands, Sweden, Canada, 2002-2012, n range 80-250):

- a higher biomedical orientation score (indicating a belief that pain and disability result from a specific structural impairment, and treatment is selected to address that impairment) was associated with: advice to delay return to work, advice to delay return to activity, and a belief that return to work or activity is a threat to the patient.
- Physiotherapists' fear avoidance scores were positively correlated with: advice to avoid return to work, and advice to avoid return to normal activity.

Qualitative studies (UK, Sweden Canada, 2004-2013, n range 8-22):

Biomedical vs biopsychosocial model of management

- When discussing cLBP, physiotherapists have consistent bias towards a biomedical approach.
- Therapists expressed lack of confidence in their ability to follow and implement a biopsychosocial model.
- Therapists disliked treating difficult patients and had poor self-efficacy and outcome expectancies regarding their treatment of these patients.
- Therapists thought that assessment of psychosocial factors was not their role.

Patient related factors

- Physiotherapists often chose interventions that facilitated a relationship with and satisfied the patient.
- Clinical decisions were based on the classification of the patient according to the perceived 'passivity of patient'.
- The degree to which a therapist thought a patient would engage in treatment and/or self-management influenced the treatment provided and led to an individual approach for each patient.

Cautions

- This evidence comes from exploratory studies (qualitative and cross sectional surveys), and so it is an evidence of association and exploring opinion.
- For ensuring representativeness of views, check country of study, year and sample size.
- The participants in 2 of the 5 cross sectional studies were not randomly selected, selection bias?
- Response rate to invites in the 5 cross sectional studies ranged from 30-70%. Selection bias?
- The quality of included studies is not high, with 4 out of 5 qualitative studies judged to have inappropriate qualitative methodology, sampling or data collection.

Notes

- This review addresses one aspect of the wide area of the influence of attitudes and beliefs of health care providers on their management of their patients.

Other related important questions include:

- Do health care professionals follow clinical guidelines or their beliefs and attitudes?
- What is the influence of guidelines on beliefs and attitudes?
- Do beliefs and attitudes influence adherence to guidelines?
- Do healthcare professionals' beliefs and attitudes influence patients' beliefs and attitudes?
- Does any of this influence patients' outcomes?

Yoga, physical therapy, or education for chronic low back pain: a randomized noninferiority trial. Saper, R.B. et al. Ann.Intern.Med. 2017.

Study type: RCT – USA - A large academic safety-net hospital and 7 affiliated, federally qualified community health centres.

Conclusion: Yoga is similar to PT in improving moderate to severe nonspecific cLBP symptoms.

P English-speaking adults aged 18-64 years who reported nonspecific cLBP (at least 12 weeks) with an average pain intensity in the previous week of 4/10 NRS. Recruitment strategies included clinician referrals, mailing letters to patients with cLBP who were identified through electronic health records, and distributing flyers in clinics and surrounding neighbourhoods.
I Yoga: 12 weekly 75-minute classes supervised by yoga instructors.
C1 PT: fifteen 60-minute appointments over 12 weeks: included treatment-based classification, graded exercise, and screening for fear-avoidance beliefs. Appointments included 1-on-1 work with the therapist and supervised aerobic exercise.
C2 Education (a self-care book and newsletters

Treatment phase: 12 weeks
Maintenance phase: 52 weeks: Yoga participants who completed 1 or more yoga classes in the treatment phase were randomly assigned at 12 weeks to yoga drop-in classes or home practice. Physical therapy patients who completed 1 or more PT appointments in the treatment phase were randomly assigned to PT booster sessions or home practice. Yoga maintenance classes were similarly structured except for a higher participant–instructor ratio. PT maintenance included advising the participants to see the therapist at 4, 6, 8, 10, and 12 months.

O RMDQ and pain intensity (NRS 0-10) at 12 weeks.

Findings: n=320 (Yoga 127, PT 129, Ed 64), mean age 45; 64% women; mean pain intensity 7; adherence to treatment median; attendance 7 yoga sessions, 7 PT sessions.

- **RMDQ:** improvement for yoga (mean within group change, -3.8, 95% CI, -4.6 to -2.9) was non-inferior(similar) to that for PT (mean within-group change, -3.5, 95% CI, -4.5 to -2.6)
- **Yoga and PT were not better than education at 12 weeks for RMDQ**
- **Pain:** improvement for yoga (mean within-group change, -1.7, 95% CI, -2.1 to -1.4) was non-inferior to that for PT (mean within-group change, -2.3, 95% CI, -2.7 to -1.9).
- **Maintenance phase:** RMDQ or pain changes did not significantly differ between yoga drop-in classes and yoga home practice or between PT booster sessions and PT home practice
- **AEs**: mostly mild self-limited joint and back pain, were reported in 9 yoga, 14 PT, and 1 education participants. Yoga and PT did not differ significantly in frequency or severity of AEs.

