Knee Pain (Osteoarthritis) Rapid Evidence Summaries for Versus Arthritis Decision Aids

Notes:

(1) We have defined the population as knee pain in older people (symptomatic knee osteoarthritis) to directly align with the NICE OA guidelines
(2) RCT evidence included in the NICE guidelines is unlikely to pick up adverse events, particularly in the long term. Trials also tend to exclude people who will be using treatments in the real world, including those who are older, have comorbidities, etc. Additional evidence from observational studies would better estimate harm.
(3) Presenting average improvements in pain or function with treatment would be possible, but as discussed with the oversight group, may be misleading as future likely changes strongly depend on an individual patient's current level of pain and disability. The same holds for data regarding response rates.
(4) The evidence consistently showed only small or moderate average effects for most (if not all) treatment options
(5) Consistency and way of describing harms and benefits in the green column to be agreed with the oversight group (text included in the decision aids)

Sources	NICE recommendations	Overall response rate	Pain intensity	Function	Adverse events	**Interpretation of results (for decision aid)**
PART 1: Early presentation of Knee OA						
Tests & scans						
NICE Guidelines Sakellariou 2017 EULAR recommendations (systematic review & expert consensus)	1. Diagnose osteoarthritis clinically without investigations if a person: a. is 45 or over and b. has activity-related joint pain and c. has either no morning joint-related stiffness or morning stiffness that lasts no longer than 30 minutes. [new 2014] 2. Be aware that atypical features, such as a history of trauma, prolonged morning joint-related stiffness, rapid worsening of symptoms or the presence of a hot swollen joint, may	**From Sakellariou 2017** Imaging is not required to make the diagnosis in patients with typical presentation of OA. usage-related pain, short duration morning stiffness, age>40, symptoms affecting one or a few joints. [Level of evidence: III-IV; Level of agreement (evidence and experts, range 0 strong disagreement to 10 strong agreement): 8.7 (7.9, 9.4)] In atypical presentations imaging is recommended to help confirm the diagnosis of OA and/or make alternative or additional diagnoses. [Level of evidence: IV;	*There may be studies on patient outcomes or healthcare use (similar as for back pain), but our rapid searches have not yet identified these.* **And from Sakellariou 2017** "There is a lack of studies in which imaging was applied in addition to clinical findings to evaluate its additional impact on the certainty of diagnosis".			– – – **0** + + + Usually a health professional can diagnose someone from their symptoms and by examining them, so most people do not need tests or scans. If a person's knee problems do not get better, they may need an X-ray. Most of the time, people do not need more scans before a provider makes a referral.

Sources	NICE recommendations	Overall response rate	Pain intensity	Function	Adverse events	**Interpretation of results (for decision aid)**
	indicate alternative or additional diagnoses. Important differential diagnoses include gout, other inflammatory arthritides (for example, rheumatoid arthritis), septic arthritis and malignancy (bone pain). [new 2014]	Level of agreement (evidence and experts): 9.6 (9.1, 10)]				
Education/Information						
NICE guideline NICE Surveillance 2017 (updated evidence for NICE guideline)	**7. Offer accurate verbal and written information to all people with osteoarthritis to enhance understanding of the condition and its management, and to counter misconceptions, such as that it inevitably progresses and cannot be treated. Ensure that information sharing is an ongoing, integral part of the management plan rather than a single event at time of presentation. [2008]**	**From NICE surveillance 2017** "Specific interventions incorporating patient education show inconsistent results. Nevertheless, the current recommendation to offer accurate verbal and written information to patients remains integral to patient-centred care"	**From NICE 2014** 2 RCTs of education programmes (n=100 & n=193) showed no statistically sig. difference in WOMAC pain scores at 9 months to 1 year compared with waiting list control groups – RCT 1: at 9 months mean pain score 10.07 (SD 3.33) vs 10.89 (SD 3.73), p=0.132; RCT 2: at 1 month MD -0.7 (95% CI -2.4 to 1.1), at 1 year MD -0.1 (95% CI -1.4 to 1.2) in favour of education. A meta-analysis of 9 RCTs of unspecified OA reported effect size of 0.16 (95% CI -0.69 to 1.02) for pain (weighted average standardised gain difference) in favour of education versus usual care.	**From NICE 2014** 1 RCT of education programme (n=100) showed sig. difference in WOMAC function scores at 9 months compared with waiting list control groups (mean 35.26 (SD 10.48) for education versus 40.89 (SD 12.64) for controls, p=0.035). 1 RCT showed no sig. difference in WOMAC function scores at 1 month (MD -5.3, 95% CI -13.2 to 2.7) or 1 year (MD -1.4, 95% CI -6.0 to 3.2) A meta-analysis of 9 RCTs of unspecified OA reported no sig difference in functional disability (weighted average standardised gain difference) between patient education and usual care		– – – **0** **+** + + Information about your knee pain is an important part of patient care. This can be verbal, online, and/or written, in a format that suits your needs.

