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SPECIAL ARTICLE

Overview of Cochrane Systematic Reviews of rehabilitation interventions for persons with rheumatoid arthritis: a mapping synthesis

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ABSTRACT

The aim of this paper was to provide an overview of Cochrane Systematic Reviews (CSRs), which synthesizes the quality and quantity of available evidence on the effectiveness of rehabilitation interventions in rheumatoid arthritis (RA). The World Health Organization (WHO) requested Cochrane Rehabilitation the CSRs search to develop the Package of Interventions in Rehabilitation (PIR). We searched the Cochrane Library using the terms "rheumatoid arthritis" and "rehabilitation." We screened the CSRs according to the search strategy based on the methodology developed for the WHO PIR. The search period for the data provided to WHO was between 1 September 2009 and 2019. We updated the search to 1 September 2022 for this paper. We summarized the CSRs identified after the screening process using an evidence map, grouping outcomes, and comparisons of included CSRs indicating the effect and the quality of evidence to provide a comprehensive view of current knowledge. We identified 10 CSRs, including 92 primary studies with 10,801 participants and 23 comparisons. They explored the effectiveness and/or safety of either non-pharmacological or pharmacological (for symptom control only) interventions. Outcomes were pain, muscle strength, grip/pinch strength, tender joints, swollen joints, fatigue, disease activity, radiological damage, physical function, hand function, participant adherence, clinical improvement, withdrawals, and adverse events. Our mapping synthesis indicates that physical activity and exercises in RA are effective non-pharmacological interventions for some outcomes, such as hand function, muscle strength and fatigue, without any deterioration of pain, disease activity and radiological involvement. Psychosocial interventions show a small beneficial effect on fatigue. Regarding pharmacological agents, celecoxib presents similar analgesic effects with traditional NSAIDs but fewer gastric adverse events. Current evidence supports physical activity and exercise programs for individuals with RA. However, well-designed studies will help document the exact effects of these programs on different outcomes and physiological mechanisms in RA. There were inconclusive results for some of the interventions due to low and very-low quality of evidence. Furthermore, due to the lack of CSRs on therapeutic patient education, orthoses, physical modalities and assistive devices in the search period, it was impossible to synthesise the evidence on those interventions.

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KEY WORDS: Arthritis, rheumatoid; Rehabilitation; Methods.

The World Health Organization (WHO) defined rehabilitation as a set of measures that assist individuals who experience or are likely to experience disability, to achieve and maintain optimum functioning in interaction with their environments.[1] Rehabilitation is an essential health service for people with various health conditions. However, there is an unmet global need for delivering rehabilitation services, particularly in low- and middle-income countries.[2]

In 2017, the World Health Organization (WHO) launched "Rehabilitation 2030: A Call for Action" to improve and strengthen rehabilitation worldwide.[3] As part of this call, the WHO Rehabilitation Programme started to develop its Package of Interventions for Rehabilitation (PIR) to support ministries of health in integrating rehabilitation services into health systems.[4] The development of the PIR includes a stepwise approach where the second step is referred to as "Best Evidence for Rehabilitation". It requires identifying high-quality evidence regarding the effectiveness of interventions for rehabilitation for several health conditions. One of the health conditions included in the PIR is rheumatoid arthritis (RA).

RA is a chronic inflammatory autoimmune systemic disease that usually presents with joint inflammation leading to pain, fatigue, and impaired physical functioning and work productivity, all of which negatively impact health-related quality of life.[5, 6] Epidemiological studies performed in Western countries show that the prevalence of RA is 0.5-1.0% in white individuals. However, there are regional and racial differences, so that the prevalence may reach up to 5-6% in Native American populations.[5] Women are 2-3 times more likely to be affected than men. The disease can occur at any age, with the peak incidence in the sixth decade.[7] Several risk factors are known to be involved in the development of RA, including genetics, female sex, and environmental factors.[5, 8] It is also reported that patients with RA have a 1.5 times higher risk of mortality than the general population.[8]

The current treatment strategy for RA comprises a treat-to-target approach based on tight monitoring of disease activity to achieve remission or low disease activity with appropriate pharmacological therapy.[5, 9] At the same time, all considerations to reduce the impact of RA and its comorbidities on the individual should be a priority for all health professionals of the multidisciplinary team taking part in managing persons with RA.[10, 11] Aggressive and early use of biological and non-biological disease-modifying antirheumatic drugs have been associated with substantial gains in clinical, radiological and disability outcomes in the last two or three decades. Nevertheless, about 20% to 25% of the patients do not reach low disease activity,[7] and a considerable proportion of patients still report significant problems of physical, emotional and social functioning and unmet needs.[6] Therefore, rehabilitation interventions are also administered in RA, aiming to reduce the impact of disease on the individual and enhance daily functioning.[10, 12] Rehabilitation interventions in RA imply mainly non-pharmacological therapy (excluding surgery) and include therapeutic patient education, exercises, physical modalities, orthoses, assistive devices, balneotherapy and dietary interventions.[12]

