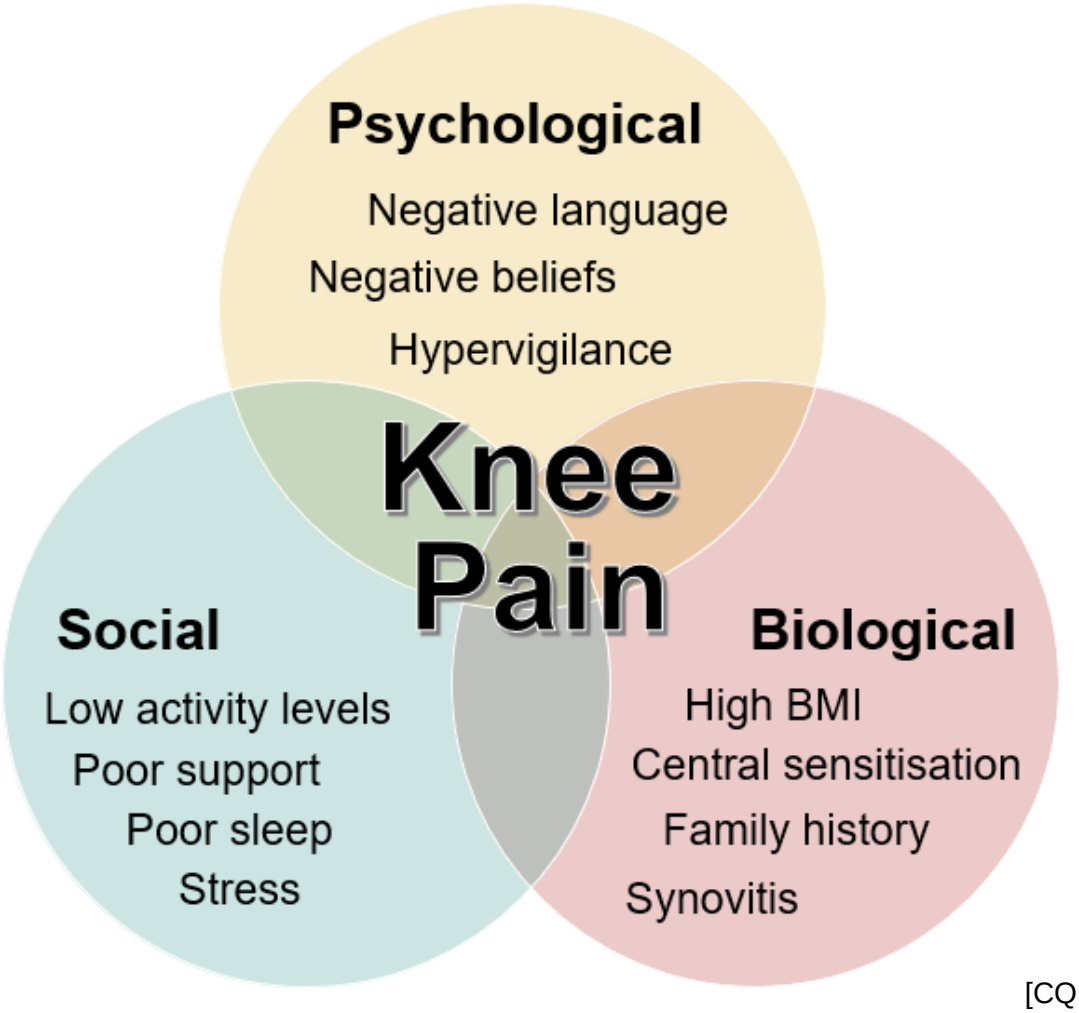
Small Group Education

📖 South Tyneside - Pre-reading

Persistent Pain (Osteoarthritis)
Changing the Narrative

November 2021



[CQE 2021]

Aims of the Small Group education meeting

Background
Pain is an output from the brain secondary to interpretation of sensory input. Persistent (or chronic) pain is thus influenced by context: multiple biopsychosocial factors affect immune and stress responses altering the experience of pain. Osteoarthritis (OA) is an example of persistent pain that is affected by the 'whole person condition'. Consideration of factors that modulate inflammatory processes, tissue sensitivities and behavioural responses is necessary [Berenbaum 2013, Caneiro 2020].

Management of OA can be improved by holistic collaboration with the patient and the primary health care team. This includes minimising iatrogenic harm by avoiding the use of words that have negative connotations and by prudent use of imaging to avoid sending patients on a negative trajectory e.g., changing the narrative from joint 'wear and tear' to 'wear and repair', explaining expected normal age-related radiological changes before imaging is performed.