Sources	NICE recommendations	Overall response rate	Pain intensity	Function	Adverse events	**Interpretation of results (for decision aid)**
Self-management						
NICE guidelines Elbers 2018 (systematic review) Schafer 2018 (systematic review) Kroon 2014 (Cochrane review)	**9. Agree individualised self-management strategies with the person with osteoarthritis. Ensure that positive behavioural changes, such as exercise, weight loss, use of suitable footwear and pacing, are appropriately targeted. [2008]** **GDG comments** **The members of this working group have considered these limitations yet accept that with the expected changes in the population with a doubling of chronic disease and elderly patients by 2020 the healthcare system has to consider encouraging a greater degree of self management principles in line with current health policy. If longer term outcomes are to be achieved, such as reduction in the use of health resources, effective use of therapeutic options and more adequately prepared and informed patients seeking interventions such as joint replacement surgery, then self management may be an appropriate and cost effective tool.**		**From Elbers 2018** Post treatment self-management sig. more effective vs control for pain in people with MSK pain conditions (mixed sites/types) SMD= -0.28 (95% CI -0.56 to -0.01) [8 studies, n=506] At median 12 months, self-management no sig. difference compared to control for pain (mixed MSK conditions): SMD= -0.04 (95% CI -0.17 to 0.09) [10 studies, n=1767] **From Schafer 2018** Beneficial short-term (< 6 months) effect on pain of eHealth supported home exercise interventions compared to no or other interventions (SMD=−0.31, 95% CI −0.58 to −0.04) [6 studies, n=742] & long-term effects (SMD= −0.30, 95% CI −0.07 to −0.53) [3 studies, n=416]	**From Elbers 2018** Post-treatment self-management sig. more effective vs control for function in people with MSK pain conditions (mixed sites/types) SMD= -0.28 (95% CI -0.52 to -0.03) [8 studies, n=957] At median 12 months, self-management no sig. difference compared to control on physical function for msk mixed MSK conditions: SMD -0.07 (95% CI -0.16 to 0.02) [12 studies, n=2068] **From Schafer 2018** Short term (< 6 months) effect of eHealth support home exercise interventions on function not sig. vs no or other interventions (SMD=−0.30; 95% CI −0.76 to 0.17) [4 studies, n=479], but sig. long term (9-12 months) effect (SMD=0.41, 95% CI 0.17 to 0.64) [3 studies, n=416]	**From Kroon 2014** Withdrawals at 6 to 12 months was higher for self-management groups than control groups (130 per 1,000 (95% CI 91 to 183) vs 117 per 1,000; absolute risk difference 1% (95% CI -3% to 5%)). Relative percentage change 11% (95% CI -22% to 57%)	− − − 0 **+** + + People with knee OA can expect benefit (although small) from supported self-management Self-management advice related to knee OA will include advice to remain active and exercise, achieve or maintain a healthy weight and look after your mental health**.**

Paracetamol						
NICE guideline NICE Surveillance 2017 (updated evidence for NICE guideline) Ton 2020 (Systematic review of systematic reviews (RCTs of responder criteria)) Leopoldino 2019 (Cochrane review)	**Healthcare professionals should consider offering paracetamol for pain relief in addition to core treatments (see recommendation 1.2.5); regular dosing may be required. Paracetamol and/or topical non-steroidal anti-inflammatory drugs (NSAIDs) should be considered ahead of oral NSAIDs, cyclo-oxygenase 2 (COX-2) inhibitors or opioids. [2008]** **If paracetamol or topical NSAIDs are insufficient for pain relief for people with osteoarthritis, then the addition of opioid analgesics should be considered. Risks and benefits should be considered, particularly in older people. [2008]** **From NICE Surveillance 2017** **Recommendations due to be updated to take into account of up to date MHRA guidance**		**From Ton 2020** No more OA patients attaining meaningful pain relief compared with control (47% vs 43%, RR 1.17; 95% CI 0.83-1.64) [2 RCTs, n=991, 6 to 24 weeks; Low GRADE] **From Leopoldino 2019 (effects up to 12 weeks)** Mean change in pain (VAS, 0 to 100) in the paracetamol group clinically unimportant improvement compared with placebo (MD –3.23 (95% CI –5.43 to –1.02); absolute change -3% (95% CI -5% to -1%); relative change 5% (95% CI 2% to 8%), control mean change -23 [7 studies, n=2355]	**From Leopoldino 2019 (effects up to 12 weeks)** Mean physical function score in the paracetamol group clinically unimportant improvement compared with placebo (MD –2.92 (95% CI –4.89 to –0.95); absolute change -3% (95% CI -5% to -1%); relative change 5% (2% to 9%), control mean change -12 [7 studies, n=2534]	**From Leopoldino 2019 (adverse effects up to 24 weeks)** Sig. higher risk of abnormal liver function tests for paracetamol than placebo; absolute change 5% more abnormal tests with paracetamol than placebo (95% CI 1% to 10%); RR 3.79 (95% CI 1.94 to 7.39); control rate 18 per 1000 [3 studies, n=1237] Difference in withdrawals due to adverse events not statistically or clinically significant; absolute change 1% more withdrew with paracetamol than placebo (95% CI -1% to 3%); RR 1.19 (95% CI 0.91 to 1.55); control rate 65 per 1000 [7 studies, n=3023] Difference in % total experiencing adverse events not statistically or clinically significant; absolute change: 0% more with paracetamol than placebo (95% CI -3% to 3%); RR 1.01 (95% CI 0.92 to 1.11); control rate 325 per 1000 [8 studies, n=3252] No more serious adverse events for paracetamol than placebo; RR 1.36 (95% CI 0.73 to 2.53); control rate 11 per 1000 [6 studies, n=3209]	– – – **0** + + + Some people with knee pain will get some help from paracetamol. It is less likely to cause side effects than other medicines, so it may be good to try it first. Many people find that paracetamol works better if they take it regularly instead of waiting for pain to get bad.

