Non-pharmacological and non-surgical interventions to manage patients with knee osteoarthritis: an umbrella review

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ABSTRACT

Objective: Update the last known umbrella review and summarize the available high-quality evidence from systematic reviews on the effectiveness of non-pharmacological and non-surgical interventions for patients with knee osteoarthritis (OA).

Methods: The systematic reviews were identified throught electronic databases, such as: MEDLINE, Embase, Physiotherapy Evidence Database (PEDro), The Cochrane Library, SciELo, Science Direct, Google Scholar, Research Gate and B-ON. The studies' selection respected the following terms to guide the search strategy using the P (humans with knee osteoarthritis) I (non-pharmacological and non-surgical treatments) C (pharmacological, surgical, placebo, no intervention, or other non-pharmacological/ non-surgical conservative treatments) O (pain, functional status, stiffness, inflammation, quality of life and patient global assessment) model.

Results: Following the PRISMA statement, 41 systematic reviews were found on the electronic databases that could be included in the umbrella review. After methodical analysis (R-AMSTAR), only 35 had sufficient quality to be included. There is gold evidence that Standard Exercise programs can reduce pain and improve physical function in patients with knee OA. Additionally, there is silver evidence for Acupuncture, Aquatic Exercise, Electroacupuncture, Interferential Current, Kinesio Taping, Manual Therapy, Moxibustion, Pulsed Electromagnetic Fields, Tai Chi, Ultrasound, Yoga, and Whole-Body Vibration. For other interventions, the quality of evidence is low or did not show sufficient efficacy from the systematic reviews to support their use.

Conclusion: Comparing to the last known umbrella review, similar results were achieved on Acupuncture and Exercise interventions to improve the patients' pain, stiffness, function and quality of life, but different results were found regarding the utilization of Transcutaneous Electrical Nerve Stimulation and Low-Level Laser Therapy as they do not improved the patients' pain and physical function.

Keywords: Non-pharmacologic; Non-surgical; Knee; Osteoarthritis

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INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis that can affect all the movable joint tissues and is a major contributor to functional and social impairment, disability, reduced independence and poorer quality of life in older adults[1-9]. From all the joints that can be affected by OA the knee is the most prevalent (especially in elderly women), where a third of older adults in the general population show radiological evidence of knee OA[10-16]. Moreover, there is an increasing need for attention to this disease due to the societal trends such as ageing, obesity prevalence and joint injury, which are estimated to increase the number of people affected with OA by 50% over the next 20 years[7,15,17,18].

Knee OA evolution is highly variable, with the disease improving in some patients, remaining stable in others and gradually worsening in others[19, 20]. Treatment strategies for OA include pharmacological, non-pharmacological, surgical and non-surgical interventions[7,12,21-28]. However, as the majority of the non-pharmacological and non-surgical interventions are safe, low cost, low tech, incorporate self-management performed at home or in the community and have a substantial public health impact, they are nowadays the

first step in the knee OA management and play a critical role in its treatment[7,12,22,25-29].

In the last few years, evidence-based practice has become increasingly popular. Evidence-based practice uses the available literature to guide clinical decision making and assess the strength of clinical recommendations[30,31]. When diagnosing and treating patients, practitioners employ evidence, frequently from systematic reviews of randomized controlled trials (RCTs), to advocate for or against an intervention[30]. Although systematic reviews summarize the effects of a specific intervention for a specific condition, an umbrella review typically assesses the quality, collate the results and summarizes the evidence providing a wider picture on the research topic[32-39]. In 2008 Jamtvedt et al.[32], published an umbrella review about knee OA, with very useful results and conclusions that increase the knowledge and evidence-based practice, establishing as well a platform for future investigation in this topic. However, it was shown that at least 10% of all systematic reviews need updating at the publication time because of the length of time taken in preparing a systematic review and the accelerated pace of new evidence scientific production[40]. There is, to our knowledge, no available updated umbrella review on the effectiveness of non-pharmacological and non-surgical interventions for knee OA. Therefore, the aim of this umbrella review is to summarize and update the available high-quality evidence from systematic reviews on the effectiveness of non-pharmacological and non-surgical interventions for patients with knee OA.

METHODS

There is, to our knowledge, no widely accepted guideline to conduct an overview[39]. Therefore, in an attempt to ensure a high-quality study, this overview was conducted following the PRISMA (*P*referred *R*eporting *I*tems for *S*ystematic reviews and *M*eta-*A*nalyses) guidelines[41].

DATA SOURCES AND SEARCHES

The literature search aimed to identify systematic reviews that evaluated the effect of non-pharmacological and non-surgical treatments for knee OA. Systematic and comprehensive searches were conducted in electronic databases: MEDLINE, Embase, Physiotherapy Evidence Database (PEDro), The Cochrane Library, SciELo, Science Direct, Google Scholar, Research Gate and B-ON. Papers were accepted only in English and excluded if duplicated. The search begun in May 2017 and finished in August 2017.

The studies' selection respected the following terms to guide the search strategy using the Population (P) (humans with knee osteoarthritis), Intervention (I) (non-pharmacological and non-surgical treatments), Control (C) (pharmacological, surgical, placebo, no intervention, or other non-pharmacological/non--surgical conservative treatments), Outcome (O) (pain, functional status, stiffness, inflammation, quality of life and patient global assessment) model.

The keywords used in the search were: "Knee"; "Osteoarthr*"; "Gonarthr*". These keywords were identified after preliminary literature searches and by cross-checking them against previous relevant systematic reviews.

An example of an online search strategy draft used in MEDLINE database is presented: (Systematic Review[ptyp]) AND ("2007/01/01" [Pdat] : "2017/05/29"[Pdat]) AND ("humans"[MeSH Terms]) AND (English[lang]) AND ((("Knee"[All Fields]) AND ("Osteoarthr*"[All Fields])) OR ("Gonarthr*"[All Fields]))

Additional publications that were not found during the original database search were identified through manual searches in the related articles and reviews reference lists.

STUDY SELECTION

In this paper, the two reviewers independently screened the titles and abstracts yielded by the search against the inclusion and exclusion criteria and selected the potential studies. The inclusion and exclusion criteria applied to this review are described in Table I.