Learning Objectives
After completing the pre-reading and attending this Small Group meeting, participants will be able to:

- Describe persistent pain and how it is influenced by multiple biopsychosocial factors
- Assess elements that contribute to an individual's pain using the biopsychosocial model of health and wellbeing and discuss how they can be addressed
- Recognise how your interaction with a patient can positively or negatively affect a patient's journey
- Explain how imaging correlates poorly with level of pain or loss of function
- Review the current evidence for medications and surgical interventions and understand their limitations
- Identify inequity and outline ways to reduce barriers contributing to persistent knee pain
- Outline a teamwork approach to supporting patients with persistent pain

Included in this pre-reading

- Introduction
- Inequity
- Definitions
- Persistent pain as a **bio**-**psycho**-**social** problem
  - The 'bio' part: OA and its different mechanisms
  - The 'psych' part: The impact of psychology on pain
  - The 'social' part: The social impacts of living with knee OA
- Changing the narrative
- Management strategies for persistent pain
  - Non-pharmacological components
  - The role of medication and surgery

This pre-reading provides 1 hr continuing professional development.

Acknowledgements

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Introduction

Persistent (otherwise known as chronic) pain affects between one-third and one-half of the population of the UK [Fayaz 2016] and it carries significant burden for the individual, family, society and economy. It often presents as a result of an injury or a disease; however, it is itself a separate condition, with its own definition and classification system [Mills 2019].

Persistent (chronic) pain is defined as pain which has persisted beyond normal tissue healing time, generally considered to be >3 months. It requires a multi-disciplinary biopsychosocial approach for managing, that is represented well by holistic models of health and is an important component of patient centred care [Health Education England 2018]. Another example of this is the six dimensions of health that make up the dynamic concept of health proposed by Huber et al [Huber 2016]. Clinicians can explore six dimensions of health: bodily and mental functions, spiritual dimensions, quality of life, social and societal participation and daily functioning [Huber 2016]. NICE also outlines a holistic approach to osteoarthritis assessment and management [NICE 2017].

Persistent (chronic) pain is a complex disease that typically does not respond well to medication [Swain 2018]. However, pain for most patients can be successfully managed by addressing biopsychosocial factors although evidence on outcomes for those with chronic pain is mixed. Some report that many will recover and lead normal lives [CHHPWs 2020, NZ Pain Society], others report different pain trajectories – mild persistent pain (24%), moderate (22%) or severe persistent pain (13%), fluctuating between mild and severe (31%) or gradual improvement (11%) [Glette 2020].

South Tyneside has a localised HealthPathway on Chronic Pain which highlights non-medical approaches: https://southtyneside.communityhealthpathways.org/37163.htm

Osteoarthritis (OA) is a leading cause of persistent pain and disability in older adults, most commonly affecting the knee, hip, and hand [Rice 2019]. In the UK over 6 million people >65y have a musculoskeletal condition. Accurate data on how many of these is OA related is not possible, however

estimations suggest 18% of those aged >45y in England have OA knee, 11% OA hip [Arthritis Research UK 2013, Versus Arthritis 2019].

Approximately 8.75 million people aged >45y (33%) in the UK have sought treatment for osteoarthritis. If you break this further into age groups that have sought treatment, the figures are:

- Approximately 25% men and 33% women aged 45y-64y
- Almost 50% people aged >75y [Versus Arthritis 2019]

Over the last few decades there has been a profound shift in understanding of OA aetiology and pathophysiology, away from symptoms being solely due to structural damage and towards a multifactorial 'whole person condition' where different biopsychosocial factors influence the experience of the disease and level of pain and disability [Berenbaum 2013]. This evidence reinforces the need to change the focus of the assessment and management of OA [Caneiro 2020].

Inequity

Research in Aotearoa New Zealand demonstrates higher rates of persistent pain (of any type) amongst women, Māori, disabled, and the most deprived populations [MOHa 2020]. Ethnic disparities also exist in access to pain clinics, with a 2018 study finding lower than expected attendance for Pasifika and Asians, and higher than expected for NZ Europeans (and as expected for Māori). Of those attending, Māori, Pasifika, and to a lesser extent, Asians, had significantly more pain, greater psychosocial impairment and had a larger impact on their life, compared with NZ Europeans [Lewis 2018].

Ethnicity has been shown to be one of the best predictors of pain intensity in those presenting at pain clinics [Lewis 2018]. It is likely that a similar picture exists in the UK with the burden of disease (persistent pain, OA) impacting more on the most deprived.