Topical NSAIDs						
NICE guideline Ton 2020 (Systematic review of systematic reviews (RCTs of responder criteria)	**1.5.3 Consider topical NSAIDs for pain relief in addition to core treatments (see recommendation 1.2.5) for people with knee or hand osteoarthritis. Consider topical NSAIDs and/or paracetamol ahead of oral NSAIDs, COX-2 inhibitors or opioids. [2008]** **From Surveillance** **New evidence highlighted in 1 MA & 4 RCTs supports current recommendations to consider topical NSAIDs in addition to other core treatments for osteoarthritis. However, part of recommendation in this section states: 'Consider topical NSAIDs and/or paracetamol ahead of oral NSAIDs, COX-2 inhibitors or opioids.' Any change to the recommended use of oral analgesics will impact on this recommendation**	**From NICE** Knee, hand or mixed OA sites Topical NSAIDs vs placebo for clinical response rate (% of patients reporting at least moderate to excellent or > 50% pain relief or improvement in symptoms rate **at week 1:** rate ratio 1.64, 95% CI 1.26 to 2.13, p≤0.05; NNT 3.3, 95% CI 2.3 to 6.2 [1 MA, 1 RCTs, n=149] & **at week 2** rate ratio 1.59, 95% CI 1.30 to 1.95, p≤0.05; NNT 2.9, 95% CI 2.1 to 4.7, p≤0.05 [1 MA, 1 RCT, n=152 No sig. difference at week 4 [1 MA, 1 RCT, n=114]	**From Ton 2020** Topical NSAIDs led to more OA patients attaining meaningful pain relief (1-12 weeks) compared with control (61% vs 47%, RR = 1.27, 95% CI 1.16 to 1.38; NNT 8) [1-12 weeks; 22 RCTs, n=7265, Low GRADE] **From NICE** Topical diclofenac vs placebo for pain (WOMAC pain score): SMD –0.33, 95% CI –0.48 to –0.18, p<0.0001 at end of treatment - Favours topical diclofenac [1 MA, 3 RCTs, n=697] Topical ibuprofen vs placebo Topical ibuprofen better than placebo for overall pain – No data reported [1 RCT, n=50] Knee, hand or mixed OA sites Topical NSAIDs vs placebo **Week 1**: Effect size 0.41, 95% CI 0.16 to 0.66, p≤0.05 [1 MA, 7 RCTs, n=1000] & **Week 2**: Effect size 0.40, 95% CI 0.15 to 0.65, p≤0.05 in favour of topical NSAIDs [6 RCTs, n=893]. No sig. difference between topical NSAIDs & placebo at **3 weeks** [1 MA, 2 RCTs, n=442] & **4 weeks** [3 RCTs, n=558]	**From NICE** Only knee OA Topical diclofenac vs placebo for function (WOMAC physical function) SMD –0.35, 95% CI –0.50 to –0.20, Favours topical diclofenac [1 MA, 3 RCTs, n=696] Topical NSAIDs vs placebo Knee, hand or mixed OA sites Improvement in function from baseline - Week 1: Effect size 0.37, 95% CI 0.20 to 0.53, [1 MA, 4 RCTs, n=556] & Week 2: Effect size 0.35, 95% CI 0.19 to 0.53, [4 RCTs, n=540] in favour of topical NSAIDs [4 RCTs, n=540]. No sig. improvement in function between topical NSAIDs & placebo at 3 weeks [1 MA, 1 RCT, n=208] & 4 weeks [1 RCTs, n=208]	**From NICE** For knee OA only Paraesthesia, Rash, Any adverse events & GI adverse events – No sig. difference between topical diclofenac & placebo [1 MA, 3 RCTs]. Minor skin dryness - RR 1.74, 95% CI 1.37 to 2.22 in favour of topical diclofenac over placebo [1 MA, 3 RCTs] For mixed OA site: No sig difference between topical NSAIDs and placebo for number of patients with adverse events; Number of patients with GI adverse events; Number of patients with CNS adverse events; Local adverse events – skin reactions [1MA< n=1108] Versus oral NSAIDs [1 MA, 1 RCT: GI adverse events - RR 0.72, 95% CI 0.59 to 0.87 in favour of topical diclofenac Severe GI adverse events - RR 0.35, 95% CI 0.17 to 0.72 in favour of topical diclofenac Dry skin reactions - RR 20.8, 95% CI 7.7 to 55.9 in favour of oral diclofenac	– – – 0 **+** + + Topical NSAIDs may benefit people with knee OA and may reduce the need for oral pain-killers. NSAID creams have fewer side effects than tablets, so most people should try these first. Use NSAID creams regularly, rather than 'as needed'.