The full versions of the systematic reviews that appeared to meet the inclusion criteria or where there was any uncertainty were obtained. As the last known umbrella review was the Jamtvedt et al.[32] study, it was chosen to start the search for systematic reviews of non-pharmacological and non-surgical treatments for knee OA published in the electronic databases after January 2007. Furthermore, due to biomechanical and disease relationship, other systematic reviews exploring hip and knee OA were included, only if the results from patients with knee OA could be extracted separately. The reviewers read the full text versions and decided whether they actually meet the inclusion criteria. When insufficient data was presented, the authors were contacted by email in order to request fur-

TABLE I. INCLUSION AND EXCLUSION CRITERIA

Inclusion	Exclusion
The systematic reviews must include:	**The systematic reviews cannot include:**
at least one of the keywords;	papers with experimental or control group composed by any kind of animal;
papers with an intervention group that has primary knee OA, either clinical or radiological criteria (or a combination);	papers with participants that do not have a knee OA (healthy subjects) or who have secondary knee OA (traumatic or post-surgical);
with or without meta-analysis exclusively from randomized controlled trials after January 2007;	with or without meta-analysis of randomized controlled trials prior to January 2007;
papers with non-pharmacological and non-surgical interventions	papers with exclusively pharmacological or surgical interventions;
peer-reviewed scientific literature journals;	books, non-randomized controlled trials, case reports, expert opinions, conference papers or academic thesis;
papers that evaluate pain or other knee-related symptoms, functional status or quality of life;	papers with subjects with other illnesses namely cancer, heart diseases, kidney diseases, neurological diseases, respiratory diseases, rheumatoid arthritis, gout arthritis, septic arthritis or Paget's disease;
detailed description of the non-pharmacological and non-surgical intervention;	papers with subjects exclusively with osteoarthritis in the hip, foot, shoulder, elbow, wrist and/or fingers.
their full version, in English.	

ther data. In case of study selection disparities, the reviewers reached an agreement through verbal discussion or arbitration.

DATA EXTRACTION AND QUALITY ASSESSMENT

For this review, the authors independently scored the bias of the studies by using the R-AMSTAR (*R*evised *A* *M*ea*S*urement *T*ool to *A*ssess systematic *R*eviews) 11--item questionnaire. In R-AMSTAR each domain's score ranges between 1 (minimum) and 4 (maximum), and the total score has a range of 11 (minimum) to 44 (maximum) that, posteriorly based on the overall score, can translate in A (high quality: 44-33 score), B (moderate quality: 32-23 score), C (low quality: 22-13 score) and D (very low quality: 12-11 score) quality grade[42]. Considering the recommendations that only total scores of 23/44 are considered to have at least moderate methodological quality, it was established as the cutting-point for include a systematic review in this overview[42].

Furthermore, principles from GRADE (*G*rading of *R*ecommendations *A*ssessment, *D*evelopment, and *E*valuation) were used for an overall assessment and integration of the strength of the evidence for each intervention[43, 44]. The GRADE concept is based on an assessment of the following criteria: quality of primary studies, design of primary studies, consistency, and directness. An overall assessment of the quality of evidence was based on a summary of these 4 criteria, as presented in Table II.

DATA SYNTHESES AND ANALYSIS

The data that was extracted from the selected publications to assess the effectiveness of non-pharmacological and non-surgical interventions included: title, authors' name, year of publication, knee OA conditions, participants' sample size and their characteristics, objectives, description of the interventions, description of the control groups, studies' outcomes, assessment times, studies' results and studies' conclusions. Also, studies were combined using qualitative best evidence synthesis. Considering the broad scope of clinical conditions, it was decided to restrict the work to pain, functional status, stiffness, inflammation, quality of life and patient global assessment[45].

RESULTS

SELECTION OF THE STUDIES

A set of 2188 records were identified through database

TABLE II. GRADING QUALITY OF EVIDENCE

Level	Criteria
High-quality evidence (A) (Further research is very unlikely to change our confidence in the estimate of effect)	One or more updated, high-quality systematic review that are based on at least 2 high-quality primary studies with consistent results
Moderate-quality evidence (B) (Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate)	One or more updated systematic reviews of high or moderate quality • Based on at least 1 high-quality primary study • Based on at least 2 primary studies of moderate quality with consistent results
Low-quality evidence (C) (Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate)	One or more systematic reviews of variable quality • Based on primary studies of moderate quality • Based on inconsistent results in the reviews • Based on inconsistent results in primary studies
Very low-quality evidence (D) (Any estimate of effect is very uncertain)	No high-quality systematic review was identified on this topic

searching. After the application of the inclusion and exclusion criteria, 41 articles have emerged[46-86]. The selection process is summarized Figure 1.

METHODOLOGICAL QUALITY

After the selection of the studies, the reviewers independently applied the R-AMSTAR to evaluate the methodological quality of the 41 selected papers[46-86]. After this process, they reached an agreement through verbal discussion or arbitration. The percentage of agreement for individual items ranged from 36.4% to 100%. The methodological quality assessment using the R-AMSTAR revealed a mean score of 32.7 (range 18 – 40). At the end, 6 of the systematic reviews[46,54,57,66,71,81] were excluded because they did not reach 23/44, raising the mean score to 34.9. The classifications obtained are described in Table III.

STUDY CHARACTERISTICS

Overall, the 35 included systematic reviews[47-53,55,56,58-65,67-70,72-80,82-86] were published from 2007[48] to 2017[59,62,80] and were conducted in America (Canada[64]), Asia (China[49,53,56,60-63,72,77,79,80,84-86], Japan[73-75], Saudi Arabia[83] and South Korea[70,78]), Europe (Denmark[47,55], England[65,76], France[50,67], Germany[58], Ireland[52], Norway[48] and Switzerland[68,69]) and Oceania (Australia[51,59,82]).

The total RCTs included in the systematic reviews were 571, with an average of 16.3±14.41 studies (maximum=60[76]; minimum=4[52,60]) per systematic review. Overall, 52,152 subjects were enrolled in the systematic reviews, with an average of 1,490.06± 1,797.11 (maximum=8,218[76]; minimum=165[83] per systematic review and 82.08±47.2 per RCT. In the studies, several non-pharmacological and non-surgical treatments were found (Figure 2).

Supplementary file Table IV provides a summary of the included systematic reviews characteristics.

DISCUSSION

The discussion will be presented according to the interventions of the selected systematic reviews.

PHYSICAL ACTIVITY

The physical component of 4 different activities were investigated, such as Aquatic Exercise, Standard Exercise, Tai Chi and Yoga.