Systematic reviews (SR) and meta-analyses of randomized controlled trials represent the most robust form of design in the hierarchy of research evidence.[13] With their methodological rigor and quality, Cochrane Systematic Reviews (CSRs) consider evidence on the effects of health or social care interventions and answer essential questions relevant to decision-making.[14, 15] The evidence gathered from CSRs is the strongest available and was therefore considered by the WHO as highly relevant for PIR development. Cochrane Rehabilitation has been charged with finding this evidence. This paper aims to provide an overview of CSRs, synthesizing the quality and quantity of available evidence on the effectiveness of rehabilitation interventions in RA, supplemented by a specific evidence-mapping methodology.[16]

Materials and methods

The WHO Rehabilitation Program introduced and published, in collaboration with Cochrane Rehabilitation, the methodology to develop the WHO PIR with the guidance of the WHO's guideline review committee.[4] We performed an overview of the CSRs relevant to developing the WHO PIR for RA, summarizing and quantifying high-quality research on the effectiveness of rehabilitation interventions in persons with RA. We report the overview following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA 2020 statement).[17] We registered the protocol on Open Science Framework Registries (https://doi.org/10.17605/OSF.IO/26TQN).

Search strategy

We based the search strategy on the methodology developed by the WHO and Cochrane Rehabilitation for WHO PIR.[4, 18] Cochrane Rehabilitation team led the search for CSRs using the already described tagging process.[19] The CSRs relevant to rehabilitation are constantly updated in an online database (https://rehabilitation.cochrane.org/evidence). The search strings included the terms defining the health condition of the present study, "rheumatoid arthritis" and "rehabilitation", and was run in the Cochrane Library. We selected the CSRs relevant to rehabilitation for persons with RA using the following criteria: interventions provided or prescribed by rehabilitation professionals.[19] We also considered for inclusion pharmacological agents that could be used in

the rehabilitation process to control symptoms (such as pain or fatigue) that affect overall functioning. We excluded pharmacological agents that aim to cure or prevent the deterioration of RA, such as disease-modifying anti-rheumatic drugs or corticosteroids. As the keyword "rehabilitation" was not sufficient to search all the CSRs relevant to the inclusion criteria, we also used the keywords "non-pharmacological" and "treatment". According to the described methodology,[4, 18] we limited the searches to the last ten years (01 September 2009 – 01 September 2019). We delivered these data to WHO to develop the PIR, and we updated the search for this paper on 01 September 2022.

Evaluation of methodological quality of included systematic reviews

We evaluated the methodological quality of the included CSRs using the 16-item AMSTAR 2, a critical appraisal tool for systematic reviews that include randomised or non-randomized studies of healthcare interventions or both.[20] The AMSTAR 2 is not designed to generate an 'overall score'; a high score may disguise critical weaknesses in 7 specific items.[21] We followed a process of 'considered judgement' firstly to interpret weaknesses detected by these critical items and then to reach a consensus on the methodological quality of the included reviews. Two independent evaluators applied AMSTAR 2 to all included CSRs, with any disagreements resolved through discussion with a third evaluator (BKT, AAK, and CA).

Data extraction and quality of evidence appraisal

Starting from the 'Table of Findings' in each identified CSR, we extracted the data on each reported outcome related to the intervention(s). These data included: number of primary studies, type of population, number of participants, type of outcome, outcome measure(s), intervention(s) and control intervention(s), effect (in favor of intervention or control or no effect), and the quality of evidence for each comparison and outcome.

We extracted the quality of evidence for each comparison and outcome using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) rating system as reported in each CSR; where authors did not report the GRADE ratings, two members of the Cochrane Rehabilitation team independently judged the quality of evidence for the primary outcomes, using the standard GRADE approach.[21, 22] We resolved disagreements through consensus involving a third member. This post-hoc GRADE judgement included retrieving the original primary studies within each CSR and tabulating the quality of evidence presented in the Summary of Findings tables using GRADEPro software. We did not update the searches or evidence in the original CSR during this process. We present in this paper only GRADE judgments for the reported primary outcomes.

Presentation of the data within an evidence map

We present the results on both effects and adverse events (where reported) of interventions using an evidence map, which is a specific methodology used to identify the literature within a research field to provide a comprehensive overview of what is known.[16] We used an Excel sheet to map the evidence, grouping the outcomes and interventions presenting the effect (in favor of intervention, in favor of control, no effect) and the quality of evidence (very low, low, moderate, and high). We did not present in the evidence map tables comparisons with not estimable results for the effects.

Results

The authors identified ten tagged CSRs related to rehabilitation interventions in RA, fulfilling the inclusion criteria. All CSRs included adult participants with RA. Five CSRs reported on non-pharmacological interventions[23-27] and the others on pharmacological agents administered for symptom control.[28-32] These 10 CSRs, included in this mapping synthesis, consist of 92 primary studies with 10,801 participants and 23 comparisons that explored the effectiveness and/or safety of either non-pharmacological or pharmacological (for symptom control only) interventions. The outcomes are pain, muscle strength, hand impairment (grip/pinch strength), tender joints, swollen joints, fatigue, disease activity, radiological damage, physical function, hand function, participant adherence, clinical improvement, withdrawals, and adverse events. All the CSRs reported the quality of evidence using the GRADE approach. We present the characteristics of the CSRs in Supplementary Digital Material 1, Supplementary Table I.[23-32]

AMSTAR 2 evaluation revealed that 5 CSRs published between 2013 and 2019 were of high quality, whereas 5 CSRs published between 2009 and 2012 were of moderate quality (Supplementary Digital Material 2, Supplementary Table II).[23-32] Item 15 was not applicable for 9 of the CSRs due to insufficient studies to analyze publication bias. In addition, 6 studies did not report the sources of funding.