Cautions

- Only assessors were blinded to treatment allocation and delivery.
- Loss to follow up not equal in trial arms: lower in PT than in yoga or education at 12 weeks (88% vs. 98% and 95%, respectively) and 52 weeks (84% vs. 93% and 93%, respectively).
- No economic evaluation.

Notes and linking with current guidelines

- Mind and body exercise interventions are not currently provided by the NHS.
- NICE guidelines 2016 describes the findings from a number of RCTs on yoga as inconsistent, and do not include any recommendations regarding yoga.
- A systematic review published in 2015 (Searl et al) included yoga as a type of a 'combined group exercise', comprising multiple components such as strengthening, stretching, endurance and aerobic training'. It also found the evidence inconsistent and concluded that the overall evidence suggests that these exercise modalities, such as yoga, are ineffective.

Early rehabilitation after lumbar disc surgery is not effective or cost-effective compared to no referral: a randomised trial and economic evaluation. Oosterhuis T. et al. J.Physiother. 2017.

Study type: Multicentre RCT with economic evaluation – The Netherlands - secondary care.

Conclusion: Early rehabilitation after lumbar disc surgery was neither more effective nor cost-effective than no rehabilitation.

P Adults who underwent discectomy for herniated lumbar disc (confirmed by MRI, and signs of nerve root compression corresponding to the herniation level).
I Early rehabilitation (exercise therapy) for 6 to 8 weeks immediately after discharge.
C No rehabilitation, clinicians and patients were requested to refrain from referral for exercise therapy or other allied health interventions in the 6- to 8-week period before consulting the neurosurgeon after surgery.
O ODI; leg and back pain (NRS 0 to 10); global perceived recovery, assessed 3, 6, 9, 12 and 26 weeks after surgery.

Findings: n=169 (I: 92, C: 77) mean age 47 years, 98% women. Baseline mean ODI 49/100, leg pain 7.7/10, back pain 6.3/10. No statistically significant or clinically relevant overall mean differences between rehabilitation and control for any outcome adjusted for baseline characteristics:

- **Functional status** (MD 1.5, 95% CI –3.6 to 6.7),
- **Back pain** (MD 0.3, 95% CI –0.3 to 0.9)
- **Leg pain** (MD 0.1, 95% CI –0.7 to 0.8)
- **Global perceived recovery** (OR 1.0, 95% CI 0.6 to 1.7),

Cost effectiveness: after 26 weeks, there were no significant differences in quality-adjusted life years and societal costs.

Cautions

- Neither patients nor therapist were blinded. The researchers assessed expectations in the trial arms to try to assess and address any possible risk related to that, but this remains a potential risk of bias.
- The findings should be applied only to the type of spinal surgery specified in the trial, as there is a broad range of types of spinal surgery that might have different response to early rehabilitation.

Notes

- Notwithstanding the important caution regarding blinding, this is a well-conducted large pragmatic RCT that attempted to answer the important question of clinical and cost effectiveness of early rehabilitation.
- However, the optimum timing of the rehabilitation is also important, and this trial did not compare different timings.
- There are currently no UK guidelines on post-operative rehabilitation for this patient group, including its optimum timing. Approaches therefore vary among hospitals, and the most common approach is physiotherapy input during the post-operative hospital stay, followed by advice (leaflet) on home exercises.

Trial of pregabalin for acute and chronic sciatica. Mathieson S. et al. N.Engl.J.Med. 2017.

Study type: RCT – Australia – setting is not clear, mixed primary/secondary.

Conclusion: Compared with placebo, pregabalin did not significantly reduce leg pain and other outcomes associated with sciatica.

P Patients referred to an outpatient in New South Wales, for moderate- to-severe sciatica.
I Pregabalin: 150 mg per day adjusted to a maximum of 600 mg per day for up to 8 weeks.
C Matching placebo
O Leg-pain intensity score on a 10-point NRS, at week 8 and 52.
Blinding: all patients and research staff were blinded and treatment allocation concealed.

Sciatica was defined as pain radiating into one leg below the knee, accompanied by nerve-root or spinal-nerve involvement as indicated by the presence of at least one of the following clinical features: dermatomal leg pain, myotomal weakness, sensory deficits, or diminished reflex, as determined by the trial clinician.

Findings: n=209 (I: 108, C: 101), mean age 53 years, 50% women, baseline mean (±SD) leg-pain intensity score 6.3±1.8 in the pregabalin group and 6.1±1.9 in the placebo group.

Pain intensity: Adjusted between group mean differences:

- Week 8: 0.5; 95% CI −0.2 to 1.2; P = 0.19).
- Week 52: 0.3; 95% CI, −0.5 to 1.0; P = 0.46).
- Between-group difference did not reach a clinically important treatment effect of 1.5 points out of 10 for the leg-pain intensity score.

