Knee osteoarthritis related pain: a narrative review of diagnosis and treatment

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Abstract

Background: Osteoarthritis is a common progressive joint disease, involving not only the joint lining but also cartilage, ligaments, and bone. For the last ten years, majority of published review articles were not specific to osteoarthritis of the knee, and strength of evidence and clinical guidelines were not appropriately summarized.

Objectives: To appraise the literature by summarizing the findings of current evidence and clinical guidelines on the diagnosis and treatment of knee osteoarthritis pain.

Methodology: English journal articles that focused on knee osteoarthritis related pain were searched via PubMed (1 January 2002 – 26 August 2012) and Physiotherapy Evidence Database (PEDro) databases, using the terms 'knee', 'osteoarthritis' and 'pain'. In addition, reference lists from identified articles and related book chapters were included as comprehensive overviews.

Results: For knee osteoarthritis, the highest diagnostic accuracy can be achieved by presence of pain and five or more clinical or laboratory criteria plus osteophytes. Some inconsistencies in the recommendations and findings were found between the clinical guidelines and systematic reviews. Generally, paracetamol, oral and topical non-steroidal anti-inflammatory drugs, opioids, corticosteroid injections and physical therapy techniques, such as therapeutic exercises, joint manual therapy and transcutaneous electrical nerve stimulation, can help reduce pain and improve function. Patient education programs and weight reduction for overweight patients are important to be considered.

Conclusions: Some inconsistencies in the recommendations and findings were found between the clinical guidelines and systematic reviews. However, it is likely that a combination of pharmacological and non-pharmacological treatments is most effective in treating patients with knee osteoarthritis.

Keywords
Arthritis, Guidelines, Humans, Physiotherapy, Review

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Introduction

Osteoarthritis is a as an illness (the ill health identified by the person themselves, often based on self-reported measures or physical symptoms) and a disease (a condition that is diagnosed by a clinician).[1, 2] Osteoarthritis commonly affects middle age to elderly population. It is the most common disease of arthritis and can occur together with other types of arthritis. It is a disease of the entire joint, involving not only the joint lining but also cartilage, ligaments, and bone. It is characterized by breakdown of the cartilage, bony changes of the joints, deterioration of tendons and ligaments, and various degrees of inflammation of the synovium.[3] Scott and Kowalczyk[4] reported that a cohort study found that radiologic features of knee osteoarthritis were very common in adults: 13% of women 45 – 65 years of age (an incidence of 3% per year). In Saudi Arabia, Al-Arfaj and Al-Boukai[5] in their cross-sectional study found radiographic knee osteoarthritis in 53.3% males and 60.9% females. Approximately 18% of women and 10% of men suffer symptoms due to osteoarthritis.[6] Women demonstrated higher levels of pain, physical disability and pain behavior than men with knee osteoarthritis.[7] In men aged 60 to 64, the right knee is more commonly affected than the left knee, whereas the right and left knees are nearly equally affected in women.[8] Al-Arfaj and Al-Boukai[5] found that patella was involved with radiographic osteoarthritic changes in 80.7% of women and 87.8% of men with knee osteoarthritis. Investigators have theorized the increase in osteoarthritis in women during menopause may partially be attributed to the hormonal factors. However, observational studies on osteoarthritis have shown conflicting results.[9]

Extensive records, including systematic reviews, clinical trials, clinical guidelines, and book chapters are available for osteoarthritis. However, for the last ten years, the review articles about osteoarthritis were limited to rehabilitation and physical therapy interventions [10-13] or emphasized on pharmacological therapies.[14, 15] Although comprehensive reviews covering etiology, epidemiology, pathology, clinical features, diagnosis, markers of tissue damage, and treatment of osteoarthritis were reported,[16-18] they were not specific to osteoarthritis of the knee. In addition, strength of evidence and clinical guidelines were not summarized. The aim of the current review was to appraise the literature and summarize current evidence and clinical guidelines on diagnosis and treatment of knee osteoarthritis pain.