Evidence for the effects of non-pharmacological interventions

We present the evidence map on the effects of non-pharmacological interventions for RA in Table I.

High quality evidence

One comparison showed that hand exercises, compared to no exercise, had little or no effect on grip and pinch strength of both hands in the medium (3 to 11 months) and the long (12 months and beyond) term.[24] Another comparison provided no effects at 24 months on muscle strength, disease activity, and radiological damage of long-term (2-years) land-based aerobic capacity and muscle strength training over other forms of exercise or no exercise regarding.[27]

Moderate quality evidence

One comparison indicated that hand exercises improved hand function in the medium (3 to 11 months) and the long (12 months and beyond) term compared to the no-exercise group.[24] Patient adherence in the medium term was also better in the hand exercise group compared with the routine care group.[24] Short-term (12-weeks) land-based aerobic capacity and muscle strength training positively affected muscle strength at 12 weeks.[27] Additional radon in carbon dioxide baths was superior to carbon dioxide baths only on pain intensity at the 6-month follow-up.[25] Physical activity interventions improved fatigue more effectively than control (placebo, an alternative intervention, or usual care) at the end of the intervention period.[26]

There were also results with no effects of interventions over comparators. For example, hand exercises were not superior to the no-exercise group in terms of pain intensity in the medium (3 to 11 months) and long (12 months and beyond) term, as well as patient adherence in the long term.[24] Short-term land-based aerobic capacity and muscle strength training showed no effects on pain intensity and physical function compared to other forms of exercise or

TABLE I.—*Evidence map on the effects of non-pharmacological interventions in rheumatoid arthritis.*

Treatment	Tai Chi	Hand Exercise	Short-Term Land-Based Aerobic Capacity and Muscle Strength Training	Short-Term Land-Based Aerobic Capacity Training	Short-Term Water-Based Aerobic Capacity Training	Long-Term Land-Based Aerobic Capacity and Muscle Strength Training	Balneotherapy: Mineral-rich mud compresses
Comparison	No Tai Chi	No exercise	Other form of exercise or no exercise				Placebo
Pain intensity (8 weeks)							
Pain intensity (<3 months)		VL *					
Pain intensity (12 weeks)	VL *		M ***	M ***	M ***		VL ***
Improvement in pain (12 weeks)							
Pain intensity (≥3 months)		M ***					
Pain intensity (6 months)							
Improvement in pain (6 months)							
Pain intensity (24 months)						L ***	
Muscle (Grip) strength (11 weeks)					L ***		
Muscle strength (12 weeks)			M *	L ***			
Muscle strength (24 months)						H ***	
Hand impairment (<3 months)		VL *					
Hand impairment (≥3 months)		H ***					
Tender joints (3 months)							VL *
Tender joints (8 weeks)							
Swollen joints (3 months)							VL ***
Swollen joints (8 weeks)							
Fatigue							
Disease activity (12 weeks)	VL ***						
Disease activity (24 months)						H ***	
Improvement, global (8 weeks)							
Clinical improvement (3 months)							VL ***
Radiological damage (24 months)						H ***	
Physical function (12 weeks)	VL *		M ***	L ***			
Hand function (≥3 months)		M *					
Participant adherence (3-11 months)		M *					
Participant adherence (≥12months)		M ***					

*favor intervention; **favor comparison; ***no effect.
Quality of evidence: H: high; M: moderate, L: low; VL: very low.

no exercise at 12 weeks.[27] Short-term (8-12 weeks) land-based and short-term (10-12 weeks) water-based aerobic capacity training also showed no effects over control on pain intensity at 12 weeks.[27] Additional radon in carbon dioxide baths did not provide extra benefit on pain intensity at 12 weeks compared with carbon dioxide baths.[25] Finally, the effects of the Mediterranean diet on fatigue were not superior to the control group.[26]

Low quality evidence

Additional radon in carbon dioxide baths had positive effects over carbon dioxide baths in pain improvement at six months.[25] Psychosocial interventions improved fatigue more effectively than control at the end of the intervention period.[26]

Short-term land-based aerobic capacity training showed no effects over the control group regarding muscle strength and physical function at 12 weeks.[27] Similarly, short-term water-based aerobic capacity training versus control indicated no effects on grip strength. Another comparison from the same CSR provided no effects of long-term land-based aerobic capacity and muscle strength training over other forms of exercise or no exercise regarding pain intensity at 24 months.[27] Additional radon in carbon dioxide baths had no effects over carbon dioxide baths in pain improvement at 12 weeks.[25]

Finally, four non-pharmacological interventions, herbal Andrographis Paniculata, omega-3 fatty acids, data tracker and reflexology, had no positive effects on fatigue compared with the control group.[26]

Very-low quality evidence

Very low-quality evidence suggested that 8 to 12 weeks of Tai Chi intervention had inconclusive clinical effects compared with no/alternate therapy, such that effects on pain intensity and physical function at 12 weeks slightly favored Tai Chi. In contrast, effects on disease activity were similar in both groups.[23] Due to very low-quality evi-