					Rash - RR 7.2, 95% CI 2.9 to 18.1 in favour of oral diclofenac	
Oral NSAIDs & Cox-2 inhibitors						
NICE guideline Ton 2020 (Systematic review of systematic reviews (RCTs of responder criteria)) NICE Surveillance 2017 (updated evidence for NICE guideline) de Costa 2017 (Network meta-analysis, 76 RCTs, n=58,451) Song 2016 (Network meta-analysis, 8 RCTs, n=5,942) Puljak 2017 (Cochrane review)	**Guidance on pharmacological treatments to be reviewed in light of more recent evidence.** **27. Where paracetamol or topical NSAIDs are ineffective for pain relief for people with osteoarthritis, then substitution with an oral NSAID / COX-2 inhibitor should be considered. [2008]** **28. Where paracetamol or topical NSAIDs provide insufficient pain relief for people with osteoarthritis, then the addition of an oral NSAID / COX-2 inhibitor to paracetamol should be considered. [2008]** **29. Use oral NSAIDs / COX-2 inhibitors at the lowest effective dose for the shortest possible period of time. [2008]** **30. When offering treatment with an oral NSAID / COX-2 inhibitor, the first choice should be either a standard NSAID or a COX-2 inhibitor (other than etoricoxib 60mg). In either case, co-prescribe with a proton pump**	**From NICE Surveillance 2017 & Song 2016** Proportion of patient withdrawals due to lack of efficacy sig. lower for etoricoxib 30–60 mg (OR 0.21, 95 % CrI 0.12–0.38), celecoxib 200–400 mg (OR 0.29, 95 % CrI 0.18–0.47), and naproxen 1000 mg (OR 0.31, 95 % CrI 0.18–0.51) than placebo. Number of patient withdrawals due to lack of efficacy tended to be lower in etoricoxib 30–60 mg group than in naproxen 1000 mg and celecoxib 200–400 mg groups, although not sig. (OR 0.68, 95 % CrI 0.36–1.33 and OR 0.70, 95 % CrI 0.38–1.37, respectively	**From Ton 2020** Oral NSAIDs led to more OA patients attaining meaningful pain relief compared with control (57% vs 39%, RR = 1.44, 95% CI 1.36-1.52; NNT 6) [43 RCTs, n=28,699, 4 to 104 weeks; Moderate GRADE] **From NICE Surveillance 2017 & de Costa 2017** All preparations, irrespective of dose, improved point estimates of pain symptoms when compared with placebo. Statistically sig. effect sizes shown for 11 drugs/doses, but clinically important effect size (i.e. 95% CI >= -0.37) for: Diclofenac 150 mg/day; Etoricoxib 30 mg/day; Etoricoxib 60 mg/day; Rofecoxib 25 mg/day; Rofecoxib 50 mg/day. Treatment effects appeared to increase as drug dose increased but only Naproxen showed sig. linear dose response (p=0.034) **From Puljak 2017** 3% absolute improvement (95% CI 2% to 5%) in pain scores (WOMAC, 0 to 500)	**From de Costa 2017 (most studies 12 weeks follow-up)** 20 out of 21 drugs/doses included improved physical function when compared with placebo. 9 drugs/doses had effect sizes over clinical minimal importance (-0.37), but only 2 interventions, diclofenac 150 mg/day (effect size –0·51, 95% CrI –0·65 to –0·37) & rofecoxib 25 mg/day (effect size –0·48, 95% CrI –0·56 to –0·40), were significant. **From Puljak 2017** 4% absolute improvement (95% CI 2% to 6%) in function (WOMAC physical function, 0 to 1700) for celecoxib versus placebo, 12% relative improvement (95% CI 5% to 19%), SMD -0.17 (-0.27 to -0.07), NNTB 14 (9 to 34) [4 RCTs, n=1622, control mean score 540]	**From NICE Surveillance 2017 & Song 2016** Number of withdrawals due to adverse events not sig. different among etoricoxib, celecoxib, naproxen, & placebo, although tended to be lower with etoricoxib and placebo. From NICE guideline Total number with adverse events no sig. difference between NSAIDs and paracetamol over mean duration of 13.1 weeks [1 MA] Number of gastrointestinal adverse events higher for non-selective NSAIDs than paracetamol (RR 1.47, 95% CI 1.08 to 2.00, p<0.05, sig. heterogeneity), but no sig. difference between [other?] NSAIDs and paracetamol or COX-2 versus paracetamol [1 MA, 5 RCTs, mean duration of 13.1 weeks]. 0.2% with gastrointestinal adverse events for paracetamol vs 0.3% for ibuprofen [1 cohort, n=3124] **From Puljak 2017** (based on RCTs)	– – **–** 0 **+** + + Most people with knee pain will have less pain in the first 3 months of taking NSAID tablets. These should be taken at the lowest dose that works for the shortest possible time, and usually with tablets to protect the stomach. People with some health conditions should avoid NSAID tablets. NSAID creams have fewer side effects, so should be tried first. NSAIDs work better if you take them regularly instead of waiting for pain to get bad.

	inhibitor (PPI), choosing the one with the lowest acquisition cost. [2008] **31. All oral NSAIDs / COX-2 inhibitors have analgesic effects of a similar magnitude but vary in their potential gastrointestinal, liver and cardio-renal toxicity; therefore, when choosing the agent and dose, take into account individual patient risk factors, including age. When prescribing these drugs, consideration should be given to appropriate assessment and/or ongoing monitoring of these risk factors. [2008]** **32. If a person with osteoarthritis needs to take low-dose aspirin, healthcare professionals should consider other analgesics before substituting or adding an NSAID or COX-2 inhibitor (with a PPI) if pain relief is ineffective or insufficient. [2008]**		for celecoxib over placebo, 12% relative improvement (95% CI 7% to 18%), SMD -0.22 (-0.32 to -0.12), NNTB 11 (7 to 18) [4 RCTs, n=1622, control mean score 136]		Number of withdrawals due to adverse events for celecoxib vs placebo: 0% absolute change (95% CI -1% to 1%), 1% relative change (95% CI -15% to 15%), OR 0.99 (95% CI 0.85 to 1.15) [24 RCTs, n=10996, control rate 57 per 1000] Number experiencing any serious adverse events: 0% absolute change (95% CI 0% to 0%), 5% relative change (95% CI -34% to 36%), OR 0.95 (95% CI 0.66 to 1.36) [22 RCTs, n=10926, control rate 10 per 1000] Number with gastrointestinal events: 0% absolute change (95% CI 0% to 1%), 91% relative change (95% CI -76% to 1390%), OR 1.91 (95% CI 0.24 to 14.90) [8 RCTs, n=3263, control rate 1 per 1000] Number with cardiovascular events: 0% absolute change (95% CI 0% to 1%), 240% relative change (95% CI =27% to 1488%), OR 3.40 (95% CI 0.73 to 15.88) [4 RCTs, n=2112, control rate 1 per 1000]	
Topical Capsaicin						
NICE Guideline	**Topical capsaicin should be considered as an adjunct to core treatments**		**From Laslett 2014:** Capsaicin was moderately more effective than placebo over 4 weeks - change in		**From Laslett 2014:** Mild burning at application site in 35-100% of capsaicin-treated	– – – 0 **+ +** +