Aquatic Exercise was only investigated in one study[47]. According to the authors[47] this type of exercise decreases pain and disability, and increases quality of life. However, this was only found in short-term follow-up (12 weeks), but it could not be confirmed in long-term. Additionally, this data was gathered in knee and hip OA and only moderate-evidence can support these statements.

Regarding land type Standard Exercise, it was explored in 10 systematic reviews[50,51,55,63,67,73-76,82]. High-evidence shows that Standard Exercise programs are effective in pain and stiffness reduction and in increa-

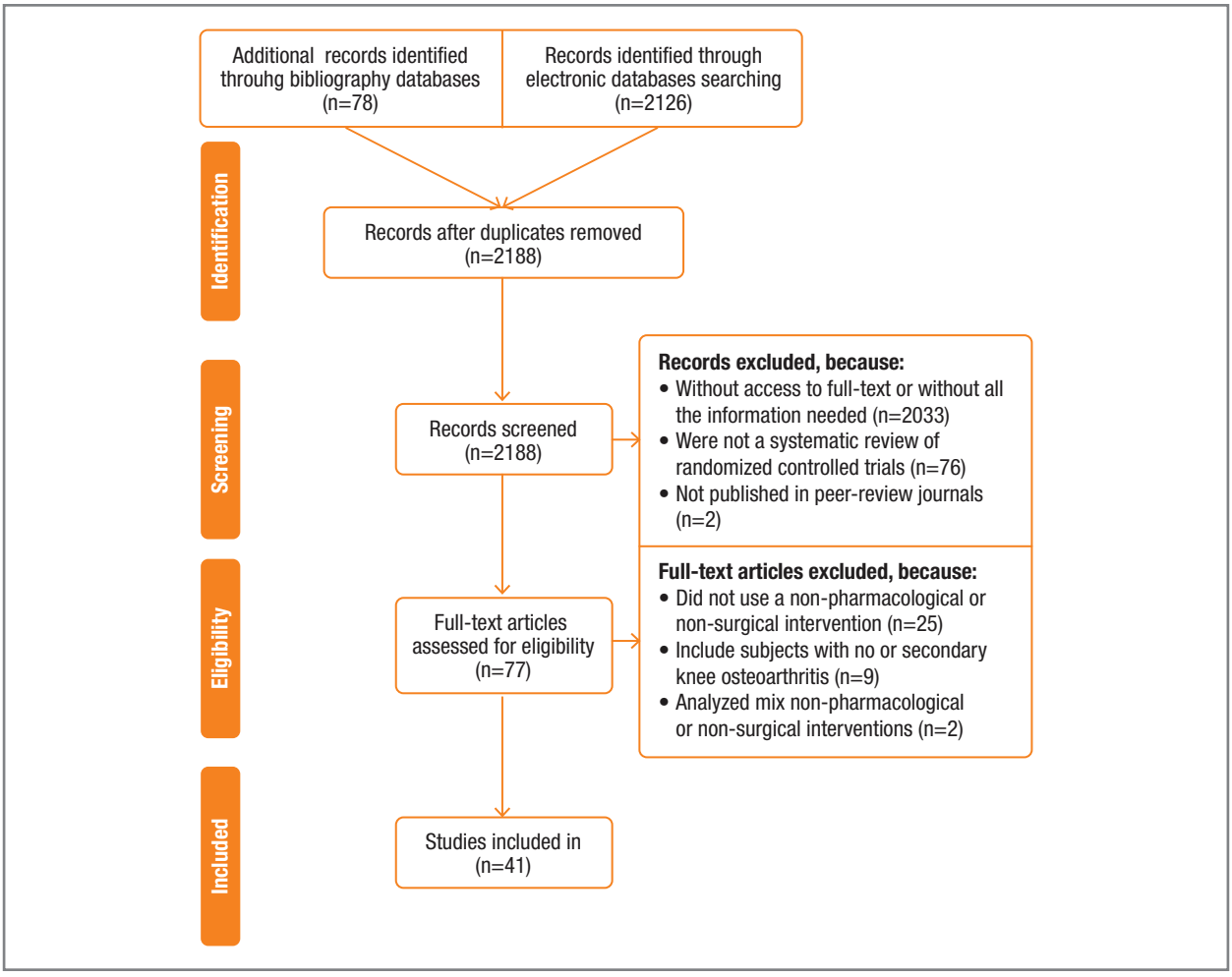

FIGURE 1. Results of the inclusion and exclusion criteria (flow diagram applied in this umbrella review)

sing function and quality of life[51,55,63,74-76,82]. Also, pain and disability reduction were found in moderate-quality evidence[50,73]. All types of Standard Exercise programs (aerobic, strengthening or resistance) were found to be beneficial in patients with knee OA. However, there are still some doubts between the low and high-intensity training. Li et al.[63] concluded from high-evidence that high-intensity training program was more effective than the low-intensity training, Regnaux et al.[67] found no differences between low and high-intensity training programs from low to very low-evidence and Zacharias et al.[82] have shown that both were beneficial to this type of population, however there was high-evidence to support the low-intensity training program and low to moderate-evidence to support the high-intensity training program.

There was only one study[58] that explored the repeated practice of Tai Chi as a method to treat patients with knee OA. Lauche et al.[58] perceived, from moderate-evidence, that Tai Chi practice could decrease pain and stiffness, and increase function in these patients, with the best results reached in patients that were intervened at least 2 times/week, 30 or more min/session. Similarly, Kan et al.[56] analyzed the effectiveness of Yoga regular practice to treat these patients and saw positive effects on pain and mobility, for the most common Yoga protocols (40-90 min/session, every day during at least 8 weeks).

