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## MASTERCLASS

### Knee osteoarthritis: key treatments and implications for physical therapy

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#### KEYWORDS

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#### Abstract

**Q2** *Background:* Knee osteoarthritis (OA) is a chronic progressive disease that imparts a substantial socioeconomic burden to society and healthcare systems. The prevalence of knee OA has dramatically risen in recent decades due to consistent increases in life expectancy and obesity worldwide. Patient education, physical exercise, and weight loss (for overweight or obese individuals) constitute the first-line knee OA treatment approach. However, less than 40% of patients with knee OA receive this kind of intervention. There is an unmet need for healthcare professionals treating individuals with knee OA to understand the current recommended treatment strategies to provide effective rehabilitation.

*Objective:* To guide physical therapists in their clinical decision making by summarizing the safest and most efficacious treatment options currently available, and by delineating the most traditional outcome measures used in clinical research for knee OA.

*Conclusion:* There is a need for healthcare providers to abandon low-quality and ineffective treatments and educate themselves and their patients about the current best evidence-based practices for knee OA.

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## Introduction

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**Q3** Life expectancy has increased globally over time; however, the growing burden of chronic diseases results in a large portion of society living longer, but in poorer health.<sup>1</sup> This scenario is indeed a reality for people suffering from one of the leading causes of chronic pain and disability

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worldwide, knee osteoarthritis (OA).<sup>1</sup> The disease is ranked as the 10<sup>th</sup> largest contributor to global years lived with disabilities,<sup>2</sup> and its prevalence has more than doubled in the last 10 years.<sup>1,3</sup> In addition, medication intake, hospital stays, and joint surgeries associated with managing knee OA impose billions of dollars per year in costs to healthcare systems.<sup>2,3</sup>

The pathology of knee OA affects the whole joint, causing synovial inflammation, cartilage damage, bone remodeling, and osteophyte formation.<sup>4</sup> Typical symptoms include pain, muscle weakness, joint instability, brief morning stiffness, crepitus, and functional limitations.<sup>4</sup> Frequently, symptoms are related to physical inactivity, which has been linked to morbidity and mortality in the contemporary era and is a significant contributor to the incidence of chronic diseases worldwide.<sup>5,6</sup> Methodologically rigorous international guidelines strongly recommend non-pharmacological strategies as the first line of treatment for knee OA.<sup>7–13</sup> Exercise, patient education, and weight loss – when needed – are the recommended first-line strategies to manage symptoms of these patients.<sup>7–13</sup>

There is high-quality evidence demonstrating the effectiveness of education and exercise to improve function in individuals with knee OA.<sup>8,13</sup> Data from 9825 patients with hip or knee OA showed that a 6-week combination intervention comprising three sessions of patient education delivered over the course of two weeks and 12 sessions of neuromuscular exercise delivered twice per week had beneficial effects on OA symptoms, physical function, medication intake, and sick leave time.<sup>14</sup> Furthermore, some beneficial effects introduced by the interventions, including increased physical activity and quality of life, were maintained after one year. These results suggest that a combination of education and exercise could result in long-term reductions in the burden of knee OA and its costs to patients and the healthcare system.

Although non-pharmacological strategies are of paramount importance, less than 40% of patients with knee OA receive this kind of treatment approach, indicating that the uptake of evidence-based guidelines in clinical practice and rehabilitation is still suboptimal.<sup>14,15</sup> Instead, pharmacological strategies remain dominant, despite the fact that chronic use of many of these treatments has been associated with severe adverse side effects.<sup>16,17</sup> The neglect of evidence-based strategies in clinical practice applies to both clinicians and patients. Factors such as the strong beliefs regarding old and low-value treatments, the lack of knowledge regarding current evidence, and a significant increase in the number of current published guidelines are considered barriers to the successful adoption of evidence-based clinical practice.<sup>18–20</sup>

A basic understanding of treatment strategies for knee OA is necessary to target and improve rehabilitation. In this article, we aim to provide updated information for physical therapists and show that exercise, weight maintenance, and patient education are vital for the optimal treatment of knee OA. We also aim to describe key outcome measures used in knee OA studies and to increase awareness about useful tools for data collection for clinicians and researchers.

## Key treatments

### Non-pharmacological strategies

Current clinical practice guidelines recommend education and self-management, exercise, and weight loss (for overweight or obese patients) as the first-line treatments for knee OA.<sup>7–13</sup> We consider these strategies to be the core of knee OA rehabilitation, because they have been proven to effectively decrease pain and improve overall joint function and patient quality of life. In patients for whom knee OA has a significant impact on ambulation or joint stability, or for whom pain is severe, some guidelines strongly recommend the use of tibiofemoral knee braces, canes or walkers, orthopedic footwear, and other assistive technologies.<sup>12,13</sup>

### Patient education

Patient education plays an essential role in decision making, disease self-management, and medication adherence of individuals with knee OA.<sup>21</sup> The negative impact of the disease on the patients' self-esteem can be high, and oftentimes, pain becomes a central aspect of their lives. Misleading beliefs that OA is an incurable, progressive disease that is associated with specific causal factors can lead patients to cut down on physical activities and adapt to a restricted lifestyle with less spontaneity, which in many cases results in a great feeling of loss and isolation associated with a reduction in social relationships.<sup>22–24</sup> There is an urgent need to mitigate this negative impact, using proper patient-education strategies to better manage the disease and improve the concordance between patients' expectations and treatment outcomes. Overall, patient knowledge about the disease is still inadequate. Although guidelines organizations attempt to disseminate health information targeting the general public, most patient education materials for people with knee OA are of fair quality and written at inappropriate readability levels, frequently equal to, or more complicated than the recommended level (7<sup>th</sup> to 8<sup>th</sup> grade).<sup>25,26</sup>

As healthcare providers, it is essential to develop a clear understanding of the disease to direct patients toward high-quality health information. However, before educating patients with knee OA, it is crucial to understand how they experience the disease. A systematic review of qualitative studies highlighted the importance of considering patient attitudes and experiences to plan and implement the best treatment options for knee OA.<sup>27</sup> From the seven critical themes that emerged, three call for attention: (1) *"The perceived causes of knee osteoarthritis are multifactorial and lead to structural damage to the knee and deterioration over time,"* where patients perceived knee OA as a consequence of internal factors such as aging, working occupation, family history, or external factors such as a trauma or weather conditions; (2) *"Interactions with health professionals can be positive or negative,"* where patients related that positive interactions resulted in feeling listened to and hopeful for the future, whereas negative interactions were characterized by receiving less attention and less information about the condition and treatment options; and (3) *"Knee osteoarthritis leads to life adjustments,"* where

some patients mentioned climbing fewer stairs, not carrying heavy things, looking for places to sit, and avoiding public transportation, while others reached a point where there was a profound feeling of loss because the disease led to giving up all enjoyable activities of daily living.

In a consensus statement reached by experts and patients with OA in 13 countries, 21 key messages were identified that should be communicated to patients.<sup>28</sup> The top 3 messages were related to (1) how regular physical activity and individualized exercise programs can reduce pain, prevent worsening, and improve daily function in OA; (2) the benefits of losing weight for overweight or obese patients, and the benefits of maintaining a healthy weight using diet changes and exercise; and (3) the fact that OA symptoms can often be significantly reduced without the need of undergoing a surgery. Other key messages pertained to disease knowledge (e.g., *"The symptoms of osteoarthritis can vary greatly from person to person"* and *"Osteoarthritis is not an inevitable part of getting older"*); medication intake (e.g., *"You should avoid the use of nonsteroidal anti-inflammatory drugs for your osteoarthritis over the long term"*); and about diagnostic methods (e.g., *"Joint damage on an X-ray does not indicate how much your osteoarthritis will affect you"*). These messages are fundamental to facilitate the translation of evidence into patient knowledge and to optimize the patient-clinician interaction, therefore providing insights into how to conduct education and improve decision-making for patients with knee OA.