Balneotherapy: Mineral baths	Balneotherapy: Additional Radon in Carbon Dioxide Baths	Physical Activity Intervention	Psychosocial Interventions	Mediterranean Diet	Andrographis Paniculate	Omega-3 Fatty Acid	Data Tracker	Reflexology
Cyclosporin-A	Carbon Dioxide Baths only	Placebo, an alternative intervention, or usual care						
VL ***								
	M ***							
	L ***							
	M *							
	L *							
VL **								
VL ***								
		M *	L *	M ***	L ***	L ***	L ***	L ***
VL *								

dence, there was uncertainty about whether hand exercises versus no exercise improved pain intensity and grip/pinch strength in the short term (<3 months). However, analysis results slightly favored the intervention.[24] Compared with a placebo at three months, mineral-rich mud compresses for rheumatoid hand slightly favored intervention regarding tender joint count. In contrast, no effects were provided in terms of pain, swollen joint count and clinical improvement.[25] Another comparison of mineral baths versus Cyclosporin-A, evaluated at eight weeks, provided no effects on pain and swollen joints, whereas some benefit on global improvement in favor of intervention, and some benefit on a tender joint count in favor of comparator.[25]

Evidence for the effects of pharmacological interventions on symptom control

We present the evidence map on the effects of pharmacological interventions for symptom control in Table II.

Moderate quality evidence

One comparison indicated that celecoxib is more effective on pain intensity (at 12 weeks) and clinical improvement by ACR20 (4-12 weeks) than placebo. However, when compared with traditional NSAIDs, celecoxib had no effects on pain intensity (6-24 weeks) and clinical improvement by ACR20 (12-24 weeks).[28]

Low quality evidence

Two comparisons, nefopam versus placebo and topical capsaicin versus placebo, indicated the positive effects of both interventions on pain intensity at two weeks.[30] One comparison showed that opioids were superior to placebo regarding the patient-reported global impression of change.[32]

One comparison indicated that muscle relaxants (diazepam) had no effect over the comparator on pain intensity in the short-term (<24 hours).[29] Similarly, topical capsaicin versus placebo was not effective on pain at four weeks.[30] Compared to placebo or traditional NSAIDs, Celecoxib provided no positive effects on physical function at 6-12 weeks.[28] Similarly, two other comparisons, tricyclic antidepressants versus placebo at 4-12 weeks[31] and opioids versus placebo at 1-2 weeks, showed no effects in terms of physical function.[32]

Very-low quality evidence

Two comparisons with very low-quality evidence suggested inconclusive results presenting no effects on pain intensity: 1) tricyclic antidepressants over placebo at less than one week,[31] 2) muscle relaxants over comparator at 1-2 weeks.[29]

Evidence for the adverse effects of rehabilitation interventions

All CSRs on pharmacological interventions reported the outcome adverse events. Regarding non-pharmacological interventions, only one study in one CSR (hand exercises) evaluated adverse events. However, no adverse events due to hand exercises were reported.[24] We present the evidence map on adverse effects in Table III.

TABLE II.—*Evidence map on the effects of pharmacological interventions for symptom control in rheumatoid arthritis.*

Treatment	Celecoxib	Celecoxib	Nefopam	Capsaicin	Muscle relaxants	Tricyclic antidepressants	Opioids
Comparison	Traditional NSAIDs		Placebo		Placebo, other pharmacological treatment		Placebo or other treatment plus placebo
Pain intensity (24 hours)					L ***		
Pain intensity (<1 week)						VL ***	
Pain intensity (1-2 weeks)					VL ***		
Pain intensity (2 weeks)			L *	L *			
Pain intensity (4 weeks)				L ***			
Pain intensity (12 weeks)		M *					
Pain intensity (6-24 weeks)	M ***						
PGIC							L *
Clinical improvement (4-12 weeks)		M *					
Clinical improvement (12-24 weeks)	M ***						
Physical function (1-2 weeks)							L ***
Physical function (6-12 weeks)	L ***						
Physical function (12 weeks)		L ***				L ***	

*favor intervention; **favor comparison; ***no effect.
NSAID: non-steroidal anti-inflammatory drug; PGIC: patient reported global impression of clinical change.

TABLE III.—*Evidence map on adverse effects of pharmacological interventions for symptom control in rheumatoid arthritis.*

Treatment	Celecoxib	Celecoxib	Nefopam	Muscle Relaxant	Tricyclic antidepressant	Opioids
Comparison	Traditional NSAIDs	Placebo		Placebo, other pharmacological treatment		Placebo or other treatment plus placebo
Withdrawal due to adverse events (2 weeks)				VL ***		
Withdrawal due to adverse events (4 weeks)			M ***			
Withdrawal due to adverse events (1-6 weeks)						L ***
Number of withdrawals due to adverse events (0-12 weeks)					VL ***	
Incidence of gastroduodenal ulcers (12 weeks)		L ***				
Incidence of gastroduodenal ulcers (12-24 weeks)	M *					
Short term serious adverse events (12 weeks)		L ***				
Short term serious adverse events (6-24 weeks)	L ***					
Central nervous system adverse events (1-2 weeks)				VL **		
Cardiovascular events (6 weeks)	L ***					
Total number of adverse events (single dose studies) (24 hours)				VL ***		
Total number of adverse events (only studies >24 hours duration) (2 weeks)				VL **		
Total adverse events (4 weeks)			L **			
Participants reporting adverse events (1-6 weeks)						L **
Total number of adverse events (0-12 weeks)					VL **	

*favor intervention; **favor comparison; ***no effect.
NSAID: non-steroidal anti-inflammatory drug.