Search strategy

English peer-reviewed journal articles that predominantly focused on knee osteoarthritis related pain were included in this review. The articles were identified via a search of PubMed (1 January 2002 – 26 August 2012). The term 'knee' was combined with the terms 'osteoarthritis' and 'pain'. This search, which was limited to humans and journal article, yielded 3180 citations. Moreover, Physiotherapy Evidence Database (PEDro) using the term 'knee' combined with 'osteoarthritis' was searched. The titles and abstracts of the identified records were reviewed. This search, which was restricted to terms in the record title and to articles published between 2002 and 26 August 2012, resulted in 331 records. All types of articles, including primary research and review reports were included. Reference lists from identified articles and additional citations of interest located manually were also searched. In addition, related book chapters were included as comprehensive overviews. All information in the selected articles relevant to the sections of the review, particularly on diagnosis and treatment, were extracted and used for this review.

Clinical features

The natural history of knee osteoarthritis is poorly understood.[4] Osteoarthritis symptoms can vary greatly among patients.[3] Symptoms include joint pain and stiffness, swelling, decreased function, and cracking or grinding noise with joint movement.[3] Pain features are the pain itself, including its intensity, quality, and predictability as well as the pain's impact on mobility, mood, and sleep.[19] Symptoms

usually start gradually in a prolonged history of discomfort associated with exacerbation.[20] Symptoms are often variable in severity and change slowly.[21] Some patients may indicate that pain and functional disability increased over time and have symptoms that may progress from occurring during weight-bearing activities towards symptoms at rest, especially at night.[20] Others, however, may have their pain improved over the years (e.g., if more activities such as walking are being performed after retirement from sedentary work).[20] Based on the European League Against Rheumatism (EULAR) evidence-based recommendations,[21] typical symptoms of knee osteoarthritis are pain, often worse towards the end of the day, relieved by rest; feeling of 'giving way'; only mild morning or inactivity stiffness and impaired function. In advanced cases, more persistent rest and night pain may occur. In adults aged >40 years with knee pain, there are only short-lived morning stiffness, functional limitation and one or more typical examination findings (crepitus, restricted movement, bony enlargement).[21] Typically, the patient may grasp around the knee, indicating deep pain in the joint or bone.[20]

On physical examination, findings indicative of knee osteoarthritis include crepitus, painful and/or restricted movement, bony enlargement and absent or modest effusion.[21] Other features may include deformity (fixed flexion and/or varus – less commonly valgus), instability, periarticular or joint-line tenderness and pain on patellofemoral compression.[21] Accessory and physiological movement of the tibiofemoral, and possibly patellofemoral joint, may be pain provoking and restricted.[20] Sensorimotor deficits and neuromuscular control changes can also occur in patients with knee osteoarthritis.[22] Adopting pain-relieving postures and refrain from painful activity may be in part a conscious effort but also reflects the effect of joint afferents on motor reflexes.[22] Inhibition of quadriceps muscle may result from reduced capacity of the muscle to contract due to pain and swelling.[22] Proprioceptive deficits in osteoarthritic knees are bilateral in unilateral involvement, inferring central control mechanisms.[22] Deficits in control of knee stabilizing muscles demonstrated in delay in activation occur as a result of pain.[22]

Based on the literature, special questions during patient history taking, which are relevant to knee osteoarthritis, may relate to issues such as acute injury, swelling, giving way, locking, generalized pain, pain at rest, pain rising from chair, pain climbing stairs, inactivity stiffness and night pain. However, inter-examiner reliability differed considerably between these factors (*k* ranged -0.03 to 0.90).[23]