Other outcomes: No significant between-group differences were observed with respect to any secondary outcome at either week 8 or week 52.

A/Es: 227 in the pregabalin group and 124 in the placebo group. Dizziness was more common in the pregabalin group than in the placebo group.

Cautions

- The method for identifying eligible participants is not clear. This is important to ensure no risk of selection bias, and also when generalising the results to various settings.
- Excluded were patients with sciatica symptoms of >1 year duration and those on waiting list for surgery.

Notes (See SR by Shanthanna et al 2017 above).

- This is a large well powered and well-conducted RCT that should have detected an effect were an effect existed.
- Evidence is now strong against using gabapentinoids for LBP.
- NICE guidelines 2016 recommend not prescribing anticonvulsants medications for treating patients with LBP with or without sciatica.

Long-term effects of repeated injections of local anaesthetic with or without corticosteroid for lumbar spinal stenosis: a randomized trial. Friedly J.L. et al. Arch.Phys.Med.Rehabil. 2017.

Study type: Multi-centre, double-blind RCT – USA – setting is not clear.

Answer: For patients with lumbar *central* canal spinal stenosis, treatment with epidural injections of corticosteroid (CS) plus lidocaine (up to 4 injections in 3 months) offers no additional benefits from 6 weeks to 12 months beyond that of injections of lidocaine alone.

P Patients age >50 years with neurogenic claudication, leg pain >4/10, and RMDQ >7/24; with imaging-confirmed lumbar *central* spinal stenosis and referred for an epidural CS injection.
I CS + lidocaine: Under fluoroscopic guidance: 1-3mL of 0.25% - 1% lidocaine with triamcinolone (60-120mg), betamethasone (6-12mg), dexamethasone (8e10mg), or methylprednisolone (80-120mg). Up to 2 epidural injections during the initial 6 weeks of the study prior to being offered crossover, and up to 2 injections between 6 and 12 weeks.
C Lidocaine only: the procedure was identical to the corticosteroid + lidocaine procedure except that the injectate was an equivalent volume of lidocaine alone.
O RMDQ and patient's rating of average buttock, hip, or leg pain intensity in the past week, use of other pain treatment and surgery. Length of follow: 12 months.

Findings: n=400 (I: 200, C: 200).
At 12 months: No statistically significant differences between the corticosteroid plus lidocaine and lidocaine alone groups:

- **RMDQ**: adjusted mean difference, -0.4; 95% CI, -1.6 to 0.9; P=0.55.
  The proportion with >50% improvement from baseline on the RMDQ at 12 months was similar between groups: corticosteroid plus lidocaine group: 25.6%, 46/180; lidocaine alone group: 27.6%, 48/174; P=0.33.
- **Leg pain intensity**: adjusted mean difference, 0.1; 95% CI, -0.5 to 0.7; P=0.75.
- **Opioid use**: corticosteroid plus lidocaine: 41.4% vs lidocaine alone: 36.3%; P=0.41.
- **Spine surgery**: corticosteroid plus lidocaine: 16.8% vs lidocaine alone: 11.8%; P=0.22.

Cautions

- **Spinal 'stenosis':** the study unfortunately uses this term loosely, at times 'central' and at times just 'stenosis'. It is important to note that 'central' stenosis is different from 'lateral' stenosis in its nature and prognosis and response to treatment. 'Central' stenosis should correctly only refer to stenosis due to spinal canal changes, and not due to disc herniation.
- The setting is not clear and this is relevant to generalising the results to various settings. In the UK this intervention is rarely provided in the primary care setting.
- Neither blinding status of treating clinicians and patients nor concealment of allocation to treatment were reported. This is important, as it poses a risk of bias.

Notes and linking with current guidelines

- This is a long term follow up of the trial that was published in 2014 and found no benefit in the short term, at 6 weeks.
- NICE guidelines 2016 although recommend considering "epidural injections of local anaesthetic and steroid in people with acute and severe sciatica." They state: "Do not use epidural injections for neurogenic claudication in people who have central spinal canal stenosis". See comment in 'cautions' re stenosis.

SHOULDER PAIN

Effectiveness of massage therapy for shoulder pain: a systematic review and meta-analysis. Yeun Y.R.J.Phys.Ther.Sci. 2017.

Study type: SR & MA of RCTs and non-randomised CTs.

Conclusion: Not possible to draw clear conclusions from this review which was poorly conducted and reported.

