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General review

The effectiveness and safety of non-pharmacological intervention for pain management in Parkinson's disease: A systematic review

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ABSTRACT

Chronic pain is a non-motor symptom affecting from 60 to 80% of patients with Parkinson's disease (PD). PD patients can suffer from different types of pain, either specific or not specific of the disease, and depending on various pathophysiological mechanisms (nociceptive, nociplastic or neuropathic), which can be present at any stage of the disease. Non-pharmacological interventions (NPIs) are essential to complement routine care interventions in PD pain management. Moreover, in the literature, it has been shown that 42% of PD patients are already using complementary therapies. Hence, our aim was to investigate the effectiveness and safety of NPIs for pain management in PD. A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Eighteen published randomized control trials (RCTs) were included between 2004 and 2021 leading to a total of 976 PD patients. From them, we reported fifteen different NPIs classified in seven categories: physical exercises, balneotherapy, manual therapy, acupuncture, botanical preparation, body-psychological practice and multiprotection care. Our results have shown that NPIs for PD pain management had a low-to-moderate level of evidence showing mainly favourable results, even if some NPIs presented inconclusive results. Moreover, our review highlighted the clinical relevance of some specific NPIs in PD pain management: NPIs consisting of active physical activities, opposed to passive activities. The safety of NPIs was also confirmed since only few minor transient adverse events were reported. Nevertheless, even if some interesting results were found, the methodology of future studies needs to be more robust and to include comprehensive descriptions in order to offer reliable and sound recommendations to clinicians.

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1. Abbreviation

BWSTT	body weight support treadmill training
EA	electro-acupuncture
JLT	Jiawei Liujunzi Tang
LSVT	Lee Silverman voice treatment
MBI	mind-based intervention
MDT	multidisciplinary team care
MPQ	McGill pain questionnaire
NMSS	non-motor symptoms scale
NPI	non-pharmacological interventions
NPIS	Non-Pharmacological Intervention Society
NRS	numeric rating scale
NW	Nordic walking
PD	Parkinson disease
PDQ-39	Parkinson disease questionnaire 39 items
PICO	population intervention comparison and outcome
PRISMA	preferred reporting items for systematic reviews and meta-analyses
PT	physiotherapist
RCT	randomized controlled trials
RoB	risk of bias
RODI	revised Oswestry disability index
RTM	rest to music
SEM	standard error of the mean
TIDieR	template for intervention description and replication
TT	tactile touch
TTM	therapeutic Thai massage
VAS	visual analogue scale

2. Introduction

Q2 Parkinson's disease (PD) is a neurodegenerative disease characterised by degeneration of the nigrostriatal dopaminergic pathway responsible for motor symptoms (akinesia, resting tremor and rigidity) [1], as well as many non-motor symptoms including sensory disorders such as pain [2,3]. Indeed, chronic pain is experienced by 60 to 80% of PD patients [4]. These painful sensations can emerged from various pathophysiological mechanisms (nociceptive, nociplastic and neuropathic pain [5,6]), and can be present at any stage of the disease. Indeed, pain in PD may arise from numerous pathways such as both central and peripheral degeneration [7], as well as specific cortical plasticity and/or connectivity [8] or even anatomical changes in brain structures involved in nociceptive mechanisms [9]. Inherently, chronic pain is a multidimensional perception with a major biopsychosocial impact responsible for a decrease in patients' quality of life, professional activity and social ties [10].

There are different pain subtypes in PD patients and it has been proposed to classify pain in PD into nociceptive, neuropathic and nociplastic pain, either specific or unspecific to PD [5,6]. This classification is of importance since specific types of pain may respond differently to diverse treatments: for example, it is known that musculoskeletal PD pain can be alleviated by lévodopa [11], which is not true for every PD-related pain. A meta-analysis suggests that the increased prevalence and intensity of clinical pain complaints in PD may be, at least in part, influenced by abnormal nociceptive processing [12]. Functional imaging have shown an hyperactivation of the median pain pathway (affective pathway) in PD patients with chronic central pain compared to PD patients without pain during an acute pain stimulus, suggesting physiological mechanisms proper to PD chronic pain [13]. Several neurotransmitters such as dopamine, norepinephrine, serotonin, and opioids could participate in abnormal pain processing in PD [14].