Diagnosis and prognosis

Although both joints are often involved, differentiation testing of the tibiofemoral and patellofemoral joints is frequently possible.[20] The differential diagnoses of knee chronic pain and osteoarthritis include: conditions involving soft tissue of knee such as bursitis, iliotibial band syndrome, ligamentous instability (medial and lateral collateral ligaments), meniscal pathology; other forms of arthritis like gout and pseudogout, rheumatoid arthritis and septic arthritis; referred pain from neuropathy or radiculopathy; and other diagnoses such as avascular necrosis, patellofemoral pain syndrome and tumor.[21, 24] Diagnostic criteria for osteoarthritis have been developed by the American College of Rheumatology. These criteria are outlines in Box 1. Another classification of knee osteoarthritis is Kellgren and Lawrence grading scale. It is based on radiological imaging and consists of different grades: Grade 1: doubtful narrowing of joint space and possible osteophyte lipping; Grade 2: definite osteophytes and possible narrowing of joint space; Grade 3: moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends; and Grade 4: large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends.[25] In a review article, however, Schiphof et al[26] found disagreement between major cohort studies and even among themselves on the definition and grading of osteoarthritis according to the original Kellgren and Lawrence system.

Box 1. Criteria for diagnosis of knee osteoarthritis[24, 27]

Clinical criteria
- Age older than 50 years
- Bony enlargement
- Bony tenderness
- Crepitus
- No palpable warmth
- Stiffness for < 30 minutes

Laboratory criteria
- Erythrocyte sedimentation rate < 40 mm/hour
- Rheumatoid factor < 1:40
- Synovial fluid analysis: clear, viscous, white blood cell count < 2,000/µL (2.00 x 109 per L)

Radiographic criteria
- Presence of osteophytes

	Sensitivity (%)	Specificity (%)	LR+	LR–
– Pain plus ≥ 3 clinical criteria	95	69	3.1	0.07
– Pain plus ≥ 5 clinical or laboratory criteria	92	75	3.7	0.11
– Pain plus ≥ 5 clinical or laboratory criteria, plus osteophyte	91	86	6.5	0.10

LR+ = positive likelihood ratio; LR– = negative likelihood ratio.

Although not related to clinical features, radiologic progression shows that 25% of osteoarthritic knees with initially normal joint space demonstrate major damage after 10 years.[4] Patients with severe peripheral joint osteoarthritis have generally poor outcomes, high levels of physical disability, anxiety, depression, as well as high levels of health care, including joint replacement, drugs and walking aids.[4] Outcome measures for knee osteoarthritis are listed in Table 1. It can be noted that these outcome measures had moderate to high reliability. Some of these outcome measures need further studies to establish reliability and minimal clinically important difference in patients with knee osteoarthritis.

Table 1. Outcome measures used in patients with knee osteoarthritis

Outcome measure	Test-Retest Reliability	Minimum clinically important difference
10-cm VAS	DNA	15% [28]
100-cm VAS	DNA	(19.9% for absolute change, 40.8% for relative change) [29]
Knee pain scale	ICC > 0.84 [30]	DNA
ICOAP	ICC = 0.85 [31]	Decrease of 2 (constant) and 7 (intermittent) points: 'slight improvement' Increase of 4 points (both constant and intermittent): 'slight worsening' [32]
WOMAC	ICC = 0.90 [23]	(6.7% for improvement, 12.9% for worsening) [23] (9.1% for absolute change, 26.0% for relative change) [29]
KOOS	ICC > 0.75 [30]*	Pain: 13.4, Symptoms: 15.5, ADL: 15.4, Sport/rec: 19.6, QOL:

		21.1[33]
RAOS	ICC> 0.76 [34]	DNA
SF-36	α = 0.676 [35]	12% [37]
	ICC = 0.89 (pain), 0.93 (physical function) [36]	

α, Cronbach's alpha ; ADL, activities of daily living; DNA, data not available; ICC, intraclass correlation coefficient; ICOAP, Measure of Intermittent and Constant Osteoarthritis Pain; KOOS, Knee Injury and Osteoarthritis Score; QOL, quality of life; RAOS, Rheumatoid and Arthritis Outcome Score; SF-36, Medical Outcomes Study 36-Item Short Form; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index;
* Anterior cruciate ligament reconstruction, not osteoarthritis