Overall, Activities can be recommended to patients with knee OA, especially aerobic, resistance, strengthening or combined programs to improve pain, stiffness, function and quality of life, regardless of the patient's

TABLE III. METHODOLOGICAL QUALITY OF ELIGIBLE STUDIES (N = 41)

Study (A to Z; Year)	R-AMSTAR Items											R-AMSTAR Score (11 – 44)	GRADE (A – D)
	1	2	3	4	5	6	7	8	9	10	11		
Bjordal et al. (48)	4	1	3	3	3	4	1	2	4	4	3	32	C
Lange et al. (57)	2	1	3	2	1	1	1	1	4	1	1	18	
Rutjes et al. (69)	4	4	4	2	3	4	4	4	4	4	3	40	A
Rutjes et al. (68)	4	4	4	2	3	4	4	4	4	4	3	40	A
French et al. (52)	3	1	4	1	3	4	3	3	1	1	1	25	B
Cao et al. (49)	2	4	4	3	3	4	4	4	4	4	1	37	B
Silva et al. (71)	2	2	2	3	1	4	4	1	1	1	1	22	
Lauche et al. (58)	4	4	4	2	4	4	4	4	2	2	3	37	B
Negm et al. (64)	4	2	4	2	3	4	2	2	4	4	3	34	D
Parkes et al. (65)	2	2	3	2	3	4	4	3	4	4	3	34	B
Tanaka et al. (73)	4	4	1	1	1	4	4	4	4	4	3	34	A
Uthman et al. (76)	3	4	4	3	3	1	3	1	4	4	1	31	B
We et al. (78)	1	4	4	2	3	4	4	4	4	4	1	35	A
Juhl et al. (55)	3	1	4	2	3	4	4	4	4	4	1	34	A
Quintrec et al. (66)	1	1	3	2	1	4	1	1	1	1	2	18	
Tanaka et al. (74)	2	4	4	3	1	4	3	2	4	4	1	32	A
Ye et al. (81)	3	2	4	2	1	4	2	1	1	1	1	22	
Zacharias et al. (82)	3	4	3	2	4	4	4	4	4	4	2	38	A
Zeng et al. (84)	2	4	4	2	3	4	2	2	4	4	2	33	B
Anwer et al. (46)	2	2	3	1	1	4	1	1	1	1	3	20	
Fransen et al. (51)	4	4	4	2	3	4	4	4	4	4	3	40	A
Huang et al. (53)	3	2	3	2	3	4	3	2	4	4	2	32	B
Li et al. (61)	3	4	4	3	3	4	4	4	4	4	3	40	A
Regnaux et al. (67)	4	4	4	2	3	4	4	4	4	4	3	40	D
Tanaka et al. (75)	3	2	4	2	3	4	4	1	4	4	1	32	B
Wang et al. (77)	3	2	4	2	3	4	4	2	4	4	3	35	B
Zafar et al. (83)	2	4	2	2	4	4	4	3	4	4	1	34	B
Zeng et al. (85)	3	4	4	2	2	4	4	3	4	4	3	37	B
Zhang et al. (86)	3	4	4	3	3	4	3	3	4	4	3	38	B
Bartels et al. (47)	4	4	4	2	3	4	4	4	4	4	3	40	B
Coudeyre et al. (50)	3	2	2	2	3	4	3	2	4	4	3	32	B
Kan et al. (56)	3	4	2	2	3	4	3	1	1	1	2	26	B
Li et al. (60)	2	4	2	2	3	4	4	2	4	4	2	33	B
Li et al. (63)	3	4	2	2	3	4	3	3	4	4	3	35	A
Shim et al. (70)	4	4	3	3	3	4	4	4	4	4	1	38	B
Song et al. (72)	4	4	4	4	3	4	4	2	4	4	1	38	B
Xiang et al. (79)	3	3	3	2	3	3	3	1	4	4	1	30	A
Jorge et al. (54)	2	1	2	3	3	4	1	2	1	1	1	21	
Lee et al. (59)	4	1	3	4	3	4	4	2	4	4	3	36	C
Li et al. (62)	4	4	3	1	3	4	4	4	4	4	1	36	B
Xu et al. (80)	2	1	4	4	3	4	3	2	4	4	1	32	B
Average	3	3	3.3	2.3	2.7	3.8	3.2	2.6	3.4	3.4	2	32.7	B

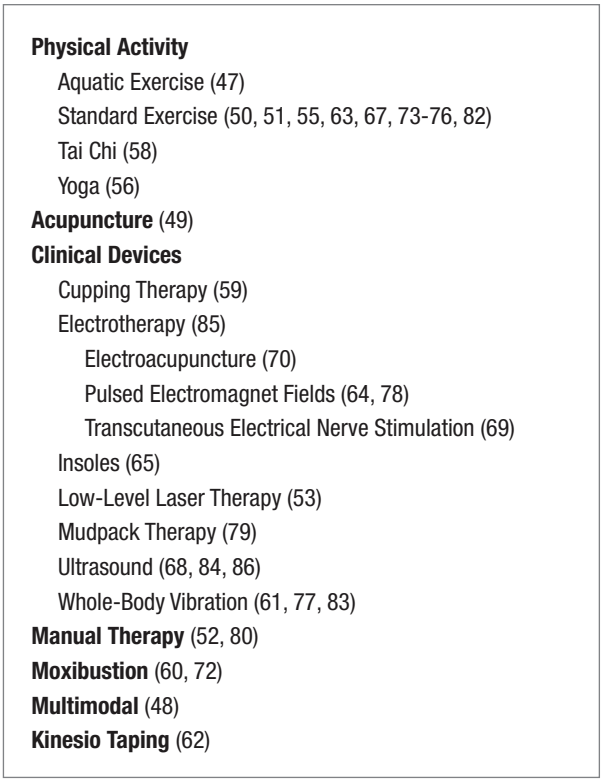

FIGURE 2. The non-pharmacological and non-surgical interventions (n=35)

age, sex, BMI, radiographic status or baseline. This could be explained by the initial neuromuscular response in an attempt to adapt to that specific exercise, usually followed by muscular hypertrophy. Also, the general feeling of well-being, reduced pain and greater ability to perform tasks could be due to the gait control mechanisms or to the central release of endorphins. Definitive conclusion on the best exercise program could not be achieved, because of the lack of differences among several exercise interventions and the small number of included studies. Nevertheless, the studies' evidence pointed out more frequently that, among all, low-intensity isokinetic (concentric-eccentric) muscular strengthening exercises (with special focus in the knee extensor muscles), done 3 or more times/week, with at least 12 supervised sessions, could lead to faster and long lasting results. Aquatic Exercise, Tai Chi and Yoga, despite showing some impact on the knee OA patients' life, cannot be fully recommended because the evidence gathered was of moderate-quality data and from one systematic review from each method of treatment. Therefore, for the treatments mentioned before there is the need to have more evidence (especially of high-quality).