Moderate quality evidence

One comparison indicated that gastroduodenal ulcers were significantly lower in celecoxib compared with traditional NSAIDs at 12-24 weeks.[28] Another comparison revealed no effects of nefopam versus placebo regarding withdrawal due to adverse events at four weeks.[30]

Low quality evidence

One comparison revealed that celecoxib versus traditional NSAIDs was not different regarding short-term serious adverse events and cardiovascular events. Another comparison of celecoxib versus placebo showed similar effects in the incidence of gastroduodenal ulcers and short-term adverse severe events at 12 weeks.[28] Withdrawal due to adverse events at 1-6 weeks did not differ significantly for opioids versus the comparator.[32]

Very-low quality evidence

One comparison, investigating the effects of muscle relaxants (diazepam, zopiclone) versus placebo, revealed that there were significantly more adverse events (studies>24-hour duration) and CNS events (1-2 weeks) in the intervention group. Withdrawal due to adverse events at two weeks and the total number of adverse events at 24 hours did not differ significantly, although the trend favored the comparator.[29] Another comparison, evaluating the effects of tricyclic antidepressants over placebo, indicated that the total number of adverse events was significantly higher in the intervention group; however, the number of withdrawals due to adverse events did not differ significantly between the two groups.[31]

Among the studies, four withdrawals not related to adverse events were also reported (Supplementary Table I). The first one was in Tai Chi exercise *versus* no Tai Chi comparison, favoring intervention with a low quality of evidence. The second one reported the comparison of celecoxib versus placebo, favoring celecoxib (low-quality evidence). Thirdly, moderate-quality evidence revealed fewer withdrawals for celecoxib than traditional NSAIDs. Finally, withdrawal due to inadequate analgesia was reported in opioids versus control comparison with no difference between the groups (low-quality evidence).

Discussion

This overview of CSRs summarizes the evidence on the effects of rehabilitation interventions in RA over a period of 13 years. We also included CSRs reporting on pharmacological agents used for symptom control (such as pain or fatigue) because those interventions can affect individuals' overall level of functioning.

Our mapping synthesis indicates that physical activity and exercises are effective non-pharmacological interven-

tions for some outcomes of individuals with RA. Hand exercises have been beneficial on hand function; contrarily, the evidence on the effect on grip/pinch strength and pain compared to no exercise is inconclusive in the short term (<3 months), and there is little or no effect after three months.[24] It is also of note that no adverse events due to hand exercises have been observed. Two earlier SRs on hand exercises support our results: the first one concluded that hand exercises might positively affect grip strength and some aspects of daily functioning without aggravating disease activity or pain, although there should be caution for subjects in the exacerbation period.[33] The second one evaluated the effects of home hand exercise programs. It reported that resistance exercises, with or without range of motion exercises, improved hand function, pain, and grip strength in the short term. In contrast, in the long term (6-12 months), benefits were less consistent but still were found in hand and upper limb function and pinch strength.[34]

Our synthesis shows the positive effects of 12-week dynamic exercises (land-based aerobic capacity and muscle strength training) on muscle strength after the intervention. The impact on muscle strength and physical function of other forms of dynamic exercises, either short-term land-based or water-based aerobic training or long-term aerobic and resistance training, have been similar to control. Another important finding is that those dynamic exercises have not deteriorated pain, disease activity and radiological involvement.[27] The effects of dynamic exercises, including aerobic and/or resistive training, have been investigated in other meta-analyses. Baillet *et al.* reported that cardiorespiratory aerobic conditioning in stable RA appeared to be safe in terms of disease activity, radiological damage, and pain; it also improved quality of life, physical function, and pain, although the degree of effect was small.[35] Resistance exercises were also safe regarding disease activity and pain and improved muscle strength and walking performance.[36, 37] Another result is that physical activity interventions, including pool-based therapy, yoga, dynamic strength training, stationary cycling, low-impact aerobics and Tai Chi, show superior effects on fatigue compared to a placebo, an alternative intervention, or usual care.[26] Another meta-analysis supported this evidence and reported the beneficial effects of aerobic land-based exercises on fatigue.[38] Our synthesis includes a recent CSR on Tai Chi exercises, where its efficacy on pain, function and disease activity was inconclusive due to very low evidence.[23]

The efficacy and safety of physical activity and exercise programs in RA have been consistently demonstrated.[39] However, there might be some variability among the studies regarding the effects on different outcomes due to probably heterogeneity of both the therapy programs (content, duration, intensity, frequency, setting) as well as the characteristics of the patients (age, clinic activity, functional status, comorbidity).[33, 35-38] Individuals with RA must be encouraged to do regular physical activity and exercise programs, not only to improve RA-related outcomes but due to the increased risk of comorbidities such as cardiovascular disease, rheumatoid cachexia and osteoporosis. Further research is needed to implement and maintain these programs in daily practice. In addition, well-designed studies will help document the effects of physical activity and exercises on different outcomes and physiological mechanisms in RA.[39]