Currently, the usual dopaminergic treatments to address PD symptoms are not effective enough for pain [15]. In addition, conventional analgesic approaches may not relieve PD pain [16]. For example, oxycodone (a strong-acting opioid analgesic) induced a significant pain reduction in PD patients at 4, 8 and 12 weeks compared to placebo, but this diminution did not reach significance at 16 weeks, while leading to some treatment-related side effects [17]. Hence, long-time effect of analgesic in PD may be insufficient. Hence, pain remains a major issue for the concerned patients [18]. In addition, despite deep brain stimulation of the subthalamic nuclei increasing heat pain threshold in PD patients with pain and therefore decreasing painful sensations [19] and some pharmacological clinical trials demonstrating an effect on pain in PD [20–24], most studies had shown insignificant or insufficient results. Therefore, the management of PD pain remains challenging and non-pharmacological interventions (NPIs) should be considered in the context of evidence-based treatments. Evidence-based NPIs are safe and effective components of holistic pain care, which may also be a strategy to reduce the analgesics consumption [25], especially since NPIs were defined as an essential add-on to routine care interventions in PD pain management [26,27]. Moreover, in the literature, it has been shown that 42% of PD patients were already using complementary therapies [28,29]. As a result, there is growing interest in complementary therapies among medical staff and a need for researchers to provide evidence of efficacy and safety.

Furthermore, NPIs have the ability to induce interdependent benefits: reducing pain, anxiety, depression, nausea, facilitating restful sleep, increasing well-being etc., as seen in fibromyalgia [30], which is a huge advantage compared to most pharmacological treatments. It also appears that, while medication-only treatment strategies may promote passive coping processes, the benefits of NPIs would emerge in part through a process of patient empowerment, active problem solving, realistic goal setting and a functional/rehabilitative perspective [31]. In addition, recent evidence has suggested that targeted NPIs, as well as some other non-motor symptom management options could have a significant beneficial effect on quality of life and should be considered in PD treatments [32].

Despite this growing interest in NPIs, evidence for the effectiveness of these practices in PD pain management is generally limited in randomised controlled trials (RCT) [33]. Implementation of positive trial findings is often slow because clinicians perceive the results as either limited, invalid, or irrelevant to their patients. Another barrier is clinicians' ability to suggest treatment based on the information provided in the

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published reports. Comprehensive descriptions of NPIs that allow their replication, as well as easily available information, would allow greater transferability of published research in clinical practice.

2.1. Aim

To investigate effectiveness and safety of NPIs in PD pain management, and to identify criteria for improvement in the scientific literature, using a systematic review.

3. Material and methods

3.1. Search strategy and information sources

This systematic review was conducted in accordance with the PRISMA statement [34]. First, the literature was screened on NPIs in PD pain to define our search terms. To identify the largest number of potentially eligible studies as possible, we determined the population intervention comparison and outcome (PICO) criteria as search terms, as described in the Cochrane handbook [35] (Table 1). The review was registered on PROSPERO in February 2022 (ID number: 309266).

In order to conduct a systematic review, we submitted our search terms in a broad panel of the database to consider the multimodal aspect of pain (biopsychosocial model). Between December 2021 and March 2022, the following databases were independently searched by two authors (M.H. and M.B.): PubMed, Cochrane, PEDro, Embase, Web of science, American Psychological Association (APA), Cairn, Pascal et Francis, Campbell Collaboration and LiSSa. This search strategy was supplemented by a manual search of reference lists of relevant included articles and reviews. Moreover, since non-invasive neuromodulation strategies are not always referenced as NPIs, we did a supplementary research in PubMed using the following keywords: ''pain'' and ''Parkinson'' and ''transcranial stimulation'', filtered for ''Randomized Controlled Trial'' and ''Adult: 19+ years''.

3.2. Eligibility criteria

Studies were included if they were clinical RCTs, with pain assessment as a primary or secondary outcome, on patients diagnosed with PD, treated with a NPI as defined by the Non-Pharmacological Intervention Society (NPIS) meaning ''non-pharmacological, targeted and non-invasive, evidence-based intervention on a person to prevent, care or cure'' [36]. Only studies published in English or French were included. No exclusion criteria were defined based on age or stage of disease but clinical trials with patients undergoing surgical treatment for PD (deep brain stimulation or pallidotomy) were excluded since there are considered as invasive interventions. The search results were then redefined using 'human studies' and '+18 adults' boundaries.