Laslett 2014 (systematic review – abstract only)	**for knee or hand osteoarthritis. [2008]**		VAS pain score was 0.44 (95% CI 0.25-0.62). Results longer than 4 weeks were conflicting.		patients - risk ratio 4.22 (95% CI 3.25-5.48, n = 5 trials); incidence peaked in week 1, declining over time	Most people with knee pain will get some pain relief from capsaicin cream if it is used 3 to 4 times every day for several weeks. It is normal to feel mild burning pain after applying the cream.
Opioids						
NICE guideline Ton 2020 (Systematic review of systematic reviews (RCTs of responder criteria)) Toupin 2019 (Cochrane review) Bedson 2019			**From Ton 2020** Opioids led to more OA patients attaining meaningful pain relief compared with control (47% vs 43%, RR = 1.16, 95% CI 1.02 to 1.32; NNT 32) [15 RCTs, n=6266, 10 days to 24 weeks; Very Low GRADE] **From NICE guideline** For knee OA, opioids improved pain (VAS) more than placebo at 2-4 weeks (MD 10.5, 95% CI 7.4 to 13.7) [1 MA, 6 RCTs, n=1057]. **From Toupin 2019** Mean pain (VAS, 0 to 100): 4% absolute improvement for tramadol vs placebo at 1-3 months (95% CI 3% to 5%), 7% relative improvement (6% to 9%), SMD –0.25 (95% CI –0.32 to –0.18) [8 RCTs, n=3972, control mean 54.3]	**From Toupin 2019** Mean function (WOMAC physical function, 0 to 1700): 4% absolute improvement at 1-3 months (95% CI 2% to 6%), 6% relative improvement (95% CI 4% to 9%), SMD –0.20 (95% CI –0.29 to –0.12) [5 RCTs, n=2550, control mean 1059]	**From Bedson 2019** Major trauma risk increased from 285 per 10,000 person-years without long-term opioids to 369/10,000 for a long-term opioid episode (<20 mg MED), 382/10,000 (20-50 mg MED), and 424/10,000 (≥50 mg MED). Adjusted hazard ratios were 1.09 (95% CI; 1.04, 1.14 for <20 mg MED vs. not being in an episode of long-term prescribing), 1.24 (95% CI; 1.16, 1.32: 20-50 mg MED) and 1.34 (95% CI; 1.20, 1.50: ≥50 mg MED). Significant dose-dependent increases in the risk of overdose (any type), addiction, falls, accidental poisoning, gastrointestinal pathology, and iron deficiency anaemia were also found. [1 cohort, n=98,140 new long-term opioids users	– – – 0 + + + People should use only use weak opioids if they cannot take NSAIDs, if NSAIDs have not worked well enough or have caused side effects. People should only use opioids for short periods as opioids can cause side effects and addiction. Guidelines recommend avoiding strong opioids, including tramadol, morphine, and oxycodone.

					(median age 61, 41% male), median follow up 3.4 years] **From Toupin 2019** Number experiencing any adverse events: 17% absolute worsening for tramadol than placebo (95% CI 12% to 23%), 34% relative worsening (95% CI 24% to 46%), NNTH 6 (95% CI 5 to 9), RR 1.34 (95% CI 1.24 to 1.46), 659 per 1000 (95% CI 610 to 718) tramadol vs 492 per 1000 placebo [4 RCTs, n=2039] Number withdrawals due to adverse events: 12% absolute worsening for tramadol vs placebo (95% CI 9% to 16%), 164% relative worsening (95% CI 117% to 220%), NNTH 9 (95% CI 7 to 12), RR 2.64 (95% CI 2.17 to 3.20), 194 per 1000 (95% CI 159 to 235) tramadol vs 73 per 1000 placebo [9 RCTs, n=4533] Number with any serious adverse events: 1% absolute worsening for tramadol vs placebo (95% CI 0% to 4%), 78% relative worsening (95% CI 11% to 184%), NNTH 68 (95% CI 29 to 477), RR 1.78	