P RCTs and non-RCTs on adults (18 years or older) with shoulder pain (shoulder pain, shoulder impingement syndrome, rotator cuff, bursitis, adhesive capsulitis).
I Massage therapy (massage, therapeutic touch, reflexotherapy, reflexion, manual, manipulative) given alone or in combination with another treatment.
C No intervention, placebo, or other intervention.
O Pain intensity

Findings: 15 studies (4 Non-RCTs) (n 635 participants). The range of ROB scores: 5 - 11 points.
Pain intensity:

- 'Short-term' efficacy: −1.08 (95% CI: −1.51 to −0.65) (All studies?)
    - 11 studies compared massage versus inactive therapies, effect size: −1.12 (95% CI: −1.60 to −0.63). (Statistically significant)
    - 4 studies compared massage with active therapies, effect size: −1.06 (95% CI: −2.18 to 0.06). (Not statistically significant)
- In 5 studies 'long-term' efficacy was assessed: −0.47 (95% CI: −0.71 to −0.23). (Statistically significant)

Cautions

- One author, so it is not clear whether the study selection, data extraction, quality assessment was done by a single person? For robustness they are usually done by at least 2 people.
- Heterogeneity
    - Of design of included studies, Non-RCTs were included and analysed with RCTs.
    - Of diagnosis of shoulder pain
    - Of interventions, massage: description, duration etc.
    - Of comparator interventions.
- Definitions:
    - 'Inactive' and 'active': definitions of these descriptions were not provided.
    - 'Short-term' and 'long-term' follow up: also not defined, so not clear what they mean.
- Quality assessment of included studies: It is not clear at all how this was assessed. It is stated that the GRADE recommendations was used to assess quality! This is obviously wrong, as the recommendations are used to describe the quality of evidence and strength of recommendations!

Notes and linking with current guidelines

- No UK guidelines for the role of massage for shoulder pain.
- NICE CKS recommendations do not include massage in the treatment list.
- The Dutch guidelines (Diercks 2014) state that there is a moderate quality evidence that massage (myofascial trigger points in the shoulder muscles, or soft tissue) appears to be more effective than placebo or no treatment in reducing pain and improving shoulder function in patients with shoulder pain.
- A systematic review published in 2013 (Kong et al) concluded that 'massage may provide immediate benefit for neck and shoulder pain, but it is not better than other active manual therapies.'

Efficacy of workplace interventions for shoulder pain: A systematic review and meta-analysis. Lowry V. et al. J.Rehabil.Med. 2017.

Study type: SR & MA of RCTs

Conclusion: Low quality evidence that workstation modifications may reduce the prevalence of shoulder pain and that a workplace exercise programme may reduce the intensity of shoulder pain.

P RCTs on healthy adult (≥18 years) workers or adult workers with shoulder pain.
I workplace interventions or an on-site rehabilitation programmes to prevent or to treat shoulder pain
C Not specified, any other type of interventions
O Pain intensity (0-10 VAS), functional limitations and prevalence.

Findings: 13 RCTs. Low quality. Meta-analysis not done for physical function outcomes because of the high heterogeneity.

- **Pain intensity:** 4 RCTs (n=368): Strengthening exercises (compared with different control interventions): a statistically significant reduction, MD 1.31 (95% CI 0.86–1.76).
- **Prevalence of shoulder pain:** 5 RCTs (n = 2,148): Workstation modifications (compared with different control interventions): a statistically significant reduction in the prevalence: a risk ratio of 1.88 (95% CI 1.20–2.96).

Cautions

- Only a small number of studies included in meta-analysis, because of wide variation.
- A mixture of studies among healthy adults and people with shoulder pain. These two populations are different in their characteristics and therefore any conclusions would be difficult to interpret or apply in practice.
- Exercises were heterogeneous across studies.
- None of the exercise programmes were specific to the worker's tasks.
- Types of occupations were heterogeneous across the included studies.
- Just because evidence was found for a specific exercise and work adaptation (workstation), this doesn't mean other interventions are not beneficial. The evidence here is for those interventions for which there were data to analyse.

Notes and current guidelines

A systematic review published in 2015 (Eerd et al) on the effectiveness of 'workplace interventions for preventing upper extremity pain disorders' concluded that:

> *"There was strong evidence that a workplace-based resistance training exercise can help prevent and manage arm/shoulder symptoms. There was moderate evidence for stretching programmes, mouse use feedback and forearm supports in preventing upper arm/shoulder symptoms. There was moderate evidence for no benefit for EMG biofeedback, job stress management training or office workstation adjustment".*

Effectiveness of corticosteroid injections in adhesive capsulitis of shoulder: A meta-analysis. Wang W. et al. Medicine, 2017.

Study type: SR & MA of RCTs and non-RCTs.

Conclusion: Intra-articular CS is effective in improving pain in the short term, but not in the long term. It improved passive ROM both in the short and the long term.

P RCTs and non-RCTs in patients with adhesive capsulitis: (bursitis, capsulitis, frozen shoulder, stiff shoulder).
I CS shoulder injection
C Sham injection, oral medications or no procedure
O VAS (0-100) for pain intensity at 24 weeks. "Short-term" follow-up: <8 weeks; "long-term": 8-24 weeks.

Findings: 5 studies (4 RCTs) (n=225).