ACUPUNCTURE

From the Cao et al.[49] systematic review and based on its high-quality evidence, pain and function can improve with needle Acupuncture in patients with knee OA. However, his recommendation cannot be fully achieved because the RCTs analyzed in the systematic review used different acupuncture points and different protocols for treating these patients. Yet, generally the best results were achieved following acupuncture points based on the Traditional Chinese Medicine meridian theory to treat the knee joint, known as the "Bi" syndrome. These points consisted of 4 local points (Yanglinquan [gall bladder 34], Yinlinquan [spleen 9], Zhusanli [stomach 36], Dubi [stomach 35]) and 4 distal points (Kunlun [urinary– bladder 60], Xuanzhong [gall bladder 39], Sanyinjiao [spleen 6], and Taixi [kidney 3]), done at least 2 times/week, 2 h/session. Yet, apart from being an invasive treatment and the lack of standardization showed, it is imprudent to recommend its use based on just one systematic review. Consequently, it is necessary to develop further high quality systematic reviews that assess this intervention.

CLINICAL DEVICES

Cupping Therapy, Electrotherapy, Insoles, Low-Level Laser Therapy, Mudpack Therapy, Ultrasound and Whole-Body Vibration were the different interventions approached in the included systematic reviews.

The Cupping Therapy was only investigated in one study[59]. Although improvements in pain and physical function on patients with knee OA were found, namely using a protocol of 10-20 min/session, 3-5 times/ /week, this was only supported by weak-quality evidence. Thus, to recommend its use, further research (of high-quality) is needed to cease any uncertainty that this intervention raised.

Electrotherapy was explored in 5 systematic reviews[64,69,70,78,85]. Shim et al.[70] studied the effects of Electroacupuncture in patients with knee OA and saw improvements in pain and quality of life from moderate-quality evidence. However, the Electroacupuncture protocols used in the RCTs varied and comparing with sham Electroacupuncture the results were less significant. Hence, despite the good results in patients with knee OA, its recommendation has to be carefully taken, because they were reached mainly in moderate-quality RCTs, and they were less significant

when comparing with sham Electroacupuncture. Also this intervention is invasive, leading to need to redouble care. So, further investigation on this intervention is needed to increase the quality of RCTs and try to build a standard protocol of treatment. Another paper[69] studied the effectiveness of Transcutaneous Nerve Stimulation in knee OA individuals and it could not be confirmed that this intervention is beneficial in pain reduction. This conclusion has been reached because only small trials of questionable-quality were included. As this was an A (R-AMSTAR – 40) conducted-quality systematic review, we agree on the authors' conclusions and cannot confirm their fully recommendations. Zeng et al.[85] not only reached the same conclusion regarding the use of Transcutaneous Nerve Stimulation, but also found similar results in the use of Neuromuscular Electrical Stimulation, Noninvasive Interactive Neurostimulation and Pulsed Electromagnetic Fields. The only Electrotherapy that this systematic review group fully recommended, due to the high-quality RCTs support, is the Interferential Current, where the greatest significant differences comparing with the control group were found. From all Interferential Current protocols, the most promising were those that used 100Hz during 20 min, for 3-5 sessions/week, through 4 weeks. However, Negm et al.[64] and We et al.[78] did not agree with the previous author's results regarding the utilization of Pulsed Electomagnetic Fields. Negm et al.[64] found, from low to very-low quality RCTs, positive results on knee OA patient's physical function but not on pain. Alternatively, We et al.[78] confirms from high-quality RCTs, not only the increase in the patients' physical function but also in pain. Therefore, the use of Pulsed Electromagnetic Fields in this population is still uncertain though, tendentially, this intervention has shown to be a useful therapy (especially using a frequency of 5-12Hz for 30 min, during at least 3 weeks) based on the most recent high quality systematic reviews and larger RCTs.

Regarding the use of Insoles, it has only been studied by Parkes et al.[65]. Although the overview of all studies showed a statistically significant difference between the use of Lateral Wedges and decreased pain in medial knee OA, when comparing these insoles with neutral insoles no statistical significant or clinically important association were established. Thus, with these B (R-AMSTAR – 34) quality findings, the use of Lateral Wedges for these patients cannot be supported. Similarly, Low-Level Laser Therapy was only studied by one group[53] wich reached the conclusion, by analyzing high-quality RCTs, that this therapy did not improve pain or function in patients with knee OA. Therefore, following this B (R-AMSTAR – 32) quality conducted systematic review, the use of this therapy cannot be recommended. Simillary, only Xiang et al.[79] studied the impact of Mudpack Therapy in patients with knee OA and did not find statistical significant differences between the several experimental and control groups in the functional and pain outcomes. So, it does not exist sufficient support to recommend the use of Mudpack Therapy in this population.

The effectiveness of Ultrasound in patients with knee OA was evaluated in 3 systematic reviews[68,84,86]. Apparently, the continuous and, even more, the pulsed Ultrasound modes (especially the 1MHz, 2.5 W/cm2, 15 min/session, 3 session/week, during 8 weeks protocol) can be effective in the patients' pain and physical function. The raised hypothesis for this positive results is the chondrocyte proliferation and matrix production in human articular cartilage. However, these findings are only supported by moderate to low quality RCTs. So, due to the quality of the RCTs, some prudence is still necessary to recommend its utilization in patients with knee OA. The performance of new high-quality RCTs is also waranted, in order to support the use of ultrasound in these patients.

Finally, the Whole-Body Vibration therapy was explored by Li et al.[61], Wang et al.[77] and Zafar et al.[83], that obtained very disperse results. Whole-body vibration exercises are a strength type exercises that uses vibrations generated by a vibrating plataform, in order to stimulate muscles and tendons, by the contac of the human body with the vibrating surfaces[61,83]. Li et al.[61] saw that Whole-Body Vibration was not different comparing with other forms of exercises in pain, strength and self-reported status. Curiously, when added to squat exercise (namely 20 min session consisting in 6 to 9 reps per session of non-weight bearing squat, 3 sec of isometric at 60° knee flexion and 3 sec of isometric flexion at 10°; plus the vibration plate with frequency of 35 to 40Hz, 20 to 70 s, amplitude of 4 mm, and acceleration that ranged from 2.78 to 3.26G – 3 times per week) it was more efficacious when compared with squat exercises alone, implying that this machine/exercise can be a good complement to more usual and well established exercises. Although Zafar et al.[83] also reached the conclusion that this exercise can be beneficial to the patients' pain and function, Wang et al.[77] only observed positive effects in function, but not in pain, raising more questions than answers regarding

this recent and not well known topic. Thus, besides being safe (only requires the person to be over the vibrating plate) and a good supplement to exercise (especially, in increasing function), there is still some uncertainty about the true influence of this machine on the patients with knee OA.