The only outcome we studied in this review was pain (chronic or not), thus we selected clinical trials, which assessed pain with measurement tools at any time point of the protocol. Studies using either specific [visual analogue scale (VAS)] or non-specific measurement tools in the assessment of pain [such as the Parkinson disease questionnaire 39 items (PDQ-39)] were included. All studies that mentioned pain without assessing it were excluded.

Table 1 – PICO Criteria.

Criteria	Search terms
Population	(Parkinson disease[MeSH Terms]) OR (Parkinson's disease[MeSH Terms]) OR (parkinson)
Intervention	(acupuncture[MeSH Terms]) OR (physiotherapy) OR (complementary therapy) OR (multidisciplinary care) OR (non-pharmacological) OR (integrative care) OR (exercise) OR (massage) OR (music)
Comparison	Clinical trials
Outcome	(chronic pain[MeSH Terms]) OR (pain) OR (pain management)

3.3. Study selection process

The steps of the selection process were depicted in the PRISMA diagram (Fig. 1), all steps were independently scrutinized by two authors (M.H. and M.B.). The results with identified search terms were collected from the databases described above, the first selection was made with the title of the articles, excluding articles with non-PD patients, articles about pharmacological or surgical interventions and duplicates, for the main screening as well as the non-invasive neuromodulation supplementary search. Then, the abstracts were screened to exclude those that did not correspond to our eligibility criteria. To ensure that all relevant articles on PD pain management by NPI were identified, the bibliography of each article was also screened for the detection of any supplementary related publications. Then we added the matching ones to our list of selected articles. Finally, we performed a last sorting by reading the whole set of articles to exclude the last doubts about their correspondence to our criteria. All disagreements were resolved by discussion to reach a consensus.

3.4. Data extraction

Data extraction was performed by the two authors (M.H., M.B.) who reviewed and selected all identified relevant articles, and is available on an adapted structured template in two tables: (i) author name and year of publication, name of the intervention, planning and description of intervention and control intervention, description of population, duration of the studies (Table 2); (ii) study design (blinded), type of pain assessment, functional state (ON or OFF states), the template for intervention description and replication (TIDieR) list completion, adverse events, and statistical results on pain outcomes (Table 3).

To compare the reproducibility of interventions, the TIDieR quality criterion was chosen [37]. The TIDieR list – as published by the CONSORT group [38] in 2010 – includes questions that focus on the precise and specific description of intervention elements. The list requests multiple information: a brief description of the intervention (No. 1), a theoretical rationale