					(95% CI 1.11 to 2.84), 34 per 1000 (95% CI 21 to 54) tramadol vs 19 per 1000 placebo [7 RCTs, n=3612]	
Exercise and physical activity						
NICE guideline Ton 2020 (Systematic review of systematic reviews (RCTs of responder criteria)) Goh 2019 (systematic review) Uthman 2013 (network meta-analysis) Quicke 2015 (systematic review)	**12 Advise people with osteoarthritis to exercise as a core treatment (see recommendation 1.2.5), irrespective of age, comorbidity, pain severity or disability. Exercise should include:** **- local muscle strengthening and** **- general aerobic fitness.** **It has not been specified whether exercise should be provided by the NHS or whether the healthcare professional should provide advice and encouragement to the person to obtain and carry out the intervention themselves. Exercise has been found to be beneficial but 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, circumstances and self-motivation, and the availability of local facilities. [2008]** **Appendix A: summary of evidence from 2017 surveillance of Osteoarthritis (2017)**		**From Ton 2020** Exercise led to more OA patients attaining meaningful pain relief compared with control (47% vs 21%, RR = 2.36, 95% CI 1.79 to 3.12; NNT 4) [11 RCTs, n=1367, 6 to 104 weeks; Low GRADE] **From Goh 2019** For knee and/or hip OA Statistically significant exercise benefits for pain vs controls at 8 weeks (ES 0.56, 95% CI 0.44-0.68) [77 RCTs, n=6472). **From NICE** Aerobic walking vs no-exercise: Effect size for reducing pain 0.52, 95% CI 0.34 to 0.70, p<0.05 favouring exercise Home-based quadriceps strengthening exercise vs no-exercise: Effect size for reducing pain 0.32, 95% CI 0.23 to 0.42, p<0.05 favouring exercise [1 MA, 4 RCTs, n=449, mean duration 7.2 months] **From Uthman 2013**	**From NICE** Aerobic walking vs no-exercise: Effect size for reducing pain: 0.46, 95% CI 0.25 to 0.67, p<0.05 favouring exercise Home-based quadriceps strengthening exercise vs no-exercise: Effect size: 0.32, 95% CI 0.23 to 0.41, p<0.05 favouring exercise [1 MA, 4 RCTs, n=449, mean duration 7.2 months] **From Uthman 2013** Strengthening + flexibility + aerobic exercise sig. more effective than no exercise - overall difference in function −1.32 units (95% credible interval −2.44 to −0.21 units, medium effect size) (WOMAC disability scale ranging from 0 to 10) and this combination had highest probability of being best overall treatment for improving function.	**From Quicke 2015** Moderate adverse events were rare, reported in 0 to 6% of physical activity participants in any included study (5 falls - 1 resulting in a fractured wrist and 1 a head laceration), 1 foot fracture (caused by a participant dropping a weight on their foot), 4 dropouts related to increased knee or other joint pain and 1 inguinal hernia attributed to physical activity. Mild adverse events reported in between 0 and 22% of physical activity participants, usually muscle soreness and temporary or mild joint pain increase. [22 RCTs]	− − − 0 **+ +** + Most people with knee pain will get some help from doing regular strength, flexibility, and aerobic exercises. If someone is overweight, losing weight can help. At first, exercise may make pain worse, but this does not mean that the knee is being damaged. It's best to start with a small amount of activity and build up.

	NICE guideline CG177 9 of 54		For studies including any lower limb joints - mainly knee OA. Strengthening exercise only, strengthening + flexibility, combined strengthening + flexibility + aerobic, aquatic strengthening, and aquatic strengthening + flexibility sig. more effective than no exercise - Overall difference in pain intensity −2.03 cm (95% credible interval −2.82 to −1.26 cm, large effect size), Strengthening only exercise, SMD −0.81 (95% CrI −1.13 to −0.50) Flexibility + strengthening exercise, SMD −0.50 (95% CrI −0.85 to −0.16) Flexibility + strengthening + aerobic SMD −0.69 (95% CrI −1.04 to −0.35) Aquatic strengthening SMD −0.75 (95% CrI −1.42 to −0.07) Aquatic flexibility + strengthening exercise SMD −0.96 (95% CrI−1.64 to −0.27)			

Weight-loss						
NICE guideline Hall 2019 (Systematic review)	**14. Offer interventions to achieve weight loss* as a core treatment (see recommendation 1.2.5) for people who are obese or overweight. [2008]**		**From NICE** No sig. difference for pain between weight loss interventions and no weight loss at 8 to 18 weeks [1MA, 4 RCTs, n=417] **From Hall 2019** Diet-only treatments did not sig. reduce pain (SMD -0.13; 95% CI: -0.37, 0.10; I2 = 49%) but combined diet and exercise treatments did sig. reduce pain (SMD -0.37; 95%CI: -0.69, -0.04; I2 = 54%) [5 RCTs]	**From NICE** Weight loss interventions versus no weight loss: For self-reported disability, weight loss 6.1 kg; effect size 0.23 (95% CI 0.04 to 0.42, p=0.02) favouring weight loss interventions at 8 to 18 weeks [1 MA, 4 RCTs, n=417] **From Hall 2019** Physical function improved moderately with diet treatments (SMD -0.30; 95%CI: -0.52, -0.08; I2 = 47%) and combined diet and exercise treatments (SMD -0.32; 95%CI: -0.56, -0.08; I2 = 24%) [7 RCTs]		– – – 0 **+** + + Losing weight (if overweight or obese) can be beneficial for people with knee OA. This should be a combination of diet and exercise.