Treatment

Management of osteoarthritis requires multidisciplinary approach that includes, but not limited to, pharmacotherapy, psychology, physical therapy, occupational therapy and surgery. The goals of treatment of patients with osteoarthritis are to reduce pain and other symptoms and to improve functional capacity.[38] Guidelines about interventions for knee osteoarthritis are summarized in Table 2. The American College of Rheumatology has recently published recommendations for pharmacological and non-pharmacological therapies in osteoarthritis of the hand, hip, and knee.[39] The authors categorized the strength of recommendation into three categories: strong, conditional, and non-recommended.[39] Evidence of the effectiveness of treatments techniques in patients with knee osteoarthritis pain, based on independent systematic reviews and/or meta-analyses, is shown in Table 3.

Table 2. Summary of the guidelines recommendations for the treatment of knee osteoarthritis

Intervention	Guidelines recommendations				
	EULAR [40]	AAOS [41]	OARSI [42]	NHMRC/ RACGP [6]	ACR [39]
General	SOR=DNA Optimal management is combination of non-pharmacological and pharmacological modalities Non-pharmacological treatment should include regular education, exercise, appliances (sticks, insoles, knee bracing), and weight reduction	DNA	SOR=96% Optimal management of is combination of non-pharmacological and pharmacological modalities.	DNA	DNA
Oral paracetamol	SOR=A Try first and, if successful, the preferred for long term	SOR=B Up to 4 g/day; recommended unless contraindicated; with an increased gastrointestinal risk	SOR=92% Up up to 4 g/day, effective initial oral analgesic for mild to moderate pain	SOR=A Up to 4 g/day as first line due to lower risk of adverse events, particularly of the gastrointestinal	DNA
Topical NSAID, capsaicin	SOR=A Clinically effective and safe	SOR=B Recommended unless contraindicated	SOR=85% Can be effective as alternatives to oral analgesic/anti-inflammatory agents	SOR=C (topical NSAIDs) Some evidence for short term treatment SOR=D (topical capsaicin) Weak evidence for short term treatment	SOR=conditional Topical NSAIDs SOR=conditionally not to use topical capsaicin
Non-selective NSAIDs or selective COX-2 inhibitors	SOR=A For patients with increased gastrointestinal risk	SOR=B For patients with increased gastrointestinal risk	SOR=93% To be used at lowest effective dose; for patients with increased gastrointestinal risk; should be used with caution in patients with cardiovascular risk factors	SOR=B To reduce pain for short term where simple analgesia and non-pharmacological measures are ineffective; should be used with caution in elderly and those on concomitant medication	SOR=conditional Oral NSAIDs

Opioid, with or without paracetamol	SOR=B When NSAIDs and COX 2 selective inhibitors are contraindicated, ineffective, and/or poorly tolerated	DNA	SOR=82% Weak opioids can be considered for refractory pain; where other pharmacological agents have been ineffective or contraindicated; stronger opioids should only be used for severe pain in exceptional circumstances	SOR=A Prescribed with caution for treating at least moderate or severe pain who have not responded to, or are unable to tolerate, other analgesic medications or NSAIDS	SOR=conditional Acetaminophen Tramadol SOR=no recommendations Duloxetine and opioid analgesics
Vitamin, herbal and other dietary therapies	DNA	DNA	DNA	SOR=C Some evidence of limited or no benefit	DNA
Glucosamine and/or chondroitin sulfate or hydrochloride	DNA	SOR=A Not be prescribed for symptomatic patients	SOR=63% May provide symptomatic benefit; to be discontinued if no response within 6 months	SOR=C (Glucosamine) Role remains uncertain SOR=C (chondroitin sulfate) Some evidence of no benefit	SOR=conditionally not to use Chondroitin sulfate Glucosamine
Intra-articular injection with corticosteroids	SOR=A Indicated for flare of knee pain, especially if accompanied by effusion	SOR=B For short-term pain relief	SOR=78% Should be considered particularly with moderate to severe pain not responding to oral analgesic/ anti-inflammatory agents and with effusions or other signs of local inflammation	SOR=B Good evidence for short term treatment	SOR=conditional Intraarticular corticosteroid injections
Intra-articular hyaluronic acid	DNA	SOR=inconclusive Unable to recommend for or against patients with mild to moderate symptomatic OA	SOR=64% May be useful	SOR=C Some evidence of some benefit	SOR=no recommendations intraarticular hyaluronates,
Arthroplasty	SOR=C Total knee replacement For patients with radiographic evidence of OA who have refractory pain and disability	DNA	SOR=96% Joint replacement for patients with significant symptoms and/or functional limitations associated with reduced health-related quality of life, despite conservative therapy	DNA	DNA
Needle lavage	DNA	SOR=B Not be used for	DNA	DNA	DNA