Fatigue is one of the major symptoms of RA, and the OMERACT (Outcome Measures in Rheumatology) proposed it as an addition to the "core set" of outcome measures to be assessed in people with RA.[40] In this mapping synthesis, low evidence indicates the positive effects of psychosocial interventions (benefit finding, expressive writing, cognitive behavioral therapy, mindfulness, lifestyle management, energy conservation, self-management, and group education) on fatigue.[26] Psychosocial interventions which aim to improve coping and to decrease stress, anxiety and depression, focusing on stress management, relaxation and social functioning, are part of the therapeutic patient education in RA.[12] Other SRs have also reported the benefits of psychosocial interventions on pain, fatigue and coping.[41, 42] Another part of therapeutic patient education consists of educational interventions; aiming to make the patient competent in the daily management of the disease, including basic knowledge, self-management, physical activity, pain control/ management, joint protection, daily activities and work. Although no CSRs have evaluated the effectiveness of joint protection strategies in RA throughout the search period of this mapping synthesis, other SRs have pointed out its effectiveness on pain and physical function.[42-44]

Balneotherapy may be offered as an adjunct to rehabilitation interventions. However, evidence for the effectiveness of balneotherapy in RA is scarce.[12] In this mapping synthesis, 3-4 weeks of therapy with additional radon in carbon dioxide baths seems superior to carbon dioxide on pain at a 6-month follow-up but shows similar effects immediately after the therapy and at a 3-month follow-up. The authors of this CSR pointed out the clinical irrelevancy of this finding.[25] The benefits of radon baths on pain have been reported in some other rheumatic diseases;[45] however, it requires further investigation in RA.

It is important to note that no CSRs in this recent 13-year period investigated the effects of other non-pharmacological rehabilitation interventions like orthoses and footwear, physical modalities, dietary interventions (only evaluated for impact on fatigue) and assistive devices. The existing CSRs on physical modalities in RA (thermotherapy, electrical stimulation, therapeutic ultrasound, low-level laser therapy) were published before 2009.[12] They require an update or new search as there is a lack of other recent SRs or meta-analyses investigating the evidence on the effects of physical modalities in this patient group. The current situation regarding the evidence on orthoses is much clear. The benefits of wrist-hand orthoses, foot orthoses, and therapeutic shoes were investigated in other SRs or meta-analyses.[46-49]

Regarding the pharmacological agents administered for symptom control in RA, our mapping synthesis indicates with moderate quality of evidence that celecoxib is better than placebo, whereas not different compared to traditional NSAIDs on pain and clinical improvement. However, gastroduodenal adverse events and withdrawals have been significantly less in celecoxib than in traditional NSAIDs.[28] Thus celecoxib, a selective cox-2 inhibitor, can be prescribed safely for pain due to fewer gastrointestinal adverse events; however, more studies are needed to document its cardiovascular safety in individuals with RA. Our synthesis indicates weak evidence that neuromodulators, oral nefopam and topical capsaicin are superior to placebo in reducing pain in RA.[30] Due to adverse events observed in nefopam, capsaicin can be administered as an add-on therapy for patients with persistent local pain and inadequate response or intolerance to other analgesics. Regarding the effects of other analgesics in RA, the current synthesis shows inconclusive evidence for antidepressants and benzodiazepines and limited evidence for weak opioids.[29, 31, 32] Furthermore, significant adverse events reported for these drugs should be considered as individuals with RA take biological and/or non-biological disease-modifying anti-rheumatic drugs and other medications for their comorbidities. NICE has also indicated that the evidence on analgesics other than NSAIDs was too weak to support recommendations for or against their usage in RA and suggested further research on the effectiveness of non-NSAID analgesic drugs in controlling RA symptoms.[50]

Strengths and limitations of the study

This overview of CSRs in RA focuses on the best available evidence. The robustness and uniformity of the Cochrane methodology ensure the overview's consistency, as currently recommended by Cochrane.[14] Rating of GRADE judgements for all the included CSRs is another strength of this overview. In addition, evidence mapping emerges as a rigorous methodology for gathering and disseminating up-to-date information to end-users. In this case, the evidence map will be helpful for all stakeholders relevant to the rehabilitation of RA and hopefully promote research in the field where evidence gaps exist.[16]

One limitation of this paper arises from the search strategy, which allows only CSRs. We did not consider other high-quality SRs or meta-analyses because we had to follow the methodology of the WHO PIR.[4, 18] Thus, the evidence map constructed in this study might not have included all the current evidence and therefore did not allow us to precisely identify the evidence gaps in the field of rehabilitation interventions in RA. As mentioned above, major rehabilitation interventions such as therapeutic patient education, orthotic management or physical modalities have been lacking in our map. Another limitation might be using the search term "rheumatoid arthritis" and not including "inflammatory arthritis". We might have missed some CSRs possibly of interest for RA, as in the case of CSR, which reports on non-pharmacological interventions for preventing job loss in inflammatory arthritis.[51] Fortunately, this paper has not reported evidence specific to RA.