Pain intensity:

- Short- term: - CS is more effective -16.30 (95% CI -23.65, -8.94)
- Long-term: No difference 0.53 (95% CI -10.38, 11.44).

Range of abduction:

- Short term: CS more effective 12.78 (6.63, 18.93).
- Long term: CS more effective 11.95 (95% CI 6.36, 17.54).

Cautions

- A small number of small trials included.
- 'Long-term' is only up to 24 weeks (under 6 months)
- Both RCTs and non-RCTs included in the meta-analysis.
- Definition of 'adhesive capsulitis' for inclusion is not clear.
- Heterogeneity in comparator interventions.
- Study quality used an old tool, not the currently recommended Cochrane ROB.

Notes and linking with current guidelines

- This evidence doesn't change that based on a Cochrane review published in 2003 (Buchbinder et al), which concluded that "Intra-articular corticosteroid injection for adhesive capsulitis may be beneficial although their effect may be small and not well-maintained."
- Evidence suggests that the same small short term benefit is obtained for other shoulder pain conditions (Coombes et al 2010, Dierk et al 2014).

Comparison of high- and low-dose intra-articular triamcinolone acetonide injection for treatment of primary shoulder stiffness: a prospective randomized trial. Kim,Y.S. et al. J.Shoulder Elbow Surg., 2017.

Study type: RCT – Korea – setting is not clear.

Conclusion: No significant difference in benefit between different doses of intra-articular triamcinolone in patients with shoulder stiffness. In diabetic patients, high dose of corticosteroid may lead to short-term rise in glucose levels.

P 151 patients (mean age 56years, 40% men) with 'primary shoulder stiffness', of at least 2 months duration.
I Intra-articular injection of 40 mg of triamcinolone acetonide. *Exercises for the post-injection rehabilitation were taught to the patients after the injection, and patients were required to follow the home-based instruction daily.*
C Intra-articular injection of 20 mg of triamcinolone acetonide. *(Not clear whether they also had post-injection exercises)*
O ROM, pain intensity (VAS), the American Shoulder and Elbow Surgeons score, and the Simple Shoulder Test were evaluated before injection; at 3, 6, and 12 weeks and 6 and 12 months after injection;

Joint stiffness defined as forward flexion <100° (maximal 150°; forward flexion is glenohumeral motion without scapulohumeral rhythm), external rotation below 45° (maximal 90°), or internal rotation at a level lower than the first lumbar spine (L1; maximal T7 level).

Before enrolment, patients were required to undergo plain radiography and MRI to detect other combined lesions that can cause shoulder stiffness.

Findings:

No significant differences between the 2 groups in any outcome at any follow up point.

- The greatest improvements were within the first 3 weeks after injection in all aspects.
- A total of 13 patients in group I and 14 in group II were diabetic.
- None of the patients in both groups had a significant increase in blood glucose, fructosamine, and HbA1c levels compared with the levels before injection.
    - However, patients in group I (40mg) showed a significantly higher blood glucose level at 6 weeks after injection compared with those in group II (20mg) (P = .01)

Cautions

- Analysis is not intention to treat: only patients who completed follow up were included in analysis, those lost to follow up were excluded from the analysis: 1 in the 40mg group, and 3 in the 20mg group.
- Number of patients with DM is small, so any conclusions related to the results in those patients with DM need to be interpreted with caution.

Notes and linking with current guidelines

- The question this trial attempted to answer is very important and clinically relevant, because of the variation of dosages used in practice and because of the potential serious side effects associated with using higher dosages.
- Other related questions include:
    - For which patients with shoulder pain CSI is most beneficial?

- What is the optimum frequency & interval for repeat injections?
- What is the long term benefit/harm?

- There are no clinical guidelines or recommendations specifically on the most beneficial and least harmful dose of corticosteroid injection for the shoulder.

GOUT

Corticosteroid or nonsteroidal anti-inflammatory drugs for the treatment of acute gout: a systematic review of randomized controlled trials. Billy, C.A. et al. J. Rheumatol. 2017.

Study type: SR & MA of RCTs

Conclusion: Evidence is insufficient to determine the comparative efficacy of corticosteroids (CS) and NSAID to treat acute gout.

P RCTs or quasi- RCTs in adults with acute gout (diagnosed on clinical criteria and/or presence of monosodium urate (MSU) crystals in the synovial fluid of affected joints) and who did not receive CS or NSAID within 24 h of episode onset before randomization.
I CS (oral or injectable)
C NSAIDs
O Pain intensity (within 7 days and ≥ 7 days), the primary safety outcome was GI bleeding.

Findings: 6 studies (5 RCTs and 1 quasi-RCT) (n=817) mean follow up length 15 days (range 4–30ds). Two recruited hospitalized patients; 2 from emergency department; 1 from outpatient clinics and in 1 trial setting is not clear. Mean age 50 years, 70-100% men. In 4 trials diagnosis was clinical, while in 2 it was based on the presence of intraarticular crystals. One trial compared CS with selective and non - selective NSAID, while the remainder compared with nonselective cyclooxygenase inhibitor NSAID. The quality of studies: low to moderate.