Overall, as explored above, there is some uncertainty about the effect of clinical devices. It seems that the best clinical devices used to manage knee OA patients are Electroacupuncture, Interferential Current, Pulsed Electromagnetic Fields, Ultrasound and Whole-Body Vibration. On the other hand, Transcutaneous Nerve Stimulation, Neuromuscular Electrical Stimulation, Noninvasive Interactive Neurostimulation, Insoles, Low-Level Laser Therapy and Mudpack Therapy either did not show sufficient efficacy, or did not gather enough high-quality RCTs support, or even did not reach homogeneous results and cannot be recommended.

MANUAL THERAPY

From the available systematic reviews[52,80] based on moderate-quality evidence, Manual Therapy can be recommended to treat patients with knee OA, because it can improve the pain, stiffness and physical function. But, once again, the protocols used and the interventions varied a lot: Swedish Massage, usual Mobilization, Maitland, Acupressure, Tui Na, Shi Manipulation, usual Manipulation and Myofascial Mobilization. This could be due to the experience of the treatment provider and the individual clinical presentation, where usually the intervener tries to adapt his treatment (type of intervention, dosage, force, amplitude, rate, repetition and duration) according to the patient's case and severity. Nevertheless, the intervention that has shown more consistent positive results was Massage (one of the most widely used intervention in this type of population). Yet, since most measure instruments are self-reported and subjective, sometimes a single touch on the patient may induce him or her to report better results. Therefore, a placebo effect cannot be ruled out. Consequently, although Manual Therapy is a safe and economic way to treat patients with knee OA, more high-quality RCTs and a better exploration of their methods are needed, in an attempt to bring up more standard protocols and improve its recommendation.

MOXIBUSTION

Moxibustion treatments were analyzed in two systematic reviews[60, 72]. Both showed that the Moxibustion intervention was superior to control and sham Moxibustion in quality of life, pain and physical function. The mechanisms that can explain this positive effects might be the generated heat and the stimulation of some specific acupoints that: 1) acts through the local system neural network and releases some neurotransmission, such as opioidergics, β-endorphins, and adenosine triphosphate; 2) modulates the inflammatory reactions through the degranulation of local mastocytes and activation of thermoreceptors; 3) this enhanced activation of the thermoreceptors could also lead to a decrease of the nociceptive painful transmission. The acupoints that were more commonly used and that obtained positive results more often were similar to those used in the acupuncture interventions, such as the gall bladder 34, spleen 9 and 10, stomach 34, 35 and 36, and the 2, 4 and 5 extra lower extremity points, done at least 3 times/week, 15-20 min/session. With the moderate to high-quality evidence gathered in these systematic reviews, it seems that Moxibustion can be a relatively safe intervention (only skin flushing was observed, however it disappeared within 3 days) and a viable alternative to usual care on the knee OA patients' health management.

KINESIO TAPING

A recent systematic review, conducted by Li et al.[62] evaluated the effects of the elastic therapeutic bandages in patients with knee OA. In this systematic review, based in moderate-quality data, it was found improvements in pain, flexibility, proprioception and knee-related health status. However, identical results were achived in strength between the experimental and the control group were found. The included RCTs had different experimental protocols, such as the type of cut (I-strip, Y-strip or the combination of several strips), direction (center extremities or extremities center), patient preparation (some placed the knee in full flexion, others the knee in semi-flexion; some paid attention to the presence of sweat and hair removing, others did not) and tension (from 10 to 75%) of the Kinesio Tape. However, the results obtained were, in general, similar. This may indicate that it is not the application that counts, but rather the effect that the Kinesio Tape can induce in patients. Since Kinesio Tape fibers are manufactured with a wave-like pattern, convolutions will appear after the recoil, creating more space between the tissues and providing a tactile input through the skin, stimulating type 2 cutaneous mechanoreceptors. This may result in an improved fluid exchange, muscle function re-education and pain reduction. Although

to recommend its use, some precautions are needed because this conclusion is based on just one study with medium-quality RCTs. Therefore, more information needs to be gathered for recommending its use.

MULTIMODAL

Usually, physiotherapy interventions are multimodal, where a great variety of interventions, especially non-surgical and non-pharmacological are used. Bjordal et al.[48] analyzed the effectiveness of different treatments in knee OA patients. In this systematic review, Bjordal and his group reached the conclusion that the best treatments to these patients are the Transcutaneous Electrical Nerve Stimulation, Electroacupuncture and Low-Level Laser Therapy. On the other hand, Manual Acupuncture, Pulsed Electromagnetic Field and Static Magnets did not show significant statistical differences compared to the control groups. Conversely, these conclusions were only supported by this umbrella review in the Electroacunpuncture intervention. Regarding the Transcutaneous Nerve Stimulation, Low-Level Laser Therapy and Pulsed Electromagnetic Field, the results we found were exactly the opposite, maybe due to the higher among of information gathered with this type of study.

CONCLUSION

In conclusion, based on the included systematic reviews, there is good evidence that Standard Exercise programs can reduce pain and improve physical function in patients with knee OA. Additionally, there is moderate evidence that Acupuncture, Aquatic Exercise, Electroacupuncture, Interferential Current, Kinesio Taping, Manual Therapy, Moxibustion, Pulsed Electromagnetic Fields, Tai Chi, Ultrasound, Yoga and Whole-Body Vibration (more as a complement of exercise than a single intervention) are effective in the respective evaluated outcomes. For other interventions, the quality of evidence is low or does not show sufficient efficacy from the systematic reviews to support its use. Furthermore, comparing to Jamtvedt et al.[32] umbrella review, we confirmed the worthy use of Acupuncture and Exercise but, according to our selected systematic reviews, we found different results regarding the use Transcutaneous Electrical Nerve Stimulation and Low-Level Laser Therapy to reduce the patients' pain and improve physical function. Additionally, there is an urgent need to develop new high-quality RCTs and systematic reviews to satisfy the raised uncertainties.

The study had the limitation of only accepted RCTs in English. If the search had be done in other languages, more studies (possibility of high quality) and more interventions probability could have been included, helping in overview of the study aim.