		symptomatic patients			
Arthroscopic debridement	DNA	SOR=A Not recommend in patients with a primary diagnosis of symptomatic OA	DNA	DNA	DNA
Arthroscopic partial meniscectomy or loose body removal	DNA	SOR=C Option in patients who also have primary signs and symptoms of torn meniscus and/or loose body.	DNA	DNA	DNA
Osteotomy of tibial tubercle	DNA	SOR=inconclusive Cannot recommend for or against	DNA	DNA	DNA
Realignment osteotomy	DNA	SOR=C Option in active patients with symptomatic unicompartmental OA with malalignment	DNA	DNA	DNA
Education	DNA	SOR=B Patients to participate in self-management educational programs	SOR=97% Education about treatment objectives and importance of changes in lifestyle, exercise, pacing of activities, weight reduction, measures to unload damaged joint(s), and self-management	SOR=C Some evidence for self management education programs	SOR=conditional Participate in self-management programs
Weight reduction	DNA	SOR=A Overweight patients (BMI>25) to lose weight (≥5% of body weight)	SOR=96% Patients encouraged to lose weight and maintain their weight at a lower level	SOR=B Good evidence for weight reduction for obese patients	SOR=strong Lose weight (for persons who are overweight)
Aerobic exercise	DNA	SOR=A Low-impact aerobic fitness exercises	SOR=96% Patients to be encouraged to undertake, and continue to	SOR=B Good evidence for land based exercises	SOR= strong Participate in cardiovascular (aerobic)

			undertake, regular exercises		and/or resistance land-based exercise
Flexibility exercises	DNA	SOR=C An option for symptomatic patients	SOR=96% Patients to be encouraged to undertake, and continue to undertake, regular exercises	DNA	DNA
Strengthening exercises	DNA	SOR=B Quadriceps strengthening for symptomatic patients	SOR=96% Patients to be encouraged to undertake, and continue to undertake, regular exercises	SOR=B Good evidence for land based exercises	SOR=strong Resistance land-based exercise SOR=not recommended Participation in balance exercises, either alone or in combination with strengthening exercises
Aquatic exercises	DNA	DNA	DNA	SOR=C Some evidence	SOR=strong Participate in aquatic exercise
Tai chi	DNA	DNA	DNA	SOR=C Some evidence	SOR=conditional Participate in tai chi programs
Acupuncture	DNA	SOR=inconclusive Unable to recommend for or against	SOR=59% May be of symptomatic benefit	SOR=C Some evidence	SOR=conditional Be treated with traditional Chinese acupuncture*
Thermotherapy	DNA	DNA	SOR=64% Some modalities may be effective for relieving symptoms	SOR=C Some evidence for cold therapy	SOR=conditional Be instructed in the use of thermal agents
TENS	DNA	DNA	SOR=58% Can help with short-term pain control in some patients	SOR=C Some for TENS for ≥ 4 weeks	SOR=conditional Be instructed in the use of transcutaneous electrical stimulation*
Massage therapy	DNA	DNA	DNA	SOR=D Weak evidence	DNA
Laser therapy	DNA	DNA	DNA	SOR=D Weak evidence for short	DNA