Locally in the UK, it has been shown that the prevalence of a long term musculoskeletal condition is more likely in those people living in the most deprived decile areas compared to least deprived (17-22% vs 12-15%). Chronic pain has also been shown to be more prevalent among people of lower income groups [Versus Arthritis 2019].

Definitions

Pain: An international multidisciplinary task force for the International Association for the Study of Pain (IASP) recently published the revised definition of pain as: "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" [IASP 2020, Raja 2020].

It has expanded on this with the addition of six key points:

1. "Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors.
2. Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons.
3. Through their life experiences, individuals learn the concept of pain.
4. A person's report of an experience as pain should be respected.
5. Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being.

6. Verbal description is only one of several behaviours to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain".

[IASP 2020]

Acute pain: pain caused by something specific (injury or disease) that lasts up to seven days (duration dependent on mechanism and severity) and resolves when the underlying cause resolves; it can extend from seven to 30 days but not >3 months [Schug 2020]

Persistent/Chronic pain: pain that persists beyond the expected time of healing and is ongoing, lasting ≥3 months [Smith 2019] **NICE** uses the following definitions:

- **Chronic pain**:
  - An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage
  - Pain that persists or recurs for more than 3 months
  - Multifactorial — biological, psychological, and social factors contribute to the pain syndrome
- **Chronic primary pain**:
  - Pain in one or more anatomical regions that is characterized by significant emotional distress (anxiety, anger/frustration, or depressed mood) or functional disability (interference in daily life activities and reduced participation in social roles). The diagnosis is appropriate independently of identified biological or psychological contributors unless another diagnosis would better account for the presenting symptoms
  - Multifactorial — biological, psychological, and social factors contribute to the pain syndrome

[NICE 2017]

Nociceptor: a high-threshold sensory receptor of the peripheral nervous system that transmits noxious stimuli [IASP 2020]

Nociception: the neural *process* of encoding noxious stimuli (pain sensation is not implied) [IASP 2020]. An important difference between pain and nociception is that nociception is a *process* and cannot be felt, pain is always felt [Moseley 2017]

IASP describes three mechanistic descriptors for pain states:

1. **Nociceptive pain:** Pain that arises from actual or threatened damage to tissue and is due to the activation of nociceptors (i.e., pain that occurs with a normally functioning somatosensory system)
2. **Neuropathic pain:** is the clinical description of pain caused by a lesion or disease within the somatosensory nervous system
3. **Nociplastic pain:** Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage. Peripheral nociceptors are activated with no evidence for disease nor any lesion in the somatosensory system.

Patients can have a combination of nociceptive and nociplastic pain. [IASP 2020]

Central sensitization: increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input [IASP 2020]

Peripheral sensitization: increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields [IASP 2020]

Placebo: positive symptoms induced independently of the active component of a treatment due to positive expectations or perceptions of a treatment [BPAC 2019]

Nocebo: negative symptoms induced independently of the active component of a treatment due to negative expectations or perceptions of the treatment [BPAC 2019]

Neuroplasticity: the ability of the brain and nervous system to adapt and change in structure, function and organisation [Moseley 2017, Pelletier 2015]

Bioplasticity: the ability of all our body systems (neuro/immune/musculoskeletal) to change and adapt [Moseley 2017]

Pain classifications in clinical practice

Pain lasting >3 months can be coded as persistent or chronic pain; it can be further classified as:

- **Chronic primary pain** – there is no clear underlying condition for the pain or its impact is out of proportion to any observable injury or disease, e.g. fibromyalgia, complex regional pain syndrome, chronic primary headache and orofacial pain, chronic primary visceral pain and chronic primary musculoskeletal pain
- **Secondary pain** – an underlying condition adequately accounts for the pain or its impact
- **Primary pain that coexists with secondary pain**
- **Nociceptive pain** – often this type is worse with movement or lack of movement or loading, and described as sharp, throbbing or aching. It is usually well localised
- **Neuropathic pain** – this type is described as burning, sharp, shooting, lancing, itching, pins and needles, or indescribable. It is caused by conditions of the central or peripheral nervous system and can be associated with allodynia, hyperalgesia, anaesthesia dolorosa or sensory loss
- **Mixed pain** that has both neuropathic and nociceptive qualities

[STCHPW 2021]

Persistent pain: A bio-psycho-social problem

The biopsychosocial approach is crucial in understanding persistent pain. It is discussed here in relation to OA.