- **Pain:** no significant difference in pain scores between CS and NSAIDs.
  - Short-term, within 7 days (2 RCTs, n=534): SMD –0.09, 95% CI –0.26 to 0.08.
  - Long-term (2 RCTs, n=506) SMD 0.32, 95% CI –0.27 to 0.92.
- **A/Es:** NSAIDs were not associated with a higher risk of GI bleeding.
- CS had a lower risk of indigestion, nausea, and vomiting.

Cautions:

- Very small number of trials.
- Included trials had low to moderate quality.
- Diagnosis of gout: in 4/6 trials it was clinical and not based on confirmatory tests.
- Heterogeneity in diagnosis of gout and dosages of interventions.
- Evidence on AEs is only based on what was reported in the included trials.
- Renal function and impact of treatment were not assessed in the included trials.

Notes and linking with current guidelines

The BSR guideline (Hui et al 2017) recommends for treating acute gout "an NSAID … or colchicine".

> *"Joint aspiration and injection of a corticosteroid are highly effective in acute mono-articular gout and may be the treatment of choice in patients with acute illness and co-morbidity. A short course of oral corticosteroid or a single injection of an intramuscular corticosteroid is an alternative in patients who are unable to tolerate NSAIDs/colchicine and in whom intra-articular injection is not feasible. Such systemic therapy is also appropriate for oligo- or poly-articular attacks of gout".*

Is tea consumption associated with the serum uric acid level, hyperuricemia or the risk of gout? A systematic review and meta-analysis. Zhang,Y. et al. BMC Musculoskelet.Disord. 2017.

Study type: SR & MA of observational studies.

Conclusion: tea consumption does not seem to be associated with SUA level, HU or the risk of gout.

P Observational studies (case–control, cohort or cross-sectional study).
I Tea.
O SUA level, the prevalence of HU and the risk of gout.

Findings: 15 studies: 10 cross-sectional, 1 case–control and 4 observational cohort studies. Studies quality low to moderate.

- **SUA level:** 5 cross-sectional studies:
  - No significant difference in association, between the highest and the lowest tea intake category: MD = 7.41 µmol/L, 95%CI: −2.34 to 17.15; P = 0.136.
  - Green tea consumption was positively associated with the SUA level: MD = 17.20 µmol/L, 95%CI: 7.00 to 27.40; P = 0.01.
- **Prevalence of HU:** 5 cross-sectional studies: OR for the highest versus the lowest category of tea consumption: 0.98 (95%CI: 0.77 to 1.24; P = 0.839). Not statistically significant.
- **Risk of gout:** 2 prospective cohort studies: no significant association between tea consumption and the risk of gout in males and females.

Cautions

- This evidence, although originates from the right design studies to identify risk factors, is essentially for association rather than causation and confounders, apparent or not, always need to be taken into consideration before applying it in practice.

Notes

- Included studies are of the right design to answer this question of association.
- The question of association between tea and gout is based on a basic theoretical.

The association between gout and cataract risk: A meta-analysis. Luo,C. et al. PLoS One, 2017.

Study type: SR & MA of observational studies.

Conclusion: Evidence suggests that gout may be associated with increased odds of ARCs,

P Cross-sectional or case-control studies estimating the influence of gout on cataract risk
I Gout
C No gout
O Risk of ARCs.

Findings: 3 cross-sectional and 3 case-control studies included. The studies were considered high quality.

- Gout was significantly associated with increased odds of ARCs (OR 1.53, 95% CI 1.27-1.84).

Cautions

- The evidence is for association not causation.
- Small number of studies.
- Assessment, diagnosis and definition of ARCs varied among studies.
- Various potential confounders were accounted for in the included studies, but without consistency and 4 studies only adjusted for age and gender. A very important confounder in the context of cataract is gout medications: colchicine is known to cause lens opacification; long-term allopurinol has also been linked with lens opacity and with the increased odds of cataract extraction in elderly patients.

A randomised controlled trial of the efficacy and safety of allopurinol dose escalation to achieve target serum urate in people with gout. Stamp,L.K. et al. Ann.Rheum.Dis., 2017.

Study type: Open-label RCT – New Zealand – primary and secondary care settings.

Conclusion: Dose escalation (DE) of allopurinol is effective in people with gout, including in those with CKD.

P People with gout (defined by the American Rheumatism Association) receiving at least Creatinine Clearance (CrCL)-based dose of allopurinol for ≥1 month and with SU ≥6 mg/dL at screening.
I DE: allopurinol increased monthly until SU was <6 mg/dL on three consecutive visits or there were AEs. DE was by 50 mg/d for those with CrCL <60 mL/min and 100 mg/d in those with CrCL ≥60 mL/min.
C Continue the current dose of allopurinol throughout the study period.
O Absolute reduction in SU at the final visit (12 months or the final visit for those deceased or lost to follow-up).