				term treatment	
Electromagnetic field	DNA	DNA	DNA	SOR=B Good evidence of no benefit	DNA
Therapeutic ultrasound	DNA	DNA	DNA	SOR=C Some evidence of no benefit	
Cognitive behavioural therapy	DNA	DNA	DNA	SOR=D Weak evidence of limited or no benefit	SOR=conditional Receive psychosocial interventions
Patellar taping	DNA	SOR=B For symptomatic patients for short term pain relief and function improvement	DNA	SOR=D Weak evidence	SOR=conditional Use medially directed patellar taping SOR=not recommended Using laterally directed patellar taping
Footwear and insoles	DNA	SOR=B Lateral heel wedges not be prescribed for patients with symptomatic medial compartmental OA	SOR=77% Patients should receive advice concerning footwear; insoles can reduce pain and improve ambulation. Lateral wedges can benefit some patients with medial compartment OA	SOR=B Good evidence of little or no benefit	SOR=conditional Wear medially wedged insoles if they have lateral compartment OA Wear laterally wedged subtalar strapped insoles if they have medial compartment OA SOR=not recommended Wearing laterally wedged insoles
Knee brace	DNA	SOR=inconclusive Unable to recommend for or for patients with uni-compartmental OA	SOR=76% In patients with mild/moderate varus or valgus instability, knee brace can reduce pain, improve stability and diminish risk of falling	SOR=B Good evidence of little or no benefit	SOR=not recommended Wearing knee braces
Walking aids	DNA	DNA	SOR=90%	DNA	SOR=conditional

			Walking aids can reduce pain; cane or crutch in contralateral hand; frames or wheeled walkers for patients with bilateral disease		Receive walking aids, as needed
Manual therapy	DNA	DNA	DNA	DNA	SOR=conditional Receive manual therapy in combination with supervised exercise SOR=not recommended Receiving manual therapy alone

AAOS, American Academy of Orthopedic Surgeons; ACR, American College of Rheumatology; DNA, data not available; NHMRC/RACGP, National Health and Medical Research Council/The Royal Australia College of General Practitioners; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; SOR, strength of recommendation; SYSADOA, SYmptomatic Slow Acting Drugs for OsteoArthritis; TENS, transcutaneous electrical nerve stimulation

Table 3. Evidence for treatments of osteoarthritis based on systematic reviews / meta-analyses

Treatment		Pain	Function
Medications	Tramadol	+ [43]	+ [43]
	Non-tramadol opioids	+ [44]	+ [44]
	Paracetamol	+ [45-48]	+ [45-48]
	Oral NSAIDs	+ [47, 49-51]	+ [47, 49]
	Topical NSAIDs	+ [52]	?
	Glucosamine	+ [53-55]	+ [53-55]
	Diacerein	+ [50]	- [50]
	Doxycycline (antibiotic)	- [56]	- [56]
	SAMe	? [57]	? [57]
Corticosteroid injection		+ [58]	?
Surgery	Osteotomy	+ [59]	+ [59]
	Arthroscopic lavage (debridement)	- [60, 61]	- [60, 61]
	Autologous chondrocyte implantation	? [62]	? [62]
Physical therapy	Aerobic exercise	+ [63-66]	+ [63, 64, 66]
	Strengthening exercise	+ [63, 65-67]	+ [63, 66, 67]
	Aquatic exercise	+ [65, 68]	+ [68, 69]
	Tai chi	- [70]	- [70]
	TENS	? [71]	? [71]
		+ [72-74]	+ [74]
	Low-level laser	+ [73]	Not examined [73]
	Acupuncture	+ [75-77]	+ [75-77]
	Electro-acupuncture	+ [73]	?
	Joint mobilization	+ [78] [67]	+ [67, 78]
	Cryotherapy	- [73]	+ [73, 79]
	Therapeutic Ultrasound	+ [80, 81]	+ [80, 81]
		- [73]	
	Pulsed electromagnetic field	- [82]	+ [82, 83]
		+ [73, 83]	
	Knee brace	- [84, 85]	+ [84, 85]
Orthotics	Lateral wedge	+ [85]	+ [85]
		- [84]	- [84]
	Elastically strapped insole	+ [84, 85]	+ [84, 85]
	Lateral-wedge insoles with Subtalar strapping	+ [86]	Not examined [86]
Weight reduction		- [87]	+ [87]