The following 5 minute video was developed as a joint venture between GP services and the Health Hunter pain service in New South Wales, Australia: Understanding pain: What to do about it in less than five minutes https://vimeo.com/87769347

The 'Bio' part: Osteoarthritis (OA)

This topic focuses on knee OA; however, the principles of OA (aetiology, diagnosis and management) in any joint are similar.

Causes of OA include idiopathic, chronic repetitive trauma or joint infection, post-fracture, congenital or developmental disease, crystalline deposition diseases, and autoimmune arthritis [Dynamed 2018]. Risk factors include age over 50 years, female sex, family history, increased body mass index, prior knee injury, joint laxity, occupational or recreational overuse and increased mechanical stress on the joints caused by factors such as malalignment [Arthritis NZ 2018, Rice 2019a].

Pathogenesis – Historically OA was thought to be a cartilage-centric disease that was the result of overuse or injury resulting in irreparable damage. However, evidence now suggests OA is an

inflammatory disease with chronic abnormal remodelling affecting the entire synovial joint organ that results in structural and functional failure [Berenbaum 2013, Hunter 2018]. Low grade chronic inflammation can be the direct result of knee injury, metabolic syndrome (including obesogenic inflammation) or age [Berenbaum 2013]. It is a 'whole person condition' in which knee health is influenced by the interaction of different biopsychosocial factors that modulate inflammatory processes and tissue sensitivity, as well as behavioural responses that lead to pain and disability [Caneiro 2020].

Disease findings generally include gradual onset of activity-related knee pain and instability, which may progress to lower extremity weakness and functional limitations, crepitus, bony tenderness, bony enlargement, restricted joint movement, and/or joint effusion without palpable warmth [Dynamed 2020]. Two types of pain are typically reported in knee OA; a dull background ache, and sharp intermittent pain that can be associated with giving way and is often unpredictable [Rice 2019a]. Over time pain can be highly variable, changing in intensity within and between days. Contrary to common perceptions, OA does not always progress. Research shows that in 12- 30% of people pain improves over time [Nicholls 2014, Rice 2019a].

Diagnosis is made clinically on risk factors, symptoms, and a physical examination. Patients >45yo with activity-related knee pain, and no or short-lived (<30 min) morning stiffness, can be diagnosed without radiographic imaging [NICE 2017].

The severity and progression of OA pain can be assessed using the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index (further information available here) [Dynamed 2018].

Peripheral and Central Mechanisms of Pain

Healthy cartilage is avascular and aneural so cartilage itself cannot be a source of pain [Eitner 2017]. Despite the presence of large numbers of nociceptors in other joint structures (subchondral bone, periosteum, ligaments, capsule, synovium) a strong link between joint changes on imaging and pain has remained difficult to prove [Bedson 2008, Eitner 2017, O'Brien 2019]. It is proposed that other factors must contribute to pain [Carlesso 2019, Eitner 2017, Previtali 2020].

Local changes known as peripheral sensitisation may contribute. For example, in synovitis, inflammatory mediators act to reduce the firing threshold of the nociceptors in the synovium. The reduced threshold acts to increase the output of the synovium nociceptor both with movement and at rest, and these changes may be long lasting (hours to days) [Eitner 2017, Rice 2019a].

Central changes can occur in the brain and the spinal cord that make the central nervous system more responsive to normal or sub-threshold stimulation: a process known as central sensitisation (CS). CS may help explain the discordance between pain experienced and joint structural changes seen in some people with OA [Rice 2019a, Vargas E Silva 2020].

Current research explores quantitative sensory testing. This assesses for alterations in sensitivity to noxious or innocuous stimuli using standardised tests e.g., pressure pain threshold. Evidence is emerging that a subgroup of people with OA have neurobiological changes (reduced pressure pain thresholds and temporal summation) which may make them more susceptible to developing persistent pain [Carlesso 2019, Fingleton 2015, Neogi 2015]. In other words this may be a pre-existing pain phenotypic trait [Carlesso 2019, Neogi 2015].

To summarise, in the process of OA, changes occur at a neurobiological level in the joint tissues but also via peripheral & central sensitisation to contribute to the experience of pain. The process of

neuroplasticity or bioplasticity can contribute to the ramping up of pain experienced but also for its winding down. “Bioplasticity got you into this situation and bioplasticity can get you out” [Moseley 2017].