## Exercise

It is well-established that physical activity and exercise therapy reduce symptoms and improve physical function in individuals with knee OA.<sup>7-13</sup> Literature shows that 150 min/week of moderate intensity aerobic exercise or 2 days/week of moderate-to-vigorous physical activity muscle-strengthening exercises are beneficial for individuals with preexisting knee OA. Translating these two activities into step counts, that would be approximately 7500 steps per day for aerobic exercises and 5750 steps per day for moderate-to-vigorous physical activity. In addition, there is more pain reduction when quadriceps-specific exercises were used compared to general lower-limb exercises and when supervised exercises were performed at least three times per week. However, the current recommendations suggesting one form of exercise over another are mainly based on expert opinion.

Irrespective of pain and function, a wide range of exercise options are available for knee OA.<sup>29</sup> To improve rehabilitation, physical therapists and other health care professionals should focus on patient-centered rehabilitation, considering patient's preferences and access to exercise equipment. The National Institute for Health and Care Excellence (NICE)<sup>7</sup> recommends strengthening exercises and aerobic fitness; the Osteoarthritis Research Society International (OARSI)<sup>8</sup> recommends structured land-based exercise programs of two types: (1) strengthening and/or cardio and/or balance training/neuromuscular exercise or (2) mind-body exercise including Tai Chi or Yoga; the American College of Rheumatology (ACR)<sup>13</sup> recommends aerobic, aquatic, and/or resistance exercises; the Ottawa

Panel<sup>9-11</sup> recommends mind-body exercise (Hatha yoga, Tai Chi Qigong, sun style Tai Chi), strengthening exercise in isolation or combined with other types of exercise (coordination, balance, functional), and aerobic exercise in isolation or combined with strengthening exercise; and the European League Against Rheumatism (EULAR)<sup>12</sup> recommends pacing of activity and exercise in general for the management of knee OA.

There is high-quality evidence demonstrating the effectiveness and the clinically meaningful benefits of non-operative therapeutic exercise regimens to improve pain, physical function, and quality of life in individuals with knee OA.<sup>29,30</sup> Moreover, these improvements are sustained for at least two to six months after the end of treatment. It is highly unlikely that new research on this area will change these conclusions.<sup>30,31</sup> Therefore, there is no need to develop new trials to verify exercise effectiveness for knee OA. However, there is still a need to develop novel insights regarding treatment parameters used in rehabilitation programs, such as duration, frequency, modality (type), and intensity.<sup>32</sup> The type and dosage of exercise, when prescribing a home-based exercise protocol, should be individualized, based on the clinical evaluation and the patient's preferences.<sup>33,34</sup>

Education plays a vital role when prescribing an exercise protocol. Most current exercise protocols are noticeably under-utilized by individuals with knee OA, mainly due to patient beliefs, socioeconomic barriers, fear of movement, lack of confidence, lack of time to insert the exercise routine in daily life, and early treatment pain aggravation.<sup>33-35</sup> A survey with 123 physical therapists demonstrated that only 39% educated patients about the benefits of exercise for knee OA, 33% involved their patients in the development of the exercise program design, 28% managed to schedule follow-up appointments to review exercises and adherence, and 4% encouraged patients to keep going with exercises.<sup>36</sup> Prior to the beginning of an exercise protocol, patients need to clearly understand that pain/discomfort during the physical activity does not mean increased structural joint damage.<sup>33</sup> To optimize the effectiveness of exercise interventions, it is also essential to create strategies to increase adherence to exercise and overcome barriers, bearing in mind the environmental context and available resources of the patient.

Physical therapists can help patients with knee OA by fostering a positive therapeutic relationship. Some components of a positive therapeutic relationship may include increased relatability, supervision of exercise performance to promote success and confidence in self-management abilities of patients, use of group exercises, and follow-up telephone calls.<sup>37</sup> The top 5 behavior change techniques rated to be the most effective at increasing exercise adherence in patients with knee OA include: (1) review of progress in terms of pain and function at follow-up sessions, (2) development of a therapeutic plan which clearly states how often the patient will exercise and specifically what they will do, (3) development of specific and achievable goals related to the patient's knee pain and function, (4) review, supervision, and correction of exercise techniques at subsequent treatment sessions, and (5) follow-up sessions more than 3 months after the initial session, to check on the exercises and progress the home-based protocol, if needed.<sup>36</sup> Other

strategies such as the use of booster sessions (i.e. returning to a therapist after an initial period of treatment to perform a new session focused on review and progression of the exercise therapy) and the use of graded behavioral exercises (i.e. an exercise routine that is gradually increased into daily living) also promoted adherence in individuals with knee OA.<sup>35</sup>

## Weight loss

Over one-third of the world's population is classified as overweight or obese and research shows that if the current trends continue, more than 55% of the world population will be classified as overweight or obese by 2030.<sup>38,39</sup> Because of its systemic effects on the body due to inflammatory and metabolic changes, obesity and overweight are considered primary risk factors related to chronic diseases, including knee OA.<sup>40,41</sup> Therefore, obesity presents a significant burden to society and the public health system.<sup>39</sup>

Weight change directly affects the risk of developing knee OA.<sup>42</sup> A reduction in weight of approximately 5.1 kg decreases the risk of developing knee OA by more than 50% in women with a baseline body mass index (BMI) higher than 25.0 kg/m<sup>2</sup>.<sup>42</sup> A meta-analysis showed that in adults with mild to moderate knee OA and a mean BMI ranging from 33.6 to 36.4 kg/m<sup>2</sup>, a weight reduction of 5%–10% can significantly improve pain, self-reported disability, and quality of life. Results of the included studies demonstrated that diet strategies such as meal replacements or the use of nutrition powders, together with nutritional education and behavioral therapy, can help individuals with knee OA to achieve weight loss targets.<sup>43</sup>

For individuals with knee OA, diet-only treatments have not been shown to relieve pain; however, a combination of diet and exercise has a moderate effect on this outcome.<sup>44</sup> Physical function, on the other hand, improved moderately with both diet-only treatments and diet combined with exercise. Patients who are classified as overweight should aim for at least a 7.7% body weight loss to achieve a minimal clinically important improvement in physical function.<sup>45</sup> In addition, to lose weight, an intensive diet alone (loss of at least 10% of baseline weight) is better than exercise alone (aerobic and strengthening training). However, the combination of exercise and diet presents the best results for weight loss.<sup>46</sup>

Clearly, there is a dose-response relationship between weight loss and symptom improvement in individuals with knee OA.<sup>45,47–49</sup> However, the maintenance of weight loss in long-term rehabilitation remains a substantial challenge. Successful strategies of weight maintenance are associated with achieving an initial goal of weight loss, creating consecutive weight goals, having a regular meal pattern that includes breakfast and healthier eating, having a physically active lifestyle, and controlling over-eating through self-monitoring behaviors. These strategies can be incorporated, when needed, in knee OA rehabilitation regimens to improve goals and increase patients' overall satisfaction with treatment. Other factors strongly associated with weight maintenance include the presence of social support, better coping strategies, higher self-efficacy, and overall increased in psychological resiliency and stability.<sup>50</sup>

In individuals with other chronic diseases, the contact between patient and therapist seems to be a key factor for weight loss.<sup>51</sup> Furthermore, continuing contacts after the end of the rehabilitation regimen appears to be effective, regardless of whether the contact is face-to-face, through telephone, or via email. Risk factors for regaining weight include a range of eating behaviors that involve a lack of restraint over food intake. These factors can include binge eating disorder (i.e. recurrent episodes of eating large quantities of food), eating as a reaction to emotions and stress, and a general tendency toward passive reactions to problems.

## Adjunct therapies

Several adjunct therapies are used as complements to core knee OA treatments with the goal of maximizing outcomes for patients. Thermal modalities, laser therapy, therapeutic ultrasound, electrical stimulation, manual therapy techniques, taping, acupuncture, among others, are some interventions that are commonly used. For this article, we will review some of the adjunct therapies most commonly used by physical therapists in treating knee OA, providing details about the quality of evidence and nature of the recommendation.