Conclusions

Current evidence supports physical activity and exercise programs for individuals with RA. However, well-designed studies will help document the exact effects of these programs on different outcomes and physiological mechanisms in RA. Low and very low-quality evidence for some interventions, such as balneotherapy, Tai Chi, some forms of exercise, and non-NSAID analgesics, precluded us from reaching firm conclusions. Furthermore, due to the lack of CSRs on therapeutic patient education, orthoses, physical modalities and assistive devices in the search period, it was impossible to synthesize the evidence on those rehabilitation interventions. Therefore, further research and/or update of meta-analyses of current knowledge is needed for some rehabilitation interventions in RA.

References

1. Ackerman P, Asindua S, Blouin M, Cameron D, Clode K, Cockburn L, *et al.* Chapter 4: Rehabilitation. World Health Organization (editor).

World Report on Disability. Geneva: World Health Organization; 2011. p. 95-134.

2. Cieza A, Causey K, Kamenov K, Hanson SW, Chatterji S, Vos T. Global estimates of the need for rehabilitation based on the Global Burden of Disease study 2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2021;396:2006–17.

3. Gimigliano F, Negrini S. The World Health Organization "Rehabilitation 2030: a call for action". Eur J Phys Rehabil Med 2017;53:155–68.

4. Rauch A, Negrini S, Cieza A. Toward strengthening rehabilitation in health systems: methods used to develop a WHO package of rehabilitation interventions. Arch Phys Med Rehabil 2019;100:2205–11.

5. Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, *et al.* Rheumatoid arthritis. Nat Rev Dis Primers 2018;4:18001.

6. Taylor PC, Moore A, Vasilescu R, Alvir J, Tarallo M. A structured literature review of the burden of illness and unmet needs in patients with rheumatoid arthritis: a current perspective. Rheumatol Int 2016;36:685–95.

7. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. JAMA 2018;320:1360–72.

8. Otón T, Carmona L. The epidemiology of established rheumatoid arthritis. Best Pract Res Clin Rheumatol 2019;33:101477.

9. Fraenkel L, Bathon JM, England BR, St Clair EW, Arayssi T, Carandang K, *et al.* 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken) 2021;73:924–39.

10. National Institute for Health and Care Excellence (NICE). Rheumatoid arthritis in adults: diagnosis and management. London: National Institute for Health and Care Excellence (NICE); 2018.

11. Horton SC, Walsh CA, Emery P. Established rheumatoid arthritis: rationale for best practice: physicians' perspective of how to realise tight control in clinical practice. Best Pract Res Clin Rheumatol 2011;25:509–21.

12. Küçükdeveci AA. Nonpharmacological treatment in established rheumatoid arthritis. Best Pract Res Clin Rheumatol 2019;33:101482.

13. Kisely S, Chang A, Crowe J, Galletly C, Jenkins P, Loi S, *et al.* Getting started in research: systematic reviews and meta-analyses. Australas Psychiatry 2015;23:16–21.

14. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, *et al.* Cochrane Handbook for Systematic Reviews of Interventions (2nd Edition). Chichester (UK): John Wiley & Sons; 2019.

15. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, *et al.* Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev 2019;10:ED000142.

16. Hetrick SE, Parker AG, Callahan P, Purcell R. Evidence mapping: illustrating an emerging methodology to improve evidence-based practice in youth mental health. J Eval Clin Pract 2010;16:1025–30.

17. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. J Clin Epidemiol 2021;134:178–89.

18. Negrini S, Arienti C, Patrini M, Kiekens C, Rauch A, Cieza A. Cochrane collaborates with the World Health Organization to establish a Package of Rehabilitation Interventions based on the best available evidence. Eur J Phys Rehabil Med 2021;57:478–80.

19. Levack WM, Rathore FA, Pollet J, Negrini S. One in 11 Cochrane Reviews are on rehabilitation interventions, according to pragmatic inclusion criteria developed by Cochrane Rehabilitation. Arch Phys Med Rehabil 2019;100:1492–8.

20. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, *et al.* AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008.

21. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, *et al.*; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.

22. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, *et al.* GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383–94.

23. Mudano AS, Tugwell P, Wells GA, Singh JA. Tai Chi for rheumatoid arthritis. Cochrane Database Syst Rev 2019;9:CD004849.

24. Williams MA, Srikesavan C, Heine PJ, Bruce J, Brosseau L, Hoxey-Thomas N, *et al.* Exercise for rheumatoid arthritis of the hand. Cochrane Database Syst Rev 2018;7:CD003832.

25. Verhagen AP, Bierma-Zeinstra SM, Boers M, Cardoso JR, Lambeck J, de Bie R, *et al.* Balneotherapy (or spa therapy) for rheumatoid arthritis. Cochrane Database Syst Rev 2015;2015:CD000518.

26. Cramp F, Hewlett S, Almeida C, Kirwan JR, Choy EH, Chalder T, *et al.* Non-pharmacological interventions for fatigue in rheumatoid arthritis. Cochrane Database Syst Rev 2013;(8):CD008322.

27. Hurkmans E, van der Giesen FJ, Vliet Vlieland TP, Schoones J, Van den Ende EC. Dynamic exercise programs (aerobic capacity and/or muscle strength training) in patients with rheumatoid arthritis. Cochrane Database Syst Rev 2009;2009:CD006853.

28. Fidahic M, Jelicic Kadic A, Radic M, Puljak L. Celecoxib for rheumatoid arthritis. Cochrane Database Syst Rev 2017;6:CD012095.