A 2-minute video on neuroplasticity: https://www.youtube.com/watch?v=ELpfYCZa87g

The ‘Psych’ Part: The Impact of Psychology on Pain

In the experience of pain, messages sent from the tissues (nociception), are interpreted by the brain via filters for meaning and context. These come from the many other influences on pain: our senses, our beliefs, our past experiences, our mental state. The brain then determines whether pain is felt. Pain is always an *output* of the brain [Moseley 2017].

Anxiety, depression, catastrophising, beliefs of poor disease outcome - can all have a negative impact on the experience of pain [Rice 2019a]. In contrast positive self-efficacy, thoughts, experiences and safe environments can reduce the experience of pain [Degerstedt 2020, Moseley 2017, Wallis 2019].

Placebo and Nocebo

Health professionals have the power to both benefit or harm the health of their patients with their words and actions. Factors that impact the placebo or nocebo effects include our patient interactions, discussing our beliefs, and the information we provide (written or verbal) about treatment. Other patient placebo/nocebo factors include previous experiences, media, and social modelling (modified behaviour due to observation of others response to treatment) [BPAC 2019].

Several qualitative studies on knee OA report on the impact of the patient/health professional interaction. Negative or dismissive phrases e.g. ‘it’s your age, it’s inevitable’, can have detrimental (nocebo) effects [Wallis 2019]. Education to dispel patient and caregiver negative beliefs (e.g. ‘it hurts so I’m harming myself further if I exercise’, ‘I’ll wear it out if I use it’) may lead to better adherence to treatments and therefore improved outcomes [Darlow 2018, Wallis 2019].

Health professionals may need to challenge their own beliefs and phrases used in discussions on OA to avoid further harm, and to promote placebo effects from clinical interactions and management strategies.

The Power of Caring

There is increasing evidence to support the beneficial effects of care and compassion from healthcare professionals on patient wellbeing, including better patient outcomes and improved patient satisfaction. Caring can induce a placebo effect, without implementing an intervention, and improves connection with the patient [Dieppe 2020].

The ‘Social’ Part:

There is significant burden from OA at societal and individual levels [Jones 2018].

Societal costs may be financial related to health care provision, to loss of productivity or to caring for people. The total cost to the UK economy is estimated at 1% of annual gross national product. In 1999/2000, 36 million working days were lost because of osteoarthritis, costing the economy nearly £3.2 billion in lost production. A third of people in the UK with osteoarthritis retire early, give up work or reduce the hours they work because of their condition [Versus Arthritis 2019].

At the individual level cost is the loss of well-being due to difficulties in participating in meaningful activity: sport, work, social activities, relationships. This can have negative effects on mood and self-worth, contribute to loneliness and reduced quality of life [Hunter 2014].

Lifestyle factors have a role in amplifying or reducing the pain experienced, and in central sensitisation [Rice 2019a]. For example:

- There is a bidirectional relationship between pain and sleep [Finan 2013], so this may be a useful treatment target [Rice 2019a]
- Higher levels of social support have been associated with reduced pain intensity and greater activity levels [Sherman 2003]

Changing the Narrative

The words ‘wear and tear’ and ‘degeneration’ are now considered damaging, archaic, and inaccurate [Hunter 2018]. As with non-specific low back pain where a continued focus on a biomedical model has been described as creating iatrogenic harm [Lin 2013], a focus on a fatalistic view of OA as degenerative, and conservative treatment as less effective has been described as harmful and suboptimal care [Hunter 2018, Hunter 2020].

Terminology such as ‘wear and repair’ may be more accurate and reflect the process of OA as a metabolically active disease [O'Brien 2019]. Biomechanical beliefs that a joint replacement is the end point to ‘fix’ the knee may act as a barrier to exploration of other evidence based treatments [Darlow 2018].

OA evidence-based guidelines recommend education, self-management programs, exercise and weight loss (when indicated) as key management strategies with consideration of cognitive behavioural therapy [Bannuru 2019, Geenen 2018, NICE 2017, RACGP 2018].

Rehabilitation is safer and more effective than pharmacological interventions [Rice 2019]. However, analgesics and arthroplasty are still seen by many health practitioners as the main solutions, despite increasing evidence to the contrary [Jones 2018].

Adjunctive therapies (see page 10) have their place. While most lack high grade evidence they may be useful tools for empowering patients to self-manage their symptoms [Rice 2019a].