### Thermal modalities

There is still a lack of evidence to support the use of thermal modalities such as cold and heat in individuals with knee OA.<sup>52,53</sup> The overall quality of evidence for thermal modalities is classified as very low by the OARSI guidelines and as low by the ACR guidelines.<sup>8,13</sup> Research shows that patients with knee OA have individual preferences regarding heat, cold, or contrast therapy to improve pain and physical function status.<sup>54</sup> Women tend to prefer heat treatments and generally respond with more improvements in subjective quality of life and physical function to thermal modalities. Conversely, men favor cold or contrast therapies but were less likely to report benefits.<sup>54,55</sup> In humans, the use of cryotherapy was not superior to placebo to improve pain, physical function, and quality of life in individuals with knee OA.<sup>56</sup> Interestingly, clinical-like cryotherapy was recently shown to improve not only gait and function, but also to modulate the inflammatory process by reducing the number of leukocytes and cytokines in the synovial fluid in animal model with knee OA compared to placebo.<sup>57</sup>

### Laser, therapeutic ultrasound, and electrical stimulation

The OARSI guidelines strongly recommended against the use of laser therapy for knee OA, citing an implausible biological mechanism and no efficacy, with a very low overall quality of evidence.<sup>8</sup> The potential mechanisms of pain relief by laser therapy are due to the stimulus of tissue metabolism and modulation of the inflammatory process. However, literature shows contrasting evidence regarding the use of laser therapies, more specifically low-level laser therapy (LLLT), in treating individuals with knee OA. A meta-analysis eval-



uating the effectiveness of LLLT on symptoms and function in patients with knee OA, showed no therapeutic benefit of LLLT compared with placebo for patients.<sup>58</sup> A more recent meta-analysis showed that LLLT seems to reduce pain and disability in individuals with knee OA when compared to placebo in randomized controlled trials.<sup>59</sup>

Studies regarding therapeutic ultrasound, although reporting beneficial effects of the therapy for knee OA, show methodological limitations that hinder the evidence synthesis, such as the inclusion of mixed interventions.<sup>60–64</sup> Thus, there is low quality of evidence to support the use of therapeutic ultrasound for individuals with knee OA.<sup>8</sup> However, the ACR guidelines conditionally recommends its use (i.e. the therapy is considered preference-sensitive to patients), meaning that therapists need to give a complete and clear explanation of benefits, harms, and burdens of the treatment when presenting it as an option to a patient.<sup>13</sup>

Evidence for electrical stimulation shows that there is a lack of adequate studies to support its use in patients with knee OA.<sup>65</sup> OARSI guidelines corroborates this information by presenting a very low quality of evidence for transcutaneous electrical stimulation.<sup>8</sup> In addition, the ACR strongly recommended against the use of transcutaneous electrical stimulation in all patients with OA.<sup>13</sup>

## Manual therapy techniques, taping, and acupuncture

There is a low level of evidence to recommend the use of manual therapy techniques for knee OA.<sup>8,13</sup> Available techniques encompass the use of manual lymphatic drainage, massage, mobilization/manipulation, manual traction, and passive range of motion. There is low level of evidence showing that manual therapy techniques provide little additional benefit when compared to exercise alone for managing knee OA symptoms, and the ACR guidelines conditionally recommended against its use.<sup>13</sup>

There is very low level of evidence to support the use of taping for the management of knee OA.<sup>8</sup> With a no efficacy statement, the OARSI guidelines strongly recommends against the use of the therapy.<sup>8</sup> However, regarding Kinesio taping, the ACR guidelines conditionally recommends its use.<sup>13</sup>

For traditional acupuncture with manual stimulation, there is a low level of evidence to support the use of the therapy for patients with knee OA.<sup>8,13</sup> The ACR guidelines conditionally recommended acupuncture.<sup>13</sup> However, the OARSI guidelines stated an implausible biological mechanism and no efficacy for laser acupuncture and an unfavorable efficacy with safety issues for electroacupuncture, strongly recommending against and indicating a very low overall quality of evidence to support the use of either therapy.<sup>8</sup>

There is still an unmet need for quality randomized clinical trials regarding the majority of the adjunct therapies described above. Additionally, for the majority of the adjunct therapies, it remains to be seen whether complementary effects may be observed when they are combined with a gold standard treatment for knee OA (e.g. the complementary effects of cryotherapy when associated with an exercise protocol).<sup>66</sup> Therefore, with the current evidence, we recommend against the use of these therapies by physical

therapists in clinical practice. However, if the therapy is still considered, we recommend it to be preference-sensitive to patients, and therapists must give a complete and clear explanation to patients regarding the evidence to support the use of the therapy in knee OA.

## Pharmacological strategies

For knee OA, local therapies are preferable as core pharmacological treatments. Appropriate monitoring of the patient during a pharmacological treatment, especially for the development of adverse effects, is also recommended.

## Non-steroidal anti-inflammatory drugs (NSAIDs)

Due to minimal and mild adverse events, topical NSAIDs are strongly recommended as first-line treatment in both the OARSI<sup>8</sup> and ACR<sup>13</sup> guidelines. OARSI also recommends the use of topical NSAIDs for patients with gastrointestinal or cardiovascular comorbidities and patients with frailty.<sup>8</sup> In addition to topical NSAIDs, the ACR guidelines strongly recommends the use of oral NSAIDs and intraarticular glucocorticoid injections.<sup>13</sup>

## Opioids

Opioids, another popular group of drugs that are frequently considered as potent pain-relievers, should be heavily discouraged.<sup>16,67,68</sup> There is high-quality evidence demonstrating that opioids have only small effects on pain and physical function in individuals with knee OA.<sup>69</sup> Furthermore, when compared to placebo, patients that used opioids had three to four times higher risks of serious adverse effects and/or drop-out due to adverse events.

## Nutraceuticals

Nutraceuticals, i.e. foods or food supplements thought to have health benefits, are extremely popular in the treatment of OA. Glucosamine and chondroitin sulfate, nutraceuticals that are commonly used by patients with knee OA, lack scientific evidence to support their use. Both were strongly recommended against for the treatment of knee OA by the ACR<sup>13</sup> guidelines and classified as the lowest level of recommendation by the OARSI guidelines.<sup>8</sup> In addition, there are low efficacy and effect sizes of insufficient clinical relevance, when comparing these supplements to placebo.<sup>70–72</sup>

## Surgery

Surgery is typically a last resort for the management of knee OA. Unfortunately, a vast majority of physicians deviate from evidence-based practice regarding surgical management of knee OA. From the variety of options available, arthroscopic knee surgery, specifically arthroscopic joint lavage, is the most common procedure performed.<sup>4,73</sup> However, several high-quality studies have demonstrated the low efficacy of arthroscopic surgery in terms of pain relief and physical function improvement in individuals with

**Table 1** Patient-reported measures and their psychometric properties for knee OA.

Outcome	Observations	Scoring	Psychometrics
Visual Analogue Scale (VAS)	The purpose of VAS is to measure pain. The scale is placed in front of the patient who is asked to rate their pain intensity according to a pre-determined period of time. VAS can be used before, during, or after physical function tests.	From 0 to 10 cm (0 – the complete absence of pain, and 10 – maximum intensity).	A pain reduction of 1.75 cm on the scale is the recommended MCID in OA research. <sup>103</sup>
Numeric Rating Scale (NRS)	The purpose of NRS is to represent a unidimensional measure of pain. Usually, it is a segmented numeric version of VAS, and it can be administered verbally (also by telephone) or graphically for self-completion. The scale is placed in front of the patient who is asked to rate their pain intensity according to a pre-determined period of time. NRS can be used before, during, or after physical function tests.	A 0–10-point numeric scale with 0 representing “no pain” and 10 representing “pain as bad as you can imagine”/“worst pain imaginable.”	A pain reduction of 2 points on the scale is the recommended MCID in patients with chronic musculoskeletal pain. <sup>104</sup>
Western Ontario & McMaster Universities Osteoarthritis Questionnaire (WOMAC)	WOMAC is a self-report questionnaire designed to assess the problems experienced by individuals with lower limb OA in the past 72 h. It contains 24 specific questions divided into three domains: pain, stiffness, and physical function.	The score of each question ranges from 0 to 4. The total questionnaire score is 96, with high scores representing worse results.	An improvement greater than or equal to 12% from baseline is the recommended MCID in OA research. <sup>105</sup>
Knee Injury and Osteoarthritis Outcome Score (KOOS)	This self-report questionnaire assesses the problems experienced by people with lower limb OA in the prior week by measuring the quality of life and knee function. It contains 42 questions in 5 domains: pain, other symptoms, function in daily life, sports-related function and recreation, and knee-related quality of life.	The answers are standardized and scored from 0 to 4. The total score of the questionnaire is 168. High scores indicate worse results than low scores	A difference of 8–10 in the total score from baseline is the recommended MCID in OA research. <sup>106</sup>