NSAID, non-steroidal anti-inflammatory drugs; SAMe, S-Adenosylmethionine (dietary supplement); TENS, transcutaneous electrical nerve stimulation

+, evidence of benefit

-, no evidence of benefit

?, inconclusive evidence or no available data

From these guidelines and systematic reviews, we can recommend that combination of pharmacological and non-pharmacological modalities is required for optimal management. Pharmacological treatments have been studied extensively and demonstrated different levels of effect on pain in patients with knee osteoarthritis. For example, oral paracetamol has been recommended to be tried first at a dose up to 4 g/day for mild to moderate pain unless contraindicated. Oral non-steroidal anti-inflammatory drugs (NSAIDs) may reduce pain for short term and should be used with caution, particularly in patients with increased gastrointestinal risk, in elderly patients, and in those on concomitant medication.[6, 40-42] A meta-analysis investigating the efficacy of oral NSAIDs reported an effect size of 0.32 for pain reduction.[51] Two meta-analyses of randomized controlled trials comparing paracetamol with placebo found that paracetamol was modestly effective in decreasing pain and less effective at decreasing pain or improving function than NSAIDs.[45, 48] All clinical guidelines reviewed in the current paper showed high levels of recommendation for the positive effectiveness of topical NSAIDs in patients with knee osteoarthritis. In a meta-analysis of 13 randomized controlled trials, Lin et al[52] reported that topical NSAIDs were superior to placebo in relieving osteoarthritis related pain for short term (up to two weeks) and less effective than oral NSAIDs.

Glucosamine is one of the building blocks of cartilage, which can be taken as a tablet as a supplement to the diet, or sometimes as an injection.[55] The clinical guidelines of the American Academy of Orthopedic Surgeons[41] reported strong recommendation of not prescribing glucosamine for symptomatic patients while other three guidelines [6, 39, 42] stated fairly low level strength of recommendation for conditional use or even uncertainty about it. In 2009, a Cochrane review examined studies testing only the Rotta brand of glucosamine and reported that the high quality randomized controlled trials found no effect on pain reduction or function improvement, but that benefits were found in lower quality studies.[55] A systematic review published in the same year recommended that glucosamine may be used at the initial phase of treatment, considering its excellent safety profile.[54]

Some clinical guidelines reported that opioids are ineffective and poorly tolerated when other pharmacological agents such as NSAIDs have been ineffective or contraindicated.[40] Other guidelines, however, suggested using opioids with caution for refractory pain.[6, 42] A recent systematic review found that the largest effect on pain and function was observed with opioids compared to paracetamol, although this effect was for short term.[47]

Intra-articular injections with corticosteroids seem to be safe.[47] More than one clinical guidelines reported high recommendations that these injections reduce pain for short term, especially if accompanied by effusion.[6, 40-42] Consistently, a Cochrane meta-analysis found that corticosteroid injections were more effective than placebo in decreasing pain at up to two weeks, but not seen at the fourth week.[58]

Several physical therapy modalities have been reported in the reviewed clinical guidelines and systematic reviews. For example, land-based exercises (strengthening and aerobic exercises) were highly recommended by majority of the guidelines.[6, 39, 41, 42] There is fair to strong evidence, based on clinical guidelines and systematic reviews, to support hydrotherapy (aquatic exercises).[6, 39, 65, 68] Transcutaneous electrical nerve stimulation (TENS) seems to reduce pain and improve function for short term in some patients and may be for longer than 4 weeks in other patients.[6, 39, 42, 72, 74]