Findings: n 183 (I: 90, C: 93). Mean age 60 years, 87% men. Mean (SD) SU was 7.2 mg/dL (1.6). In 51.9% of participants CrCL was <60 mL/min and in 13.1% CrCL was <30 mL/min.

- MD in change in SU at final visit: 1.2 mg/dL (95% CI 0.67 to 1.5) (p<0.001).
- 69% achieved target SU at final visit and 59% achieved and maintained SU <6 mg/dL at the last 3-monthly visits.
- *Gout flares:* by 12 months, 59% of the control group and 54% of the DE group experienced at ≥one self-reported gout flare (p=0.58), i.e. no statistically significant difference.
- No significant difference in the mean change in index tophus size over the study period between randomised groups.
- **AEs:** 43 SAEs in 25 control participants and 35 in 22 DE participants.

Cautions

- The study was not blinded and thus, in principle, carries the inherent risks of bias in an open-label study. However, the primary outcome is objective (a laboratory measure) which would overcome the potential for bias.
- Randomisation codes were provided to study coordinators in sealed opaque envelopes for allocation to treatment, which is not considered as a robust method to ensuring concealed allocation.
- Control arm: dose of allopurinol was fixed throughout the trial, which is not what is done in clinical practice?

Notes and linking with current guidelines

- BSR guidelines (Hui et al 2017) recommend that Allopurinol:
  ".. should be started at a low dose and then increased in 100mg (50mg in patients with renal failure) increments approximately every 4 weeks until the SU target has been achieved".
- The DE approach used in this trial is similar to that recommended in the BSR guidelines. The fact that this approach led to improvement in SU levels but not to reduction in clinical flare ups raises an important question regarding the real benefit of the approach.

PMR

Polymyalgia rheumatica and risk of coronary artery disease: a systematic review and meta-analysis of observational studies. Ungprasert,P. et al. Rheumatol.Int., 2017.

Study type: SR & MA of observational studies.

Conclusion: Evidence from observational studies suggests a significantly increased risk of CAD among patients with PMR.

P Observational studies in patients with PMR
O The risk of CAD.

Findings: 4 studies, all retrospective observational cohorts, (n=34,569). Female to male ratio 2:1, mean age 72 to 74 years. All included studies were of high quality.

- Pooled RR of CAD in patients with PMR was 1.72 (95 % CI 1.21–2.45).
- Statistical heterogeneity was high with an I^2 of 97 %.

Cautions

- The evidence is for association only, not for causation and no indication for a direction. The role of possible confounders is large.
- Studies were conducted using medical registry database: risk of coding inaccuracy/incompleteness.
- Small number of studies and large heterogeneity.
- Confidence in the estimate of magnitude of risk is limited by the heterogeneity of the reviewed studies including clinical heterogeneity, e.g. differences in the definition of CAD.
- 3 out of the 4 included studies included patients with PMR and giant cell arteritis and not just PMR.
- The outcome measures from each study were not exactly the same measures: OR, RR, HR…

Note:
There is an assumed accelerated atherosclerosis with chronic inflammatory disorders.

FIBROMYALGIA

Oral nonsteroidal anti-inflammatory drugs for fibromyalgia in adults. Derry,S. et al. Cochrane Database Syst.Rev. 2017.

Study type: SR & MA of RCTs

Conclusion: Low-quality evidence suggests that NSAIDs are not better than placebo in treating fibromyalgia.

P RCTs of two weeks' duration or longer, in patients with fibromyalgia.
I Any oral NSAID
C Placebo or another active treatment
O Pain intensity: *substantial pain relief:* at least 50% reduction, *moderate pain relief:* 30% reduction.

Findings: 6 RCTs (n=292, I: 146, C: 146), mean age 39 - 50 years, and 89% to 100% were women. Baseline pain intensity: 7/10 (on a 0 -10 NRS). NSAIDs tested were etoricoxib 90 mg daily, ibuprofen 2400 mg daily, naproxen 1000 mg daily, and tenoxicam 20 mg daily. Quality of included studies was low to moderate.

- Substantial pain relief (3 RCTs, n-146): risk difference for NSAID compared with placebo was -0.07 (95% CI -0.18 to 0.04), not statistically significant difference.
- Moderate pain relief (3 RCTs, n=192): risk difference for NSAID compared with placebo was -0.04 (95% CI -0.16 to 0.08), not statistically significant difference.
- There were no serious AEs or deaths.

Cautions
The evidence comes from a small number of small size, largely inadequate studies with potential risk of bias. That bias related to small trials would usually be to increase the treatment effect/benefit, but no such benefits were seen here. Consequently, NSAIDs cannot be regarded as useful for treating fibromyalgia.