Table 1 (Continued)

Outcome	Observations	Scoring	Psychometrics
Algofunctional indices for the knee or index of severity for knee disease (Lequesne Index)	This index is used specifically for the evaluation of pain, maximum walking distance, and the daily activities of patients with OA.	The 10-question questionnaire is scored on a 0–24-point scale. Lower scores indicate there is less functional impairment, and higher scores reflect the worst outcomes. The sum of the scores is classified as: little effect (1–4 points), moderate effect (5–7 points), severe effect (8–10 points), very severe effect (11–13 points) and extremely severe effect (greater than or equal to 14 points).	The MCID for the Lesquene Index is still not established in knee OA research.
Short Form-36 questionnaire (SF-36)	The short form questionnaire is intended to measure the patient's quality of life with 36 items referring to the past four weeks. It presents a multiple-choice scale that evaluates eight domains of life: Physical Functioning, Role Limitations due to Physical Problems, General Health Perceptions, Vitality, Social Functioning, Role Limitations due to Emotional Problems, General Mental Health and Health Transition.	The sum of the total value varies from 0 to 100, with higher indexes indicating a better quality of life. Each of the eight summed scores can be linearly transformed into a scale from 0 (negative health) to 100 (positive health) to provide a score for each subscale. Each subscale can be used independently.	A difference of 10 points is recommended as an MCID in OA research. <sup>107</sup>
Short Form-12 questionnaire (SF-12)	The short form questionnaire is intended to measure the patient's general physical and mental well-being, which is based upon the SF-36 score. It has two components, the physical component summary (PCS) and the mental component summary (MCS) scores.	Scores are reported on a scale of 1–100 with a higher score representing a better health status. The score is calculated independently for each component according to the responses recorded on Likert scales of six questions (each). Scores are converted into the validated score using a defined algorithm.	An improvement of 4.5 points for the physical component and 4.8 points for pain relief and function are established as MCID in OA research for patients after knee arthroplasty. <sup>108</sup>

Table 1 (Continued)

Outcome	Observations	Scoring	Psychometrics
Health Assessment Questionnaire (HAQ)	A self-administered questionnaire consisting of 20 detailed questions of people's daily activities divided into eight categories: dressing and activities related to taking care of appearance, getting up, eating, walking, hygiene, reaching, gripping, and daily life activities.	Each patient assesses the difficulty they face carrying out each activity on a scale from 0 to 3, where zero means no difficulty performing and three means unable to perform the activity. Increasing scores indicate worse functioning with 0 indicating no functional impairment and 3 indicating complete impairment.	The MCID for the HAQ questionnaire is still not established in knee OA research.

MCID, minimal clinically important difference; OA, osteoarthritis.

knee OA.<sup>73–75</sup> The surgery also increases the chances of subsequent knee replacement surgery,<sup>76,77</sup> and there are multiple harms associated with the procedure, including venous thrombosis, infection, pulmonary embolism, and in some cases, death.<sup>73,75</sup> Clinical practice guidelines, including those published by the Journal of the American Academy of Orthopaedic Surgeons, strongly recommend against the use of arthroscopy in nearly all patients with degenerative knee disease.<sup>75,78</sup>

Joint replacement is another popular surgery in individuals with end-stage knee OA. It is a cost-effective treatment and should be considered when all non-surgical treatment options – used within a time-frame of 6-months – were unsuccessful.<sup>4,79</sup> However, although joint replacement is a successful treatment for relieving many symptoms of individuals with knee OA, persistent pain after surgery is reported by some patients.<sup>80</sup> One in five patients who undergo total knee replacement is not satisfied with the outcome.<sup>81</sup> Predictors for poor outcomes after surgery include anxiety/depression, high patient expectations for surgery, low 1-year WOMAC, pain at rest before surgery, and complications after surgery that necessitate readmission.<sup>81,82</sup> Individuals with severe radiographic knee OA who have poor quality of life due to the disease are most likely to report considerable improvements in pain and function after knee replacement.<sup>83</sup> There is low- to moderate-quality of evidence showing that a period of 8 weeks or more of exercise can improve functional outcomes and physical activity in individuals undergoing total knee replacement.<sup>84</sup>

## Key outcome measures

For researchers aiming to improve data collection in knee OA studies and for clinicians treating patients in clinical practice, there are well-established core outcome measures that can be used to evaluate the domains of pain and physical function of patients.<sup>8,13,85–87</sup> In Tables 1 and 2, we provide a comprehensive description of some of the critical subjective

and objective outcome measures used in knee OA studies, respectively. In addition to the content provided in the tables, the following outcome measures were also classified as “important” (according to GRADE criteria) in evaluating the evidence that contributed to the OARSI guidelines: structural progression of the disease measured by joint space narrowing, cartilage thickness, and cartilage volume; withdrawals due to adverse events, the total number of adverse events, serious adverse events, and other treatment-specific harms. Valid scales to measure self-efficacy and depression were also classified as important outcomes.<sup>8,88</sup>

For physical function measures, it is crucial to understand that there is a clear distinction between patient-reported measures and performance-based measures. The first evaluates what patients perceive they can do, and the latter reflects what they can do. Previous reports show that for individuals with knee OA, self-reported measures are not correlated with objective measures of physical function.<sup>89–94</sup> On the other hand, self-reported measures were related to pain, knee strength, and depression. Objective measures of physical function were correlated to functional self-efficacy (i.e. how confident an individual is to perform a physical task).<sup>95</sup> Both are different constructs and are complementary, rather than competing, when assessing individuals with knee OA. Therefore, neither clinical researchers nor clinicians should substitute self-report outcome measures with performance-based measures, or vice versa. Instead, healthcare professionals treating knee OA should focus on collecting both types of outcome measures to obtain the most comprehensive assessment possible.

## Future perspectives

Although research in OA has been documented for more than 100 years, there are still no successful therapies to stop or reduce the progression of joint degeneration. However, with technological advancements, new approaches and therapies are emerging to aid these patients.



**Table 2** Objective performance-based measures and their psychometric properties for knee OA.

Outcome	Observations	Scoring	Psychometrics
30-s Chair to Stand Test	A chair with no arms is placed against a wall to prevent oscillations. Patients sit in the middle of the chair, with their back straight, feet apart resting on the floor in line with their shoulders. The test requires to rise from a sitting to a standing position as many times as possible in 30 s.	The total number of repetitions.	An increase of 2–3 repetitions is recommended as the MCID in OA research. <sup>85</sup>
40 m (4 × 10 m) Fast Paced Walk Test	Administered at a distance of 10 m (marked by tapes), a cone is placed 2 m before the start and 2 m after the end of each marking. The participant is instructed to walk as quickly but as safely as possible the first 10 m (from the start mark), to turn around the cone and walk back the 10 m again, successively until completing the distance of 40 m.	Speed (m/s).	An increase of 0.2–0.3 m/s in the test is the recommended MCID in OA research. <sup>85</sup>
Stair Climb Test (SCT)	The participant is positioned in front of the stairs, and, at the therapist's signal, he/she has to climb the indicated steps (we use the 12-step SCT) and descend promptly, being able to use the handrail as a security instrument. We use 20 cm steps height, a handrail stair in an illuminated environment, free of traffic, or external distractions. Moreover, a pre-test was conducted to identify the need for safety measures.	The final score is calculated based on the time the participant takes to perform the test and is compared to the normative literature values available for the test.	A reduction of 5.5 s in the test is the recommended MCID in OA research. <sup>85</sup>
Timed-up and Go Test	This test assesses: balance moving from sitting to standing, stability in walking, and gait course changes without using compensatory strategies. The participant is asked to stand up from a chair, walk 3 m, turn around, return, and sit back in the chair.	The total time to complete the test.	For the MCID, a reduction of 0.8–1.4 s is recommended in OA research. <sup>85</sup>
6-Minute Walk Test	This test assesses the aerobic capacity and long-distance walking activity. In addition, it is used to assess endurance and dynamic balance when changing directions during the walking activity.	The maximum distance walked in 6 min	A small MCID of 20 m and a substantial MCID of 50 m have been estimated for the test in a sample of community-dwelling older adults with mobility dysfunction. <sup>87</sup>

MCID, minimal clinically important difference; OA, osteoarthritis.