Management strategies for OA knee

Education

- A patients’ beliefs about persistent pain impact on attitudes, behaviours and self-management. They need to be explored and addressed [Darlow 2018]
- Education should focus on self-care techniques, clear exercise guidance, dispelling myths and promoting hope and a positive expectation from treatment [Bannuru 2019, Hurley 2018]
- Booklets and online resources should be available [Darlow 2020, Geenen 2018, RACGP 2018]

Exercise

- Is considered a core treatment irrespective of age, comorbidity, pain severity or disability [Bannuru 2019, Geenen 2018, NICE 2017, RACGP 2018]
- Offers many benefits including improved pain, function, and mood as well as benefits for co-morbidities, socialisation and overall general health
- Carries minimal risk of harm; the biggest risk is temporary increased pain at the affected site
- Normally functioning muscles can have a protective effect on the joint [O'Brien 2019] and weakness of quadriceps in particular has been shown in a systematic review to be a risk factor for developing OA [Øiestad 2015]
- No specific type is superior: land or water based, strength or aerobic

  [Bannuru 2019, Geenen 2018, NICE 2017, RACGP 2018, Rice 2019a, Zampogna 2020]

Weight loss

A high BMI is a risk factor for OA. It can contribute to pain and disease progression through mechanical load, obesogenic inflammation and psychosocial health [Atukorala 2016].

- Weight loss is recommended as a core management strategy in people who are overweight or obese [Bannuru 2019, Geenen 2018, NICE 2017, RACGP 2018]
- Some improvement in pain and function for people who already have OA can occur with a minimum of 5-7% body weight loss, however a reduction of ≥10% of body weight can lead to a clinically important improvement. Further loss give incremental gains [Atukorala 2016, RACGP 2018]

Self-management

Most guidelines recommend self-care as a management strategy, although the content of self-management programmes varies, making assessment of efficacy difficult [Rice 2019a]. Self-care strategies include things that allow people to take an active role in managing their condition to improve symptoms and quality of life and could include exercise, connecting with people, healthy eating, not smoking, minimal alcohol, music, singing, art etc. [Geenen 2018, NICE 2017].

Eliciting personal preferences for an individual may improve adherence in the long term [NICE 2017]. Having **fun** is thought to improve bioplasticity and act as a distraction (or 'pain softener') to the physical activity [Moseley 2017].

Understanding pain can be a useful self-care tool as it may help with empowerment [Moseley 2017] :

- Simply knowing about pain and how it works can reduce the pain experienced
- Being aware that the body's descending inhibition (anti-nociception capacity) may be inhibited (e.g. when tired or stressed) or facilitated (e.g. by calm thoughts/meditation/distraction) has the potential to help an individual address these factors
- Oxytocin (the love or hug drug) has been shown to reduce stress/anxiety and reduce pain; increased production occurs when you are close to or hugging someone you love, including your pet [Uvnäs-Moberg 2015]
- Changing the context of pain can help to reduce the experience of it (listen to music, walk outside in nature or visit friends etc.)
- You can be sore but safe: after an injury both the tissue tolerance and the level when 'protect by pain' occurs reduces. Graded exposure to activity/exercise and realistic goals can help improve this while avoiding a 'boom bust' scenario

Cognitive behavioural therapy

Growing evidence of effectiveness of cognitive behavioural therapy (CBT) in OA has seen it added to some OA guidelines especially when psychosocial factors exist [Bannuru 2019, Geenen 2018, RACGP 2018].

Other non-pharmacological interventions

More robust trials are required to determine the place of the following interventions. However, they may have a role as adjunctive therapy when other evidence-based interventions have been insufficient or when it works for the patient. Consider potential harm, cost, and patient preference [Rice 2019a].

Knee braces: there may be some benefit to pain and function without adverse effects [Geenen 2018, Sprouse 2020]. Some guidelines suggest considering before requesting surgery.

Footwear:

- Rocker or unloading footwear does not seem to help OA knee pain; however, the authors suggest shock absorbing shoes could be considered [Rice 2019a]
- A Cochrane review found no evidence for lateral shoe wedges reducing pain in people with OA [Duivenvoorden 2015]. However podiatrist opinion differs and some suggest considering before requesting surgery [CCHPW 2021]
- A recent study found **stable supportive shoes** (a running shoe with shock absorbing properties) worn for six hours a day for 6 months produced a clinically meaningful reduction in walking pain compared to those using a flat flexible shoe [Paterson 2021]

Manual therapy: low to moderate quality evidence exists of short-term benefit on pain and function from manual therapy (physiotherapist, osteopath or chiropractor). Some guidelines recommend a short course of treatment could be considered as an adjunct to exercise [Geenen 2018, Rice 2019a].

Transcutaneous electrical nerve stimulation (TENS)**:** Evidence is inconclusive but it may provide a significant placebo effect [Rutjes 2009, Vance 2012]. If the patient finds it useful then it has a self-empowering therapeutic place. Some guidelines (e.g. NICE) recommend it as an adjunctive treatment.