Sources	NICE recommendations	Overall response rate	Pain intensity	Function	Adverse events	**Interpretation of results (for decision aid)**
PART 2: Long term care / referral options for knee OA						
Steroid injections						
NICE guideline Ton 2020 (Systematic review of systematic reviews (RCTs of responder criteria)) Juni 2015 (Cochrane review)	**33. Intra-articular corticosteroid injections should be considered as an adjunct to core treatments for the relief of moderate to severe pain in people with osteoarthritis. [2008]**	**From NICE** Overall improvement (range 1 to 104 weeks): RR 1.44, 95% CI 1.13 to 1.82; p=0.003 in favour of steroid injection vs placebo [1MA, 3 RCTs, n=156]	**From Ton 2020** IA steroids led to more OA patients attaining meaningful pain relief compared with control (50% vs 31%, RR = 1.74, 95% CI 1.15 to 2.62; NNT 6) [7 RCTs, n=706; 4 to 24 weeks; Very Low GRADE] **From NICE** At 1 week post-injection: Cortivazol injection sig. better for reducing pain (0 to 100) than placebo (WMD –21.91, 95%CI –29.93 to –13.89, [1 MA, 3 RCTs, n=161] 12 weeks: smaller effect but injection still sig. better for pain reduction than placebo WMD –14.20, 95%CI –27.44 to –0.96, p=0.04 [1MA, 1RCT, n=53] **From Juni 2015** For median 12 weeks follow up: SMD -0.40 (-0.58 to -0.22), change in pain VAS (0 to 10) sig. less for steroid injection vs sham injection (-1.0 cm, 95% CI -1.5 to -0.6, control mean -1.8 change), NNTB 8 (95% CI 6 to 13) [26 studies, n=1749]	**From NICE** No function outcomes reported **From Juni 2015** For median 12 weeks follow up: SMD -0.33 (95% CI -0.56 to -0.09), change in mean function score 2 (WOMAC, 0 to 10) sig. less for steroid injection vs sham injection (-0.7, 95% CI -1.2 to -0.2, control mean change -1.2), NNTB 10 (95% CI 7 to 33) [15 studies, n=1014]	**From Juni 2015** Number of participants experiencing any adverse event (median follow-up: 17 weeks): RR 0.89 (95% CI 0.64 to 1.23), 134 per 1000 participant-years (95% CI 96 to 185) for steroid injection vs 150 per 1000 participant-years for sham injection [2 studies, n=84] Number of participants who withdraw because of adverse events (median follow-up: 25 weeks): RR 0.33 (95% CI 0.05 to 2.07), 6 per 1000 participant-years (95% CI 1 to 35) for steroid injection vs 17 per 1000 participant-years for sham injection [2 studies, n=204] Number of participants experiencing any serious adverse event (median follow up: 26 weeks): RR 0.63 (95% CI 0.15 to 2.67), 3 per 1000 participant-years (95% CI 1 to 11) for steroid injection vs 4 per 1000 participant-years for sham injection [5 studies, n=331]	– – – 0 + + + Steroid injections may help people with knee pain that is very bad and that goes on for a long time. People will get the most relief in the first 3 months after the injection. Getting more injections later may help less, and may cause complications.

Hyaluronic acid injections						
NICE guideline Bannuru 2015 (Network meta-analysis) Bannuru 2016 (Network meta-analysis)	**34. Do not offer intra-articular hyaluronan injections for the management of osteoarthritis. [2014]** **Not recommended by GDG as inconsistent results and small effect sizes. However, the 2017 surveillance document has recommended this is reviewed in the next update.**		**From NICE** Generally small effects to no sig effect of hyaluronic acid vs sham injections – not clinically sig. Hylan GF 20 vs placebo <13 weeks: SMD -1.24 (95% CI -2.15 to -0.33) [WOMAC, 4 RCTs, n=233] Orthovisc vs placebo: <13 weeks - SMD -0.99 (95% CI -1.75 to -0.24) [WOMAC pain (5 to 25 likert, 6 RCTs, n=449] >13 weeks - SMD -0.57 (95% CI -1.11 to -0.02) [WOMAC pain (5 to 25 Likert, 5 RCTs, n=408] **From Bannuru 2015** Effect size 0.63 (95% credible interval [CrI], 0.39 to 0.88) for hyaluronic acid vs oral placebo – however only small effect size between hyaluronic acid injections and sham injections 0.34 (95% CI 0.26 to 0.42) [52 studies]	**From NICE** Generally small effects to no sig effect of hyaluronic acid vs sham injections – not clinically sig. Hylan GF 20 vs placebo <13 weeks: SMD -1.2 (95% CI -1.95 to -0.46) [WOMAC function, 4 RCTs, n=233] Orthovisc vs placebo: <13 weeks - SMD -1.21 (95% CI -2.13 to -0.28) [WOMAC function (17 to 85 likert, 4 RCTs, n=155] >13 weeks - SMD -0.55 (95% CI -1.04 to -0.06) [WOMAC pain (17 to 85 Likert, 3 RCTs, n=114] **From Bannuru 2015** Unable to access supplements for effect sizes. Intra-articular hyaluronic acid sig. better than IA placebo and IA corticosteroids. Sham injections not sig better than oral placebo (effect size, 0.15 [CrI, -0.22 to 0.53])	**From NICE** Number with local reaction <13 weeks: 23/210 (11%) for Hylan GF 20 vs 8/207 (3.9%) for sham injection (RR 1.81, 95% CI 0.36 to 9.07) [5 RCTs, n=417] Number with local skin rash 9/361 (2.5%) for Orthovisc vs 14/358 (3.9%) for placebo at >13 weeks (RR 0.63 (95% CI 0.28 to 1.45) **From Bannuru 2016** Overall incidence of local reactions reported across all products was 8.5%. Commonly reported adverse events were local reactions, such as pain, swelling and arthralgia, which subsided rapidly. None of the HA products statistically sig. different from sham injection or from each other with regard to incidence of AEs. Three treatment-related serious adverse events (SAEs) were reported among 9214 participants.	– – **–** 0 **+** + + *Injection with hyaluronic acid is currently not recommended but this is to be reviewed to incorporate recent evidence to assess if this changes recommendation and might suggest benefit to some patients*