Biomaterials such as scaffolds, hydrogels, microspheres, and nanofibers associated with cutting-edge advances in cell-based approaches that focus primarily on cartilage regeneration, hold promise in the regeneration of the OA joint.<sup>96</sup> However, high-quality evidence is still scarce regarding this topic. Computer technologies also hold promise with respect to data mining (i.e. a process designed to search databases for consistent patterns and/or systematic relationships between variables) and machine learning approaches (i.e. a statistical method of data analysis using algorithms where a computer learns from a variety of examples). These technologies can be used in tandem to create patient-specific prediction models that analyze large amounts of patient data to design and develop effective and specific personalized therapeutic interventions for knee OA. The use of such modeling techniques may also result in substantial savings in medical resources and societal costs by reducing the burden of the disease.<sup>97</sup> Moreover, these technologies can help advance the fields of imaging, electronic medical record keeping, genetic/genomic analysis, and serum sample analysis, therefore facilitating the stratification of relevant OA phenotypes.<sup>98,99</sup>

Mobile health is another promising category that offers an unprecedented opportunity to obtain real-world patient data using a smartphone's capabilities and embedded sensors, such as accelerometers, gyroscopes, magnetometers, and barometers, among others.<sup>100</sup> These sensors, when configured correctly, can be used to precisely monitor aspects related to health, such as physical activity and function.<sup>101</sup> Through the development of specific algorithms, data from these sensors can be processed and used to measure and record movement patterns that are commonly assessed in physical function tests. Researchers can collect and store large quantities of objective clinical data, at multiple time points, to help reduce patient's recall bias and to provide more reliable and precise data about patients' fluctuation in symptoms.<sup>101,102</sup>

## Conclusion

Osteoarthritis is one of the most frequent diseases worldwide. The burden to society and health care systems is gradually increasing. It is our duty as healthcare professionals to leverage our access to high-quality evidence to increase the number of individuals receiving the appropriate core non-pharmacological treatments for knee OA. By doing so, we can increase the uptake of evidence-based guidelines in clinical practice of physical therapy. Patient education, exercise, and weight maintenance are vital for the successful treatment of these patients.

## Conflicts of interest

The authors declare no conflicts of interest.

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## References

1. Kyu HH, Abate D, Abate KH, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study. *Lancet*. 2017;2018:1859–1922, [http://dx.doi.org/10.1016/S0140-6736\(18\)32335-3](http://dx.doi.org/10.1016/S0140-6736(18)32335-3).
2. March L, Cross M, Arden N, Hawker G. *Osteoarthritis: a serious disease*. 2016:1–103. [https://www.oarsi.org/sites/default/files/docs/2016/oarsi.white.paper.oa\\_serious\\_disease\\_121416\\_1.pdf](https://www.oarsi.org/sites/default/files/docs/2016/oarsi.white.paper.oa_serious_disease_121416_1.pdf).
3. Palazzo C, Nguyen C, Lefevre-Colau MM, Rannou F, Poiraudou S. Risk factors and burden of osteoarthritis. *Ann Phys Rehabil Med*. 2016;59(3):134–138, <http://dx.doi.org/10.1016/j.rehab.2016.01.006>.
4. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet*. 2019;393(10182):1745–1759, [http://dx.doi.org/10.1016/S0140-6736\(19\)30417-9](http://dx.doi.org/10.1016/S0140-6736(19)30417-9).
5. Hoffmann TC, Hons B, Maher CG, et al. Prescribing exercise interventions for patients with chronic conditions. *CMAJ*. 2016;188(7):1–9, <http://dx.doi.org/10.1503/cmaj.150684/-/DC1>.
6. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. *Comprehensive Physiology*. vol. 2. Hoboken, NJ, USA: John Wiley & Sons Inc.; 2012:1143–1211, <http://dx.doi.org/10.1002/cphy.c110025>.
7. Chae KJ, Choi MJ, Kim KY, Ajayi FF, Chang IS, Kim IS. National Institute for Health and Care Excellence, Osteoarthritis: Care and Management. *Natl Clin Guidel Cent (UK)*. 2014;(December).
8. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthr Cartil*. 2019;27(11):1578–1589, <http://dx.doi.org/10.1016/j.joca.2019.06.011>.
9. Brosseau L, Taki J, Desjardins B, et al. The Ottawa panel clinical practice guidelines for the management of knee osteoarthritis. Part one: introduction, and mind-body exercise programs. *Clin Rehabil*. 2017;31(5):582–595, <http://dx.doi.org/10.1177/0269215517691083>.
10. Brosseau L, Taki J, Desjardins B, et al. The Ottawa panel clinical practice guidelines for the management of knee osteoarthritis. Part two: strengthening exercise programs. *Clin Rehabil*. 2017;31(5):596–611, <http://dx.doi.org/10.1177/0269215517691084>.
11. Brosseau L, Taki J, Desjardins B, et al. The Ottawa panel clinical practice guidelines for the management of knee osteoarthritis. Part three: aerobic exercise programs. *Clin Rehabil*. 2017;31(5):582–595, <http://dx.doi.org/10.1177/0269215517691083>.
12. Fernandes L, Hagen KB, Bijlsma JWJ, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Ann Rheum Dis*. 2013;72(7):1125–1135, <http://dx.doi.org/10.1136/annrheumdis-2012-202745>.
13. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Rheumatol*. 2020;72(2):220–233, <http://dx.doi.org/10.1002/art.41142>.
14. Skou ST, Roos EM. Good Life with osteoarthritis in Denmark (GLA:DTM): evidence-based education and supervised neuromuscular exercise delivered by certified physiotherapists nationwide. *BMC Musculoskelet Disord*. 2017;18(1):72, <http://dx.doi.org/10.1186/s12891-017-1439-y>.