Acupuncture: A recent meta-analysis (2 systematic reviews of high quality evidence) found acupuncture more effective and safe than western medicine in helping pain and function in knee OA [Li 2019]. A 2010 Cochrane review found a small improvement in pain and function after 8 and 26 weeks, when compared with sham [Manheimer 2010].

Heat/cold packs: Heat packs may have beneficial short-term effects on pain in patients with knee OA. Cold packs may provide relief when inflammation is present in acute flares.

There are numerous other interventions suggesting possible beneficial effects that need further research, including leech [Lauche 2014] and mud bath therapy [Fioravanti 2015].

The role of medication: creating a therapeutic window

Medication has a *limited role* for persistent pain and non-pharmacological therapy should always be considered first for knee OA [NZ Pain Society , Rice 2019a]. Medications may be useful particularly for acute flare-ups and to provide 'windows' of opportunity for patients to rehabilitate, exercise and undertake other meaningful activities [NICE 2017].

Short-term pharmacological treatment in knee OA: (see your local HealthPathways for further guidance https://southtyneside.communityhealthpathways.org/LoginFiles/Logon.aspx?ReturnUrl=%2f)

First line*:* Topical or oral NSAID. Paracetamol may be useful as prn adjunctive therapy with NSAIDs. However, paracetamol alone may be of minimal value [Bannuru 2019, Machado 2021, UpToDate 2021]. Capsaicin 0.025% cream: some evidence of efficacy after 1-2 weeks of regular use, with low risk of adverse effects (burning sensation that subsides with regular application) [Guedes 2018].

Second line:

- *Weak opioid* (e.g. codeine, tramadol): Consider short-term use if NSAIDs are contraindicated or insufficient. Evidence of benefit is lacking, but low-dose opioids may be useful for elderly patients with severe inoperable disease [CCHPW 2021]
- *Intraarticular (IA) corticosteroids:* low quality evidence suggests mild short-term pain relief (possibly up to 6 weeks) and may be useful in an acute knee OA flare, particularly patients with synovitis [Bannuru 2019, da Costa 2016, Jüni 2015]. See table below regarding chronic use
- A literature search could find no evidence to support use of oral steroids

Pharmacological treatment for chronic OA:
Long-term efficacy of medicines in knee OA is poorly studied with most studies measuring effect up to 12 weeks. There is little evidence from RCTs to show significant benefit or modification of disease with any pharmacological intervention [Gregori 2018]. A meta-analysis of RCTs lasting > 12 months in patients with knee OA found negative/unconvincing results for all 33 interventions; although the number of RCTs were small and there was a large amount of uncertainty around all effect sizes [Gregori 2018].

Evidence *for long-term pharmacological treatment in knee OA*	
Capsaicin (topical)	A number of RCTs show some efficacy in knee OA pain [Guedes 2018]; but evidence is limited and not high quality. Not all guidelines recommend use [Bannuru 2019, RACGP 2018]. A meta-analysis of RCTs (any duration, any OA) concluded that topical NSAIDs and capsaicin may be equally efficacious for pain (indirect comparisons) [Persson 2018]. Further research is required in patients with a more neuropathic component. *ADRs:* mild-to-moderate burning sensation [Persson 2018]
NSAIDs (topical)	Topical NSAIDs are recommended by some as an alternative to oral NSAIDs because of their efficacy, tolerability, and low risk of adverse effects, particularly in the elderly and individuals at risk for cardiac, renal, or gastrointestinal complications [Bannuru 2019, Machado 2021, Sprouse 2020]. A network metanalysis and a Cochrane review found topical NSAIDs effective at reducing pain compared to placebo over 12 weeks [Derry 2016, Persson 2018, Zeng 2018]. Efficacy >12 weeks is unclear. A few trials comparing topical to an oral NSAID overall showed similar efficacy (low quality evidence) [Derry 2016]. *ADRs:* mostly mild skin reactions with NSAIDs [Derry 2016].
NSAIDs (oral)	*NSAIDs (non-selective):* Limited data on long term-use [da Costa 2017]. A network meta-analysis found marginal improvement compared with placebo over 12 weeks, with more effect at maximum daily doses [da Costa 2017]. *A* 2018 meta-analysis of RCTs >12 months duration found no effect in pain or function; but there was a large amount of uncertainty with effect sizes [Gregori 2018].