29. Richards BL, Whittle SL, Buchbinder R. Muscle relaxants for pain management in rheumatoid arthritis. Cochrane Database Syst Rev 2012;1:CD008922.

30. Richards BL, Whittle SL, Buchbinder R. Neuromodulators for pain management in rheumatoid arthritis. Cochrane Database Syst Rev 2012;1:CD008921.

31. Richards BL, Whittle SL, Buchbinder R. Antidepressants for pain management in rheumatoid arthritis. Cochrane Database Syst Rev 2011;(11):CD008920.

32. Whittle SL, Richards BL, Husni E, Buchbinder R. Opioid therapy for treating rheumatoid arthritis pain. Cochrane Database Syst Rev 2011;(11):CD003113.

33. Bergstra SA, Murgia A, Te Velde AF, Caljouw SR. A systematic review into the effectiveness of hand exercise therapy in the treatment of rheumatoid arthritis. Clin Rheumatol 2014;33:1539–48.

34. Hammond A, Prior Y. The effectiveness of home hand exercise programmes in rheumatoid arthritis: a systematic review. Br Med Bull 2016;119:49–62.

35. Baillet A, Zeboulon N, Gossec L, Combescure C, Bodin LA, Juvin R, *et al.* Efficacy of cardiorespiratory aerobic exercise in rheumatoid arthritis: meta-analysis of randomized controlled trials. Arthritis Care Res (Hoboken) 2010;62:984–92.

36. Baillet A, Vaillant M, Guinot M, Juvin R, Gaudin P. Efficacy of resistance exercises in rheumatoid arthritis: meta-analysis of randomized controlled trials. Rheumatology (Oxford) 2012;51:519–27.

37. Wen Z, Chai Y. Effectiveness of resistance exercises in the treatment of rheumatoid arthritis: A meta-analysis. Medicine (Baltimore) 2021;100:e25019.

38. Rongen-van Dartel SA, Repping-Wuts H, Flendrie M, Bleijenberg G, Metsios GS, van den Hout WB, *et al.* Effect of aerobic exercise training on fatigue in rheumatoid arthritis: a meta-analysis. Arthritis Care Res (Hoboken) 2015;67:1054–62.

39. Metsios GS, Kitas GD. Physical activity, exercise and rheumatoid arthritis: Effectiveness, mechanisms and implementation. Best Pract Res Clin Rheumatol 2018;32:669–82.

40. Kirwan JR, Minnock P, Adebajo A, Bresnihan B, Choy E, de Wit M, *et al.* Patient perspective: fatigue as a recommended patient centered outcome measure in rheumatoid arthritis. J Rheumatol 2007;34:1174–7.

41. Albano MG, Giraudet-Le Quintrec JS, Crozet C, d'Ivernois JF. Characteristics and development of therapeutic patient education in rheumatoid arthritis: analysis of the 2003-2008 literature. Joint Bone Spine 2010;77:405–10.

42. Carandang K, Pyatak EA, Vigen CL. Systematic review of educational interventions for rheumatoid arthritis. Am J Occup Ther 2016;70:p1, p12.

43. Siegel P, Tencza M, Apodaca B, Poole JL. Effectiveness of occupational therapy interventions for adults with rheumatoid arthritis: a systematic review. Am J Occup Ther 2017;71:p1, p11.

44. Bobos P, Nazari G, Szekeres M, Lalone EA, Ferreira L, MacDermid JC. The effectiveness of joint-protection programs on pain, hand function, and grip strength levels in patients with hand arthritis: A systematic review and meta-analysis. J Hand Ther 2019;32:194–211.

45. Annegret F, Thomas F. Long-term benefits of radon spa therapy in rheumatic diseases: results of the randomised, multi-centre IMuRa trial. Rheumatol Int 2013;33:2839–50.

46. Ramsey L, Winder RJ, McVeigh JG. The effectiveness of working wrist splints in adults with rheumatoid arthritis: a mixed methods systematic review. J Rehabil Med 2014;46:481–92.

47. Gijon-Nogueron G, Ramos-Petersen L, Ortega-Avila AB, Morales-Asencio JM, Garcia-Mayor S. Effectiveness of foot orthoses in patients with rheumatoid arthritis related to disability and pain: a systematic review and meta-analysis. Qual Life Res 2018;27:3059–69.

48. Tenten-Diepenmaat M, Dekker J, Heymans MW, Roorda LD, Vliet Vlieland TP, van der Leeden M. Systematic review on the comparative effectiveness of foot orthoses in patients with rheumatoid arthritis. J Foot Ankle Res 2019;12:32.

49. Tenten-Diepenmaat M, van der Leeden M, Vliet Vlieland TP, Roorda LD, Dekker J. The effectiveness of therapeutic shoes in patients with rheumatoid arthritis: a systematic review and meta-analysis. Rheumatol Int 2018;38:749–62.

50. National Guideline Centre (UK). Analgesics: Rheumatoid arthritis in adults: diagnosis and management: Evidence review G. London: National Institute for Health and Care Excellence (NICE); 2018.

51. Hoving JL, Lacaille D, Urquhart DM, Hannu TJ, Sluiter JK, Frings-Dresen MH. Non-pharmacological interventions for preventing job loss in workers with inflammatory arthritis. Cochrane Database Syst Rev 2014;(11):CD010208.

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