15. Basedow M, Esterman A. Assessing appropriateness of osteoarthritis care using quality indicators: a systematic review. *J Eval Clin Pract.* 2015;21(5):782-789, <http://dx.doi.org/10.1111/jep.12402>.
16. Devez LA, Hunter DJ, Van Spil WE. Too much opioid, too much harm. *Osteoarthr Cartil.* 2018;26(3):293-295, <http://dx.doi.org/10.1016/j.joca.2017.12.003>.
17. Kloppenburg M, Berenbaum F. Osteoarthritis year in review 2019: epidemiology and therapy. *Osteoarthr Cartil.* 2020;28(3):242-248, <http://dx.doi.org/10.1016/j.joca.2020.01.002>.
18. Traeger AC, Moynihan RN, Maher CG. Wise choices: making physiotherapy care more valuable. *J Physiother.* 2017;63(2):63-65, <http://dx.doi.org/10.1016/j.jphys.2017.02.003>.
19. Crossley KM, Kemp JL, Culvenor AG, Barton CJ. Do sports medicine clinicians have credible alternatives to knee arthroscopy for the degenerative knee? *Br J Sports Med.* 2018;52(14):884-885, <http://dx.doi.org/10.1136/bjsports-2017-098166>.
20. Liang L, Abi Safi J, Gagliardi AR. Number and type of guideline implementation tools varies by guideline, clinical condition, country of origin, and type of developer organization: content analysis of guidelines. *Implement Sci.* 2017;12(1):136, <http://dx.doi.org/10.1186/s13012-017-0668-7>.
21. Maly MR, Marriott KA, Chopp-Hurley JN. Osteoarthritis year in review 2019: rehabilitation and outcomes. *Osteoarthr Cartil.* 2020;28(3):249-266, <http://dx.doi.org/10.1016/j.joca.2019.11.008>.
22. Maly MR, Krupa T. Personal experience of living with knee osteoarthritis among older adults. *Disabil Rehabil.* 2007;29(18):1423-1433, <http://dx.doi.org/10.1080/09638280601029985>.
23. Nyvang J, Hedström M, Gleissman SA. It's not just a knee, but a whole life: a qualitative descriptive study on patients' experiences of living with knee osteoarthritis and their expectations for knee arthroplasty. *Int J Qual Stud Health Well-being.* 2016;11(1):30193, <http://dx.doi.org/10.3402/qhw.v11.30193>.
24. Pouli N, Das Nair R, Lincoln NB, Walsh D. The experience of living with knee osteoarthritis: exploring illness and treatment beliefs through thematic analysis. *Disabil Rehabil.* 2014;36(7):600-607, <http://dx.doi.org/10.3109/09638288.2013.805257>.
25. Murray KE, Murray TE, O'Rourke AC, Low C, Veale DJ. Readability and quality of online information on osteoarthritis: an objective analysis with historic comparison. *Interact J Med Res.* 2019;8(3):e12855, <http://dx.doi.org/10.2196/12855>.
26. Rhee RL, Von Feldt JM, Schumacher HR, Merkel PA. Readability and suitability assessment of patient education materials in rheumatic diseases. *Arthritis Care Res (Hoboken).* 2013;65(10), <http://dx.doi.org/10.1002/acr.22046>, n/a-n/a.
27. Wallis JA, Taylor NF, Bunzli S, Shields N. Experience of living with knee osteoarthritis: a systematic review of qualitative studies. *BMJ Open.* 2019;9(9):1-11, <http://dx.doi.org/10.1136/bmjopen-2019-030060>.
28. French SD, Bennell KL, Nicolson PJA, Hodges PW, Dobson FL, Hinman RS. What do people with knee or hip osteoarthritis need to know? an international consensus list of essential statements for osteoarthritis. *Arthritis Care Res (Hoboken).* 2015;67(6):809-816, <http://dx.doi.org/10.1002/acr.22518>.
29. Fransen M, McConnell S, Ar H, VDE M, Simic M, Kl B. Exercise for osteoarthritis of the knee. *Cochrane Libr.* 2015;(1):1-144, <http://dx.doi.org/10.1002/14651858.CD004376.pub3>, [www.cochranelibrary.com](http://www.cochranelibrary.com).
30. Kraus VB, Sprow K, Powell KE, et al. Effects of physical activity in knee and hip osteoarthritis. *Med Sci Sport Exerc.* 2019;51(6):1324-1339, <http://dx.doi.org/10.1249/MSS.0000000000001944>.
31. Verhagen AP, Ferreira M, Reijneveld-van de Vendel EAE, et al. Do we need another trial on exercise in patients with knee osteoarthritis? *Osteoarthr Cartil.* 2019;27(9):1266-1269, <http://dx.doi.org/10.1016/j.joca.2019.04.020>.
32. Lee AC, Harvey WF, Price LL, et al. Dose-response effects of tai chi and physical therapy exercise interventions in symptomatic knee osteoarthritis. *PM&R.* 2018;10(7):712-723, <http://dx.doi.org/10.1016/j.pmrj.2018.01.003>.
33. Bennell KL, Dobson F, Hinman RS. Exercise in osteoarthritis: moving from prescription to adherence. *Best Pract Res Clin Rheumatol.* 2014;28(1):93-117, <http://dx.doi.org/10.1016/j.berh.2014.01.009>.
34. Dobson F, Bennell KL, French SD, et al. Barriers and facilitators to exercise participation in people with hip and/or knee osteoarthritis. *Am J Phys Med Rehabil.* 2016;95(5):1, <http://dx.doi.org/10.1097/PHM.0000000000000448>.
35. Nicolson PJA, Bennell KL, Dobson FL, Van Ginckel A, Holden MA, Hinman RS. Interventions to increase adherence to therapeutic exercise in older adults with low back pain and/or hip/knee osteoarthritis: a systematic review and meta-analysis. *Br J Sports Med.* 2017;51(10):791-799, <http://dx.doi.org/10.1136/bjsports-2016-096458>.
36. Nicolson PJA, Hinman RS, French SD, Lonsdale C, Bennell KL. Improving adherence to exercise: do people with knee osteoarthritis and physical therapists agree on the behavioral approaches likely to succeed? *Arthritis Care Res (Hoboken).* 2018;70(3):388-397, <http://dx.doi.org/10.1002/acr.23297>.
37. Ledingham A, Cohn ES, Baker KR, Keysor JJ. Exercise adherence: beliefs of adults with knee osteoarthritis over 2 years. *Physiother Theory Pract.* 2019;00(00):1-16, <http://dx.doi.org/10.1080/09593985.2019.1566943>.
38. Kelly T, Yang W, Chen C-S, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. *Int J Obes.* 2008;32(9):1431-1437, <http://dx.doi.org/10.1038/ijo.2008.102>.
39. Chooi YC, Ding C, Magkos F. The epidemiology of obesity. *Metabolism.* 2019;92:6-10, <http://dx.doi.org/10.1016/j.metabol.2018.09.005>.
40. Bliddal H, Leeds AR, Christensen R. Osteoarthritis, obesity and weight loss: evidence, hypotheses and horizons - a scoping review. *Obes Rev.* 2014;15(7):578-586, <http://dx.doi.org/10.1111/obr.12173>.
41. Oliveira MC, Vullings J, van de Loo FAJ. Osteoporosis and osteoarthritis are two sides of the same coin paid for obesity. *Nutrition.* 2020;70:110486, <http://dx.doi.org/10.1016/j.nut.2019.04.001>.
42. Felson DT. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. *Ann Intern Med.* 1992;116(7):535, <http://dx.doi.org/10.7326/0003-4819-116-7-535>.
43. Chu IJH, Lim AYT, Ng CLW. Effects of meaningful weight loss beyond symptomatic relief in adults with knee osteoarthritis and obesity: a systematic review and meta-analysis. *Obes Rev.* 2018;19(11):1597-1607, <http://dx.doi.org/10.1111/obr.12726>.
44. Hall M, Castelein B, Wittoek R, Calders P, Van Ginckel A. Diet-induced weight loss alone or combined with exercise in overweight or obese people with knee osteoarthritis: a systematic review and meta-analysis. *Semin Arthritis Rheum.* 2019;48(5):765-777, <http://dx.doi.org/10.1016/j.semarthrit.2018.06.005>.
45. Atukorala I, Makovey J, Lawler L, Messier SP, Bennell K, Hunter DJ. Is there a dose-response relationship between weight loss and symptom improvement in persons with knee osteoarthritis? *Arthritis Care Res (Hoboken).* 2016;68(8):1106-1114, <http://dx.doi.org/10.1002/acr.22805>.