Arthroscopy						
NICE Brignardello-Petersen 2017 (Systematic review)	21. 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). [2008, amended 2014]	**2017 NICE surveillance summary**: Cost-effectiveness analysis on a cohort of 43 people with radiological knee osteoarthritis and mechanical symptoms, prospectively followed-up after having arthroscopic debridement, 36 patients had significant reductions in pain and in Oxford Knee Score after 1.5 years, 7 other people (16%) had undergone knee arthroplasty. Cost per quality-adjusted life year (QALY) was £2,088.	**From Brignardello-Petersen 2017** Knee arthroscopy results in very small reduction in pain up to 3 months (mean difference = 5.4 on a 100-point scale, 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 (GRADE high-certainty evidence)	**From Brignardello-Petersen 2017** Knee arthroscopy results in a very small improvement up to 3 months (mean difference =4.9 on a 100-point scale, 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) (GRADE moderate-certainty evidence)	**From Brignardello-Petersen 2017** Low-quality evidence (GRADE) but suggested a very low probability of serious complications after knee arthroscopy	– – – **0** + + + Keyhole surgery will not help most people with knee problems. But people whose knees 'lock' may get help from keyhole surgery. This surgery has a small risk of complications.
Surgery: total knee replacement (TKR)						
NICE guidelines Liddle 2015 (National Joint Registry linked to PROM records) Evans 2019 (systematic review of case series + National Joint Registry data) Beswick 2012 (systematic review) Lungu 2016 (systematic review)	**35. Clinicians with responsibility for referring a person with osteoarthritis for consideration of joint surgery should ensure that the person has been offered at least the core (non-surgical) treatment options (see recommendation 6 and Figure 3 in section 4.1.2). [2008]** **36. Base decisions on referral thresholds on discussions between patient representatives, referring clinicians and surgeons, rather than using scoring tools for prioritisation. [2008, amended 2014]**	**From Liddle 2015** Patient-reported improvement at 6 months (N= 10 557): Much better 7627 (72.3%) A little better 1702 (16.1%) Same 496 (4.7%) A little worse 436 (4.1%) Much worse 268 (2.5%) **From Lungu 2016:** Predictors of pain and function after TKR - Much of the evidence is inconsistent **From Evans 2019** The pooled registry 25 year survival of TKRs (14 registries) was 82·3% (95% CI 81·3–83·2) and of	**Beswick 2012** Studies suggested that at least 10%-34% of patients experience long-term pain after knee replacement – conservative estimate assuming missing data had similar pain outcomes. Satisfaction with pain relief ranged from 72% for going up or downstairs to 85% for walking on a flat surface. [11 studies] **Lungu 2016** Factors sig. associated with higher postop pain only in >1 study [number of studies] Higher anxiety level [2] Worse pain level [9] Presence of back pain [2] Greater comorbidity [4]	**Lungu 2016** Factors sig. associated with poor function only in >1 study [number of studies] Older age [2] Higher anxiety [2] Higher depression level [2] Greater pain catastrophizing [2] Worse function level [12] Greater comorbidity [3] Worse mental health [3] Higher BMI [2] Sig. predictors of pain & function in >1 study Female gender [2] Greater social Deprivation [2]	**From Liddle 2015** Patient reported complications for TKR at 6 months (N=10 557): Drug reaction 1358 (13.7%) Urinary 996 (10.3%) Bleeding 770 (8.0%) Wound 1203 (12.3%) Re-admitted 978 (9.3%) Re-operation 350 (3.3%) **From Garriga 2019** Out of 210 275 primary TKRs, higher probability of developing complications in 6 months after surgery associated with: Older age (≥85 years, regression coefficient, 0.55; 95% CI, 0.37 to 0.73; P < .001)	– – **–** 0 **+ +** + After 6 months or longer after having surgery, about 9 out of every 10 people are satisfied with their joint replacement. About 1 out of every 10 people are not satisfied. People's mobility usually improves after surgery. But the joint may be less mobile than a healthy knee would be. A knee replacement will still be working after 25

Garriga 2019 (retrospective cohort study of National Joint Registry, linked to HES)	**37. Consider referral for joint surgery for people with osteoarthritis who experience joint symptoms (pain, stiffness and reduced function) that have a substantial impact on their quality of life and are refractory to non-surgical treatment. [2008, amended 2014]** **38. Refer for consideration of joint surgery before there is prolonged and established functional limitation and severe pain. [2008, amended 2014]** **39. Patient-specific factors (including age, sex, smoking, obesity and comorbidities) should not be barriers to referral for joint surgery. [2008, amended 2014]**	UKRs (four registries) was 69·8% (95% CI 67·6–72·1)		Presence of depression [4] Higher anxiety level [2] Presence of back pain [2] Worse pain/function Levels [6] Worse mental health [3] Vascular comorbidity [2] Higher BMI [2] OA diagnosis [2] Greater comorbidity [2]	CCI score of 3 or higher (regression coefficient, 0.68; 95% CI, 0.58 to 0.77; P < .001), an ASA grade of 4 or 5 (regression coefficient, 0.88; 95% CI, 0.62 to 1.14; P < .001), Lower-volume hospitals (hospitals with ≤200 vs ≥500 surgical procedures per year, regression coefficient, 0.09; 95% CI, 0.01 to 0.18; P = .03), and Public hospitals (private hospitals, regression coefficient, −0.10; 95% CI, −0.16 to −0.04; P < .001)	years for about 8 out of every 10 people. It will not be working for about 2 people out of every 10 people. National Joint Registry Patient Decision Support Tool (PDST) available to help make decisions about joint replacement www.njrcentre.org.uk
Kahlenberg 2018 [systematic review]	**Patient satisfaction**	**From Kahlenberg 2018** % satisfied patients ranged from 65 to 100%, with the majority of studies (82.6%) reporting greater than 80% satisfaction; median percentage of satisfied patients was 88.9% [1 systematic review, 138 studies] Predictors of satisfaction Preoperative factors: Higher-grade osteoarthritis (4) Higher baseline patient reported function (3) Better emotional/mental health (2) Older age (3) Male gender (2) Implants Triathlon knee (compared to Kinemax) (2) Rotating platform (compared to medial pivot fixed bearing) (4) Postoperative factors: Less pain (12) No complication (2) Fulfilment of expectations (7) More improvement on functional score (8) Higher postoperative patient-reported function (16) Better function on walk test (2) Less knee stiffness/improvement in ROM (5) Higher general health score (2)					

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