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SUPPLEMENTARY FILE TABLE IV. SYSTEMATIC REVIEWS SUMMARIES (N=35)

Interventions	Authors (A to Z; year)	Objectives	N° of inclued RCTs (subjects)	Results/Conclusions
Activities (physical)				
Aquatic Exercise	Bartels et al. (47)	To evaluate the effects of aquatic exercise for people with knee or hip OA, or both, compared to no intervention.	13 (n=1190)	Based upon moderate quality evidence, aquatic exercise has beneficial effects on knee OA people. A small but clinically relevant decrease in pain and disability, and small but clinically relevant increase in QOL. There is a small short-term effect on the knee OA people at the end of an aquatic training program. The long-term effect is unclear due to the paucity of studies.
Standard Exercise	Tanaka et al. (73)	To investigate the differences in the efficacies between strengthening and aerobic exercises for pain relief in knee OA patients.	8 (n=466)	Moderate-evidence show that muscle strengthening exercises with or without weight-bearing and aerobic exercises are effective for pain relief in knee OA people. In particular, for pain relief by short-term exercise intervention, the most effective exercise is non-weight–bearing strengthening exercise.
	Uthman et al. (76)	To determine if exercise interventions are more effective than no exercise control and to compare the effectiveness of different exercise interventions in relieving pain and improving function in lower limb OA patients.	60 (n=8218)	Significant benefits of exercise over no exercise in OA patients were showed. An approach combining exercises to increase strength, flexibility and aerobic capacity is likely to be most effective in the management of lower limb OA.
	Juhl et al. (55)	To identify the optimal exercise program, characterized by type and intensity of exercise, length of program, duration of individual supervised sessions, and number of sessions per week, for reducing pain and patient-reported disability in knee OA.	48 (n=4028)	All exercise (aerobic, resistance, performance and mixed) types are beneficial in reducing pain in knee OA patients. Therefore, optimal exercise programs for knee OA should focus on improving aerobic capacity, quadriceps muscle strength and lower extremity performance. For best results, the program should be supervised and carried out 3 x per week.

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TABLE IV. CONTINUATION

Interventions	Authors (A to Z; year)	Objectives	N° of inclued RCTs (subjects)	Results/Conclusions
	Tanaka et al. (74)	To investigate the influence of land-based exercise frequency and duration on pain relief for knee OA people.	17 (n=1816)	Although the effect size did not increase over the time, continuous strengthening exercise or aerobic exercise intervention (especially ≥4x per week) had a significant effect on knee pain of knee OA people after 9 weeks.
	Zacharias et al. (82)	To analyze the effect of exercise-based rehabilitation programs for improving lower limb muscle strength in hip or knee OA individuals.	40 (n=3989)	Both exercises (high and low-intensity) interventions at short-term follow-up are beneficial for strength outcomes in knee OA patients in comparison to a control program. However high-intensity resistance exercise showed low to moderate levels of quality of evidence for greater and more sustained benefits.
	Fransen et al. (51)	To determine whether land-based therapeutic exercise is beneficial for knee OA people in terms of reduced joint pain or improved physical function and QOL.	54 (n=6345)	High-quality evidence indicates that land-based therapeutic exercise provides short-term benefit that is sustained for at least 2 to 6 months after cessation of formal treatment in terms of reduced knee pain and moderate-quality evidence shows improvement in physical function and QOL among knee OA people.
	Regnaux et al. (67)	To determine the benefits and harms of high versus low-intensity physical activity or exercise programs in hip or knee OA people.	6 (n=656)	It was found very low-quality to low-quality evidence for no important clinical benefit of high-intensity compared to low-intensity exercise programs in improving pain and physical function in the short term.
	Tanaka et al. (75)	To examine the effects of exercise therapy on the health-related QOL of knee OA people.	12 (n=1239)	Regardless of its type, high to moderate-quality showed that exercise therapy can improve health-related QOL in knee OA patients.
	Coudeyre et al. (50)	To assess the rehabilitation framework of isokinetic muscle strengthening for knee OA.	9 (n=696)	Moderate-evidence shows that isokinetic muscle strengthening is an effective way to propose dynamic muscle strengthening for knee OA rehabilitation and has a significant effect on pain and disability.
	Li et al. (63)	To analyze the effectiveness of resistance exercise in the treatment of knee OA on pain, stiffness, and physical function.	17 (n=1705)	High-quality evidence shows that both high intensity and low intensity resistance exercise are beneficial in terms of reducing pain, alleviating stiffness and improving physical function in knee OA patients. However, a high intensity program showed to be more effective than a low intensity program.

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TABLE IV. CONTINUATION

Interventions	Authors (A to Z; year)	Objectives	N° of inclued RCTs (subjects)	Results/Conclusions
Tai Chi	Lauche et al. (58)	To analyze the effectiveness of Tai Chi for knee OA.	5 (n=252)	Moderate-evidence for short-term improvement of pain, physical function and stiffness in knee OA patients practicing Tai Chi.
Yoga	Kan et al. (56)	To assess the effects of yoga on pain, mobility and QOL in knee OA patients.	9 (n=372)	Moderate-evidence shows that yoga might have positive effects in relieving pain and mobility on knee OA patients, but the effects on QOL are unclear.
Acupuncture				
	Cao et al. (49)	To evaluate the efficacy of treatment with acupuncture for knee OA.	14 (n=3835)	Moderate to high-quality evidence shows that acupuncture provides a significantly better relief from knee OA pain and a larger improvement in function than sham acupuncture, standard care treatment, or waiting for further treatment.
Clinical Devices				
Cupping Therapy	Lee et al. (59)	To evaluate the available evidence from RCTs of cupping therapy for treating knee OA patients.	7 (n=661)	Only weak evidence can support the hypothesis that cupping therapy can effectively improve the treatment efficacy and physical function in knee OA patients.
Electrotherapy	Zeng et al. (85)	To investigate the efficacy of different electrical stimulation therapies in pain relief knee OA patients.	27 (n=1249)	IFC seems to be the most promising pain relief treatment for the management of knee OA. Although the recommendation level of the other electrical stimulations therapies is either uncertain (high-frequency TENS) or not appropriate (low- frequency TENS, NMES, PES and NIN) for pain relief, it is likely that none of the interventions is dangerous.
Electroacupuncture				
	Shim et al. (70)	To verify the effects of electroacupuncture treatment on knee OA	31 (n=3187)	Moderate to low-quality evidence shows that electroacupuncture treatment can more significantly improve pain and QOL of knee OA patients than control interventions. However, comparing with sham electroacupuncture, the difference in pain was less significant.