46. Messier SP, Mihalko SL, Legault C, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis. *JAMA*. 2013;310(12):1263, <http://dx.doi.org/10.1001/jama.2013.277669>.
47. Christensen P, Henriksen M, Bartels EM, et al. Long-term weight-loss maintenance in obese patients with knee osteoarthritis: a randomized trial. *Am J Clin Nutr*. 2017;106(3), <http://dx.doi.org/10.3945/ajcn.117.158543>, ajcn158543.
48. Messier SP, Loeser RF, Miller GD, et al. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the arthritis, diet, and activity promotion trial. *Arthritis Rheum*. 2004;50(5):1501-1510, <http://dx.doi.org/10.1002/art.20256>.
49. Miller GD, Nicklas BJ, Davis C, Loeser RF, Lenchik L, Messier SP. Intensive weight loss program improves physical function in older obese adults with knee osteoarthritis. *Obesity*. 2006;14(7):1219-1230, <http://dx.doi.org/10.1038/oby.2006.139>.
50. Elfhag K, Rossner S. Who succeeds in maintaining weight loss? A conceptual review of factors associated with weight loss maintenance and weight regain. *Obes Rev*. 2005;6(1):67-85, <http://dx.doi.org/10.1111/j.1467-789X.2005.00170.x>.
51. Wadden TA, Butryn ML, Byrne KJ. Efficacy of lifestyle modification for long-term weight control. *Obes Res*. 2004;12(S12):151S-162S, <http://dx.doi.org/10.1038/oby.2004.282>.
52. Brosseau L, Yonge K, Robinson aV, et al. Ther-motherapy for treatment of osteoarthritis. *Cochrane Database Syst Rev*. 2003;(4):CD004522, [http://dx.doi.org/10.1016/S0031-9406\(05\)60490-7](http://dx.doi.org/10.1016/S0031-9406(05)60490-7).
53. Dantas LO, Moreira R, de FC, et al. The effects of cryotherapy on pain and function in individuals with knee osteoarthritis: a systematic review of randomized controlled trials. *Clin Rehabil*. 2019;(April), <http://dx.doi.org/10.1177/0269215519840406>, 0269215519840406.
54. Denegar CR, Dougherty DR, Friedman JE, et al. Preferences for heat, cold, or contrast in patients with knee osteoarthritis affect treatment response. *Clin Interv Aging*. 2010;5:199-206, <http://dx.doi.org/10.2147/CIA.S11431>.
55. Denegar CR, Schimizzi ME, Dougherty DR, et al. Responses to superficial heating and cooling differ in men and women with knee osteoarthritis. *Physiother Theory Pract*. 2012;28(3):198-205, <http://dx.doi.org/10.3109/09593985.2011.586097>.
56. Dantas LO, Breda CC, da Silva Serrao PRM, et al. Short-term cryotherapy did not substantially reduce pain and had unclear effects on physical function and quality of life in people with knee osteoarthritis: a randomised trial. *J Physiother*. 2019;65(4):215-221, <http://dx.doi.org/10.1016/j.jphys.2019.08.004>.
57. Barbosa GM, Cunha JE, Cunha TM, et al. Clinical-like cryotherapy improves footprint patterns and reduces synovial inflammation in a rat model of post-traumatic knee osteoarthritis. *Sci Rep*. 2019;9(1):14518, <http://dx.doi.org/10.1038/s41598-019-50958-8>.
58. Huang Z, Chen J, Ma J, Shen B, Pei F, Kraus VB. Effectiveness of low-level laser therapy in patients with knee osteoarthritis: a systematic review and meta-analysis. *Osteoarthr Cartil*. 2015;23(9):1437-1444, <http://dx.doi.org/10.1016/j.joca.2015.04.005>.
59. Stausholm MB, Naterstad IF, Joensen J, et al. Efficacy of low-level laser therapy on pain and disability in knee osteoarthritis: systematic review and meta-analysis of randomised placebo-controlled trials. *BMJ Open*. 2019;9(10):e031142, <http://dx.doi.org/10.1136/bmjopen-2019-031142>.
60. Rutjes AW, Nüesch E, Sterchi R, Jüni P. Therapeutic ultrasound for osteoarthritis of the knee or hip. *Cochrane Database Syst Rev*. 2010;(1):CD003132, <http://dx.doi.org/10.1002/14651858.CD003132.pub2>.
61. Loyola-Sánchez A, Richardson J, MacIntyre NJ. Efficacy of ultrasound therapy for the management of knee osteoarthritis: A systematic review with meta-analysis. *Osteoarthr Cartil*. 2010;18(9):1117-1126, <http://dx.doi.org/10.1016/j.joca.2010.06.010>.
62. Zeng C, Li H, Yang T, et al. Effectiveness of continuous and pulsed ultrasound for the management of knee osteoarthritis: a systematic review and network meta-analysis. *Osteoarthr Cartil*. 2014;22(8):1090-1099, <http://dx.doi.org/10.1016/j.joca.2014.06.028>.
63. Zhou X-Y, Zhang X-X, Yu G-Y, et al. Effects of low-intensity pulsed ultrasound on knee osteoarthritis: a meta-analysis of randomized clinical trials. *Biomed Res Int*. 2018;1-7, <http://dx.doi.org/10.1155/2018/7469197>.
64. Zhang C, Xie Y, Luo X, et al. Effects of therapeutic ultrasound on pain, physical functions and safety outcomes in patients with knee osteoarthritis: a systematic review and meta-analysis. *Clin Rehabil*. 2016;30(10):960-971, <http://dx.doi.org/10.1177/0269215515609415>.
65. Rutjes AW, Nüesch E, Sterchi R, et al. Transcutaneous electrostimulation for osteoarthritis of the knee. *Cochrane Database Syst Rev*. 2009;4(4):447-449, <http://dx.doi.org/10.1002/14651858.CD002823.pub2>.
66. Ogura Dantas L, Serafim Jorge AE, Regina Mendes da Silva Serrão P, Aburquerque-Sendin F, de Fatima Salvini T. Cryotherapy associated with tailored land-based exercises for knee osteoarthritis: a protocol for a double-blind sham-controlled randomised trial. *BMJ Open*. 2020;10(6):e035610, <http://dx.doi.org/10.1136/bmjopen-2019-035610>.
67. Volkow ND, McLellan AT. Opioid abuse in chronic pain — misconceptions and mitigation strategies. *N Engl J Med*. 2016;374(13):1253-1263, <http://dx.doi.org/10.1056/NEJMr1507771>.
68. Vowles KE, McEntee ML, Siyahhan P, et al. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain*. 2015;156(4). <http://www.nejm.org/doi/10.1056/NEJMr1507771>.
69. da Costa BR, Nüesch E, Kasteler R, et al. Oral or transdermal opioids for osteoarthritis of the knee or hip. *Cochrane Database Syst Rev*. 2014;(9), <http://dx.doi.org/10.1002/14651858.CD003115.pub4>.
70. Singh JA, Noorbaloochi S, MacDonald R, Maxwell LJ. Chondroitin for osteoarthritis. In: Singh JA, ed. *Cochrane Database of Systematic Reviews*. vol. 176. Chichester, UK: John Wiley & Sons, Ltd; 2015:139-148, <http://dx.doi.org/10.1002/14651858.CD005614.pub2>.
71. Eriksen P, Bartels EM, Altman RD, Bliddal H, Juhl C, Christensen R. Risk of bias and brand explain the observed inconsistency in trials on glucosamine for symptomatic relief of osteoarthritis: a meta-analysis of placebo-controlled trials. *Arthritis Care Res (Hoboken)*. 2014;66(12):1844-1855, <http://dx.doi.org/10.1002/acr.22376>.
72. Zhu X, Sang L, Wu D, Rong J, Jiang L. Effectiveness and safety of glucosamine and chondroitin for the treatment of osteoarthritis: a meta-analysis of randomized controlled trials. *J Orthop Surg Res*. 2018;13(1):170, <http://dx.doi.org/10.1186/s13018-018-0871-5>.
73. Siemieniuk RAC, Harris IA, Agoritsas T, et al. Arthroscopic surgery for degenerative knee arthritis and meniscal tears: a clinical practice guideline. *BMJ*. 2017;357:j1982, <http://dx.doi.org/10.1136/bmj.j1982>.
74. Reichenbach S, Rutjes AW, Nüesch E, Trelle S, Jüni P. Joint lavage for osteoarthritis of the