Only one clinical guideline reported the effectiveness of manual therapy on knee osteoarthritis. This guideline recommended manual therapy in combination with supervised exercise, not to be received alone.[39] However, the type of manual therapy in this clinical guideline was not defined. In the same year this guideline was published, a systematic review found an evidence level of B for short term and C for long-term effect of joint manual therapy on knee osteoarthritis.[78] One year

earlier, in 2011, a systematic review reported that meta-regression indicated that exercise combined with joint manual therapy improved pain significantly (moderate effect size) more than exercise alone (small effect size) ($p = 0.03$). The authors recommended physical therapists to consider adding joint manual therapy in patients with knee osteoarthritis to optimize supervised active exercise and achieve better pain relief.[67]

Other important methods of conservative treatment have been acknowledged in majority of the clinical guidelines. For instance, patient education about self-management, treatment objectives, changes in lifestyle, pacing of activities and weight reduction had fair to higher level of evidence in reducing osteoarthritis related pain. These guidelines strongly recommend overweight patients to lose weight and maintain their weight at a lower level.[6, 39, 41, 42]

Literature has shown different results regarding surgical intervention for knee osteoarthritis. For example, Richmond et al[41] strongly did not recommend arthroscopy with debridement or lavage in patients with a primary diagnosis of knee osteoarthritis. Arthroscopic partial meniscectomy and realignment osteotomy may be an option in patients with symptomatic knee osteoarthritis who also have symptomatic torn meniscus and who have symptomatic knee with malalignment, respectively.

Discussion and conclusions

Published literature identified in the current review for the past ten years related to knee osteoarthritis addressed diagnostic criteria and pharmacological and non-pharmacological treatment. Evidence of management in this review predominantly depended on the reviewed clinical guidelines and systematic reviews /meta-analyses. However, some inconsistencies in the recommendations and findings were found between the clinical guidelines and systematic reviews and even between the guidelines themselves. These differences may partly be due to differences in the methodology used in analyzing the reviewed studies, the type of selected studies in these guidelines and reviews, the heterogeneous nature of reviewed clinical trials or systematic reviews and/or the focus or aim of these guidelines and reviews. Therefore, there is a need for high quality research to evaluate the effectiveness of pharmacological and non-pharmacological interventions for knee osteoarthritis.

A limitation of the current review may be that only few databases were searched. Other databases could have been searched in order to broaden the review and not to overlook other guidelines and/or references for diagnosis and treatment of knee osteoarthritis related pain. However, the authors selected PEDro because this database provides the evidence of treatment of diseases in a way that helps the purpose of the current review, particularly in locating clinical guidelines, systematic reviews and clinical studies. Moreover, PubMed is a free database that can be accessed by anybody. Recently, Michaleff et al[88] reported that the most comprehensive databases able to retrieve trial reports, especially randomized trials evaluating physical therapy treatments, were CENTRAL, PEDro, PubMed, and EMBASE. The authors concluded that any of these databases are reasonably comprehensive.

In conclusion, diagnosis of knee osteoarthritis can be achieved if certain criteria have been met. There is evidence with different levels, on the effectiveness of some pharmacological and non-pharmacological treatments in patients with knee osteoarthritis. Paracetamol, oral and topical NSAIDs, opioids and corticosteroid injections can help reduce pain and improve function. Similar benefits may also be achieved by physical therapy techniques, such as therapeutic exercises, joint manual therapy and TENS. Patient education programs and weight reduction for overweight patients have been considered as an integral part in management of knee osteoarthritis. It is likely that a combination of pharmacological and non-pharmacological treatments is most effective. Arthroscopy with debridement or lavage for patients with primary knee osteoarthritis is not recommended. Other surgical options may be performed if knee osteoarthritis is accompanied by other

dysfunctions. In order to help minimize risk of developing knee osteoarthritis, it is advised to exercise regularly and maintain healthy body weight.

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