	COX-2 selective: Celecoxib has similar efficacy to other NSAIDs, with a lower GI risk and similar CV risk [Cooper 2019, Gregori 2018].
Paracetamol	A 2021 review of systematic reviews [Abdel Shaheed] and 2019 Cochrane review [Leopoldino 2019] found clinically unimportant benefit in pain from knee or hip OA when compared to placebo (duration up to 12 weeks). The Cochrane review found no clinical benefit in function. Similarly negative results were found in a meta-analysis of RCTs >12 months duration; although large uncertainty around effect sizes [Gregori 2018]. *ADRs:* No increase in overall or serious ADRs; 5% increase in abnormal LFTs [High level of evidence] [Leopoldino 2019].
Opioids	Opioids have limited or no benefit long-term in OA, including strong opioids (high level of evidence). Due to inefficacy and risk of ADRs, long term use is not advised [Bannuru 2019, Kolasinski 2020, Krebs 2018, Toupin April 2019]
Corticosteroids (intraarticular)	Regular use not recommended: steroid injections every 3 months do not improve pain or reduce disease progression, and instead may increase cartilage loss [Bannuru 2019, Kompel 2019].
Corticosteroids (oral)	Insufficient data to recommend use. No evidence available in knee OA.
Antidepressants	Insufficient data to recommend use. *Tricyclic antidepressants:* Anecdotal evidence of benefit in OA pain [CCHPW 2021] but no published evidence to suggest benefit [Ferreira 2021]. One RCT (n=205) found nortriptyline had no effect on pain or function after 14 weeks of treatment in patients with knee OA [Hudson 2021]. *Serotonin noradrenaline reuptake inhibitors (e.g. venlafaxine):* A 2021 meta-analysis found a small, non-clinically significant effect on pain or disability at 3-13 weeks with duloxetine [low certainty evidence], but a clinically significant reduction in pain could not be ruled out [Ferreira 2021]. Some major OA guidelines recommend considering duloxetine in patients with depression and/or widespread pain [Bannuru 2019]. *Selective serotonin reuptake inhibitors* – insufficient data [Ferreira 2021].
Gabapentinoids	Insufficient data to recommend use, and risk of CNS effects and addiction. A recent RCT (n=150) found gabapentin more effective than paracetamol (1 g BD) and as effective as duloxetine over 12 weeks in moderate to severe knee OA pain. ADRs higher for gabapentin (18%) vs. paracetamol (0%) [Enteshari-Moghaddam 2019]
Medicinal Cannabis	Insufficient data to recommend use of THC or CBD. Risk of addiction and hallucinations with THC. Animal models identify possible endocannabinoid pathways in OA but there is no clear evidence of benefit in humans. Several clinical trials are underway [Berg 2020]
Platelet-rich plasma (intraarticular)	Evidence of benefit in knee OA is emerging with promising future value but robust evidence is lacking [Bannuru 2015, UpToDate 2021, Zhang 2020].
Hyaluronic acid (intraarticular)	Evidence of benefit is conflicting; generally considered to be not established [Zhang 2020]. Some international bodies recommend considering in patients without co-morbidities [Bannuru 2019]. Some recent studies show benefit in early-moderate knee OA with sustained effects on pain, stiffness +/- function for 6-12 months when compared with IA saline or IA steroids and a good safety profile [Bannuru 2019, Cucurnia 2021, Zhang 2020]. Patients with end-stage disease had less improvement and more ADRs [Zhang 2020].

ADR= adverse drug reaction

Complementary and alternative medicines - CAMs

There is no convincing evidence for short or long-term benefit for any CAMs for the treatment of OA. Patients may trial a CAM before seeing their health provider or when other treatments have failed. Factors may include the appropriate desire for self-management, commercial marketing or that it is botanically-derived ("natural"). It is important health professionals discuss limitations to their use, such as:

- Lack of data from large, well designed clinical trials supporting efficacy and safety
- Botanically-derived does not mean free of adverse effects or interactions
- Not all herbal medicines are regulated in the UK. Those manufactured outside the UK may not be subject to any regulation
    - thus no assurance that what is on the label is correct or safe (even reputable brands have been found to contain contaminants) [Hoban 2020].

Surgical Intervention

Surgical intervention is a last resort in the management of knee OA. Despite this, there is still a lot of focus on surgery as a treatment [Nijs 2020]. HealthPathways criteria for referral include severe pain and functional limitation *and* all non-surgical options have been exhausted [CCHPW 2021]. It can be life transforming for those that need it and are appropriately selected, educated and provided with good rehabilitation programmes [Ditton 2020].

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