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TABLE IV. CONTINUATION

Interventions	Authors (A to Z; year)	Objectives	N° of inclued RCTs (subjects)	Results/Conclusions
PEMF	Negm et al. (64)	To determine if low frequency pulsed subsensory threshold electrical stimulation produced either through PEMF or PES vs sham PEMF/PES intervention is effective in improving pain and physical function at treatment completion in knee OA adults blinded to treatment.	7 (n=459)	Current evidence of low and very low-quality suggests that low frequency (≤100 Hz) pulsed subsensory threshold electrical stimulation produced either through PEMF/PES vs sham PEMF/PES is effective in improving physical function but not pain intensity at treatment completion in adults with knee OA blinded to treatment.
	We et al. (78)	To determine the efficacy of PEMF compared with a placebo in knee OA patients.	14 (n=482)	High-quality evidence supports PEMF efficacy in the management of knee OA pain and function.
TENS	Rutjes et al. (69)	To compare TENS with sham or no specific intervention in terms of effects on pain and withdrawals due to adverse events in knee OA patients.	18 (n=813)	It could not be confirmed that TENS is effective for pain relief. The systematic review is inconclusive, hampered by the inclusion of only small trials of questionable quality.
Insoles	Parkes et al. (65)	To evaluate whether lateral wedge insoles reduce pain in medial knee OA patients compared with an appropriate control.	12 (n=885)	Although meta-analytic pooling of all studies showed a statistically significant association between use of lateral wedges and lower pain in medial knee OA, restriction of studies to those using a neutral insole comparator did not show a significant or clinically important association. These findings do not support the use of lateral wedges for this indication.
LLLT	Huang et al. (53)	To investigate the efficacy of LLLT treatment of knee OA.	9 (n=518)	The best available current evidence does not show neither early nor later benefits in reducing pain or improving function, not supporting the use of LLLT as a therapy for knee OA patients.
Mudpack Therapy	Xiang et al. (79)	To evaluate the clinical efficacy of mudpack therapy for the knee OA treatment and identify the likely factors associated with the high heterogeneity of combined studies.	10 (n=1010)	Functional and pain improvements in knee OA patients treated with mudpack therapy was not significantly different from the control subjects at the end of the 4- months follow-up.
US	Rutjes et al. (68)	To compare therapeutic US with sham or no specific intervention in terms of effects on pain and function safety outcomes in knee or hip OA patients.	5 (n=341)	Therapeutic US may be beneficial for patients with OA of the knee. Because of the low quality of the evidence, there is uncertainty about the magnitude of the effects on pain relief and function.

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TABLE IV. CONTINUATION

Interventions	Authors (A to Z; year)	Objectives	N° of inclued RCTs (subjects)	Results/Conclusions
	Zeng et al. (84)	To investigate the efficacy of continuous and pulsed US in the management of knee OA.	12 (n=814)	Moderate-quality shows that pulsed US has a greater probability of being the preferred mode, as it is more effective in both pain relief and function improvement when compared with the control group. However, continuous US could only be considered as a pain relief treatment in the management of knee OA.
	Zhang et al. (86)	To explore the effects of therapeutic US with sham or no intervention on pain, physical function and safety outcomes in knee OA patients.	10 (n=645)	Both continuous and pulsed therapeutic US modes can be beneficial for reducing knee pain and improving physical functions in knee OA patients, however it has small significant differences.
WBV	Li et al. (61)	To assess the effects of WBV exercise on knee OA patients.	5 (n=168)	No differences were found in decreasing pain intensity or improving self-reported status, in addition to muscle strength enhancement compared with other forms of exercise. However, WBV combined with squat exercise was more efficacious than squat exercise alone in increasing the level of functional performance.
	Wang et al. (77)	To assess the effects of WBV for pain, stiffness and physical functions in knee OA patients.	5 (n=170)	Eight-week and 12-week WBV are beneficial for improving physical functions in knee OA patients, but not in reducing pain.
	Zafar et al. (83)	To examine the current evidence regarding the effects of WBV in knee OA individuals.	5 (n=165)	WBV has demonstrated limited but beneficial therapeutic effects in knee OA individuals in pain and function.
Manual Therapy				
	French et al. (52)	To determine if manual therapy improves pain and/or physical function in hip or knee OA people.	4 (n=280)	There is silver level evidence that manual therapy has a beneficial effect compared with exercise therapy, both in the short and long-term for pain reduction and increased physical function. But manual therapy, in the form of massage therapy, is effective compared to no intervention in knee OA.
	Xu et al. (80)	To evaluate the effectiveness and adverse events of manual therapy compared to other treatments for relieving pain, stiffness and physical dysfunction in knee OA patients.	14 (n=841)	Moderate-quality evidence shows that manual therapy might be an effective and safe treatment for improving pain, stiffness and physical function in knee OA patients.

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TABLE IV. CONTINUATION

Interventions	Authors (A to Z; year)	Objectives	N° of inclued RCTs (subjects)	Results/Conclusions
Moxibustion				
	Li et al. (60)	To determine whether the administration of moxibustion is an effective treatment for knee OA.	4 (n=746)	Limited evidence shows that moxibustion treatment has small significant differences comparing to control on managing the symptoms and improving the QOL among the selected knee OA patients.
	Song et al. (72)	To critically reassess the effects of moxibustion on knee OA	13 (n=1309)	Moxibustion treatment is superior to usual care and sham moxibustion in pain, QOL and physical function. But the effects of moxibustion on target population are nearly equal to oral drug and intra-articular injection, however with less secondary effects.
Multimodal				
	Bjordal et al. (48)	To access the efficacy of common non-pharmacological interventions for knee OA.	36 (n=2434)	TENS, electroacupuncture and LLLT administered with optimal doses in an intensive 2–4 weeks treatment regimen seem to offer clinically relevant short-term pain relief for knee OA. Manual acupuncture, PEMF, US and static magnets did not show sufficient clinical significant evidence to recommend their use.
Kinesio Taping				
	Li et al. (62)	To assess the effects of elastic taping on knee OA patients.	11 (n=168)	Significant improvements were found in self-reported pain during activity, knee flexibility, knee-related health status and proprioceptive sensibility compared with other forms of treatments. However, no differences were found between the Kinesio Taping group and control group for knee muscle strength.

Abbreviations: IFC (InterFerential Current); LLLT (Low-Level Laser Therapy); NIN (Noninvasive Interactive Neurostimulation); NMES (NeuroMuscular Electrical Stimulation); OA (Osteoarthritis); PEMF (Pulsed Electromagnetic Fields); PES (Pulsed Electrical Stimulation); QOL (Quality of Life); TENS (Transcutaneous Electrical Nerve Stimulation); US (Ultrasound); WBV (Whole Body Vibration).