Notes and linking with current guidelines
EULAR revised recommendations for the management of fibromyalgia (McFarlane et al 2016): recommended not to use NSAIDs for FMS, based on a single review (2011) identified 2 small trials with no evidence of improved outcome compared with placebo. This review supports these recommendations.

Gabapentin for fibromyalgia pain in adults. Cochrane Database. Cochrane Database. Cooper TE et al. Syst. Rev. 2017.

Study type: SR & MA of RCT

Conclusion: There is insufficient evidence from a single small trial to support or refute whether gabapentin reduces pain in fibromyalgia.

P Double-blind RCTs of eight weeks' duration or longer for treating fibromyalgia pain in adults.
I Gabapentin
C Placebo or an active comparator.
O Pain intensity: 30% or greater reduction in pain.

Findings: 1 RCT (n=150): a 12-week, multi-centre RCT. Maximum dose 2400 mg daily. Overall risk of bias was low, except for attrition bias, moderate quality.

- The outcome was achieved by 38/75 participants (49%) with gabapentin compared with 23/75 (31%) with placebo: (RR 1.65, 95% CI 1.10 to 2.48).
- A small effect on sleep (−0.71; −1.08 to −0.24) and a large effect on disability (−0.94; −1.32 to −0.56).
- **AEs:** 19 participants discontinued the study because of AEs, 12 in the gabapentin group (16%) and 7 in the placebo group (9%).

Cautions:

- The result of this review is in essence the result of the only RCT included in it.
- The included RCT is small and therefore the evidence from it is not sufficient to support any conclusion.

Notes and linking with current guidelines

- This is an update of a previous Cochrane review published in 2011 and included the same RCT!
- EULAR revised recommendations for the management of fibromyalgia (McFarlane et al 2016) drew its evidence from the same single available RCT used in this review, and recommended further research is required to establish the role of gabapentin in the management of FMS.

CWP

Effect of vitamin D supplementation in chronic widespread pain: a systematic review and meta-analysis. Yong,W.C. et al. Clin.Rheumatol., 2017.

Study type: SR & MA of RCTs.

Conclusion: A limited evidence from a small number of trials suggests that vitamin D supplementation might decrease pain in patients with CWP, but the size of benefit is not clinically important.

P RCTs on Vitamin D supplementation for treating CWP or FMS. FMS was diagnosed by either fulfilling the ACR criteria for FMS or diagnosed by a rheumatologist in patients with otherwise unexplained widespread pain. CWP was defined as chronic recurrent musculoskeletal pain without secondary causes.
I Vitamin D supplementation
C Placebo
O Pain intensity (0-10 VAS).

Findings: 5 RCTs included (n=287). 3 double-blind RCTs, 1 cross-over RCTs. Quality moderate to good.

- A significantly lower pain intensity in CWP patients who received vitamin D treatment compared with those who received placebo: pooled mean difference of 0.46 (95% CI 0.09–0.89).

Cautions:

- Small number of RCTs included.
- Heterogeneity in extent of baseline Vit-D deficiency and in treatment dosages and duration.
- Reporting the quality of included studies is not complete, as it left empty spaces which are not clear whether they are 'unclear' or 'high' risk of bias.
- A potential confounder of Vt D treatment is the geographical location of the trial and the time of the year/sunlight exposure. This has not been addressed in this review.

Notes and linking with current guidelines

- Currently there is no strong evidence supporting routine vitamin D supplementation for FMS patients in daily clinical practice.
- However, vitamin D supplementation in vitamin D deficiency is recommended.
- EULAR revised guidelines for the management of fibromyalgia (McFarlane et al 2016) does not include any recommendation for or against vitamin D in treating FMS.

Chronic widespread pain prevalence in the general population: A systematic review. Andrews,P. et al. Eur.J.Pain, 2017.

Study type: SR & MA of observational studies.

Conclusion: Evidence suggests higher prevalence of CWP in women than men, and in those with a lower than higher socioeconomic status.

P Prevalence studies in the general population (1990–2017)
O Prevalence of CWP and prognostic factors.

Findings: 39 studies included, mostly from developed countries, n= 632,937 (range 361-501,733).

- CWP prevalence range: 1.4% to 24.0%
- Overall prevalence: 9.6% (8.0– 11.2%).
- Prevalence in men: 0.8% to 15.3% and in women 1.7% to 22.1%.
- Gender, country development status, and patient socio-economic status influenced prevalence.

Cautions:

- Heterogeneity in CWP definition, survey methods and measurement processes might influence the results.
- The prognostic factors identified are associated with prevalence, on epidemiological level, which might not automatically mean association at individual level.
- The role of prognostic factors is based on association and causation.
- Most studies were from developed countries, and therefore any conclusions drawn regarding 'developed country' and 'socioeconomic status' as prognostic factors should be taken with caution.

Notes

- This review included a large number of studies with a large number of participants.