- knee. *Cochrane Database Syst Rev.* 2010;(May), <http://dx.doi.org/10.1002/14651858.CD007320.pub2>.
75. Thorlund JB, Juhl CB, Roos EM, Lohmander LS. Arthroscopic surgery for degenerative knee: systematic review and meta-analysis of benefits and harms. *BMJ.* 2015;350(jun16 3):h2747, <http://dx.doi.org/10.1136/bmj.h2747>.
76. Hawker G, Guan J, Judge A, Dieppe P. Knee arthroscopy in england and ontario: patterns of use, changes over time, and relationship to total knee replacement. *J Bone Jt Surg-Am Vol.* 2008;90(11):2337-2345, <http://dx.doi.org/10.2106/JBJS.G.01671>.
77. Rongen JJ, Rovers MM, van Tienen TG, Buma P, Hanink G. Increased risk for knee replacement surgery after arthroscopic surgery for degenerative meniscal tears: a multicenter longitudinal observational study using data from the osteoarthritis initiative. *Osteoarthritis Cartil.* 2017;25(1):23-29, <http://dx.doi.org/10.1016/j.joca.2016.09.013>.
78. Richmond J, Hunter D, Irgang J, et al. Treatment of osteoarthritis of the knee (nonarthroplasty). *J Am Acad Orthop Surg.* 2009;17(9):591-600, <http://dx.doi.org/10.5435/00124635-200909000-00006>.
79. Higashi H, Barendregt JJ. Cost-effectiveness of total hip and knee replacements for the australian population with osteoarthritis: discrete-event simulation model. van Baal PHM, ed. *PLoS One.* 2011;6(9):e25403, <http://dx.doi.org/10.1371/journal.pone.0025403>.
80. Wylde V, Hewlett S, Learmonth ID, Dieppe P. Persistent pain after joint replacement: prevalence, sensory qualities, and postoperative determinants. *Pain.* 2011;152(3):566-572, <http://dx.doi.org/10.1016/j.pain.2010.11.023>.
81. Bourne RB, Cheshworth BM, Davis AM, Mahomed NN, Charron KDJ. Patient satisfaction after total knee arthroplasty: who is satisfied and who is not? *Clin Orthop Relat Res.* 2010;468(1):57-63, <http://dx.doi.org/10.1007/s11999-009-1119-9>.
82. Kahlenberg CA, Nwachukwu BU, McLawhorn AS, Cross MB, Cornell CN, Padgett DE. Patient satisfaction after total knee replacement: a systematic review. *HSS J.* 2018;14(2):192-201, <http://dx.doi.org/10.1007/s11420-018-9614-8>.
83. Dowsey MM, Nikpour M, Dieppe P, Choong PFM. Associations between pre-operative radiographic changes and outcomes after total knee joint replacement for osteoarthritis. *Osteoarthritis Cartil.* 2012;20(10):1095-1102, <http://dx.doi.org/10.1016/j.joca.2012.05.015>.
84. Umehara T, Tanaka R. Effective exercise intervention period for improving body function or activity in patients with knee osteoarthritis undergoing total knee arthroplasty: a systematic review and meta-analysis. *Braz J Phys Ther.* 2018;22(4):265-275, <http://dx.doi.org/10.1016/j.bjpt.2017.10.005>.
85. Dobson F, Hinman RS, Roos EM, et al. OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. *Osteoarthritis Cartil.* 2013;21(8):1042-1052, <http://dx.doi.org/10.1016/j.joca.2013.05.002>.
86. Pham T, van der Heijde D, Altman R, et al. OMERACT-OARSI Initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis Cartil.* 2004;12(5):389-399, <http://dx.doi.org/10.1016/j.joca.2004.02.001>.
87. Bennell K, Dobson F, Hinman R. Measures of physical performance assessments: Self-Paced Walk Test (SPWT), Stair Climb Test (SCT), Six-Minute Walk Test (6MWT), Chair Stand Test (CST), Timed Up & Go (TUG), Sock Test, Lift and Carry Test (LCT), and Car Task. *Arthritis Care Res (Hoboken).* 2011;63(S11):S350-S370, <http://dx.doi.org/10.1002/acr.20538>.
88. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336(7650):924-926, <http://dx.doi.org/10.1136/bmj.39489.470347.AD>.
89. Stevens-Lapsley JE, Schenkman ML, Dayton MR. Comparison of self-reported knee injury and osteoarthritis outcome score to performance measures in patients after total knee arthroplasty. *PM&R.* 2011;3(6):541-549, <http://dx.doi.org/10.1016/j.pmrj.2011.03.002>.
90. Liu S-H, Eaton CB, Driban JB, McAlindon TE, Lapane KL. Comparison of self-report and objective measures of physical activity in US adults with osteoarthritis. *Rheumatol Int.* 2016;36(10):1355-1364, <http://dx.doi.org/10.1007/s00296-016-3537-9>.
91. Luna IE, Kehlet H, Peterson B, Wede HR, Hoefvegaard SJ, Aasvang EK. Early patient-reported outcomes versus objective function after total hip and knee arthroplasty. *Bone Joint J.* 2017;99-B(9):1167-1175, <http://dx.doi.org/10.1302/0301-620X.99B.BJJ-2016-1343R1>.
92. Baltaci G, Tunay VB. Is self-reported improvement in osteoarthritis pain and disability reflected in objective measures? *Osteoarthritis Cartil.* 2007;15(1):C147, [http://dx.doi.org/10.1016/S1063-4584\(07\)61893-7](http://dx.doi.org/10.1016/S1063-4584(07)61893-7).
93. Terwee CB, Mokkink LB, Steultjens MPM, Dekker J. Performance-based methods for measuring the physical function of patients with osteoarthritis of the hip or knee: a systematic review of measurement properties. *Rheumatology.* 2006;45(7):890-902, <http://dx.doi.org/10.1093/rheumatology/kei267>.
94. Stratford PW, Kennedy DM. Performance measures were necessary to obtain a complete picture of osteoarthritic patients. *J Clin Epidemiol.* 2006;59(2):160-167, <http://dx.doi.org/10.1016/j.jclinepi.2005.07.012>.
95. Maly MR, Costigan PA, Olney SJ. Determinants of self-report outcome measures in people with knee osteoarthritis. *Arch Phys Med Rehabil.* 2006;87(1):96-104, <http://dx.doi.org/10.1016/j.apmr.2005.08.110>.
96. Ondr sik M, Azevedo Maia FR, da Silva Morais A, et al. Management of knee osteoarthritis, current status and future trends. *Biotechnol Bioeng.* 2017;114(4):717-739, <http://dx.doi.org/10.1002/bit.26182>.
97. Jamshidi A. Machine-learning-based patient-specific prediction models for knee osteoarthritis. *Nat Rev Rheumatol (Box 1).* 2019, <http://dx.doi.org/10.1038/s41584-018-0130-5>.
98. Devesa LA, Nelson AE, Loeser RF. Phenotypes of osteoarthritis: current state and future implications. *Clin Exp Rheumatol.* 2019;37(suppl 1 (5)):64-72. <http://www.ncbi.nlm.nih.gov/pubmed/31621574>.
99. Kluzek S, Mattei TA. Machine-learning for osteoarthritis research. *Osteoarthritis Cartil.* 2019;27(7):977-978, <http://dx.doi.org/10.1016/j.joca.2019.04.005>.
100. Sim I. Mobile devices and health. *N Engl J Med.* 2019;381(10):956-968, <http://dx.doi.org/10.1056/NEJMr1806949>.
101. Quinby E, Dicianno BE, Kelly C, et al. Systematic review of mobile health applications in rehabilitation. *Arch Phys Med Rehabil.* 2019;100(1):115-127, <http://dx.doi.org/10.1016/j.apmr.2018.07.439>.
102. Cvrkel T. The ethics of mHealth: moving forward. *J Dent.* 2018;74(April):S15-S20, <http://dx.doi.org/10.1016/j.jdent.2018.04.024>.
103. Bellamy N, Carette S, Ford PM, et al. Osteoarthritis antirheumatic drug trials. III. Setting the delta for clinical trials: results of a consensus development (Delphi) exercise. *J Rheumatol.* 1992;19, 451-7.2.
104. Salaffi F, Stancati A, Silvestri CA, Ciapetti A, Grassi W. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numer-

- ical rating scale. *Eur J Pain*. 2004;8(4):283–291, <http://dx.doi.org/10.1016/j.ejpain.2003.09.004>.
105. Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower ex. *Arthritis Rheum*. 2001;45(4):384–391, [http://dx.doi.org/10.1002/1529-0131\(200108\)45:4<384::AID-ART352>3.0.CO;2-0](http://dx.doi.org/10.1002/1529-0131(200108)45:4<384::AID-ART352>3.0.CO;2-0).
106. Roos EM, Toksvig-Larsen S. Knee injury and Osteoarthritis Outcome Score (KOOS) – validation and comparison to the WOMAC in total knee replacement. *Health Qual Life Outcomes*. 2003;1:17, <http://dx.doi.org/10.1186/1477-7525-1-17>.
107. Escobar A, Quintana JM, Bilbao A, Aróstegui I, Lafuente I, Vidaurreta I. Responsiveness and clinically important differences for the WOMAC and SF-36 after total knee replacement. *Osteoarthritis Cartil*. 2007;15(3):273–280, <http://dx.doi.org/10.1016/j.joca.2006.09.001>.
108. Clement ND, MacDonald D, Simpson AHRW. The minimal clinically important difference in the Oxford knee score and Short Form 12 score after total knee arthroplasty. *Knee Surgery, Sport Traumatol Arthrosc*. 2014;22(8):1933–1939, <http://dx.doi.org/10.1007/s00167-013-2776-5>.