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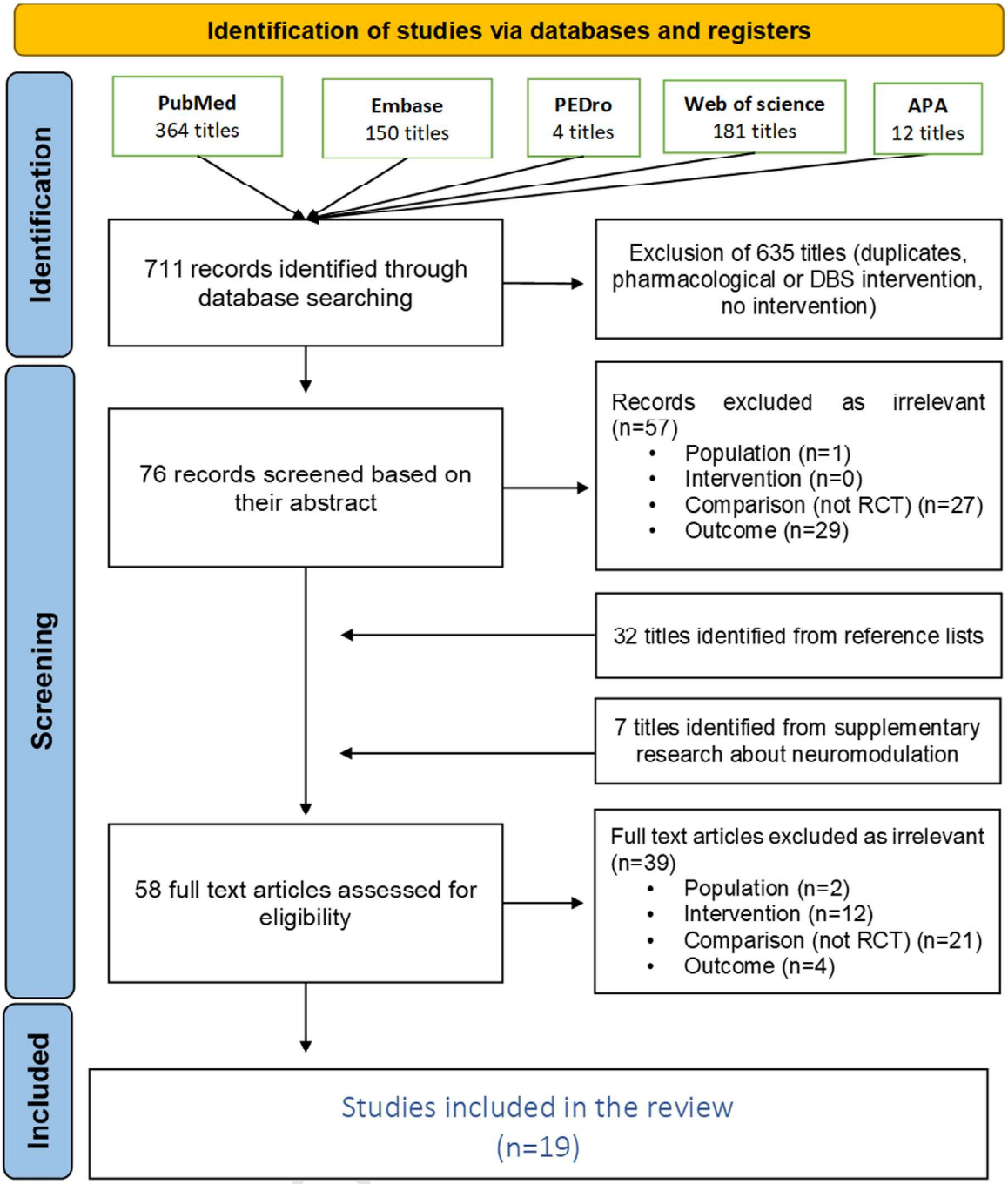

Fig. 1 – Flowchart of studies selections following PRISMA recommendations. PEDRO: Physiotherapy Evidence Database; APA: American Psychological Association. Some supplementary databases were used (Cochrane, Cairn, Pascal et Francis, Campbell Collaboration and LiSSa) but no titles were identified through their use, so there are not presented in the flowchart.

for the choice of the intervention (No. 2: why?), the equipment (No. 3) and procedure needed (No. 4), the person who provided the intervention (No. 5), the context i.e. whether the interventions are held in a group or individual session (No. 6: how), the place where it is held (No. 7), and finally the scheduling of the sessions (No. 8: when and how many).

Any missing data or unclear information were reported as such in the template.

3.5. *Data presentation*

We represented our results in two tables: Table 2 presents demographic information of the selected articles and the Table 3 displays information related to the NPI and their outcomes on PD pain management. After studies selection, interventions were categorised according to the NPIS classification (available on their website [36] and recently defined in

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Table 2 – Characteristics of studies.

Authors	Group[a]	Name of intervention	Active or passive intervention	Planning of intervention	Description of intervention	Sample size by group (*n*)	Age (year) mean ± SD; [Range]	H&Y mean ± SD; [Range]	Disease duration (year) mean ± SD; [Range]	Study duration (weeks)
Exercises										
Schaible et al., 2021	Intervention	Lee Silverman Voice Treatment (LSVT)-BIG training	Active	16 individual sessions of 60 min; 4 times a week for 4 weeks by a LSVT-BIG qualified physiotherapist (PT)	Standardized multidirectional whole-body movements performed with maximal amplitude of reaching and stepping	14	63.3 ± 8.5	2.0 ± 0.7	5.4 ± 2.6	4 (+ follow-up 4)
		Intensive physiotherapy with an individual training plan			Instructions were to work with at least 60% to 80% of their maximal effort, special focus was made on assessment of individual deficits, gait, falls, freezing of gait and dexterity	13	66.2 ± 8.7	1.7 ± 0.7	5.3 ± 3.4	
	Comparator (sham)	Regular physiotherapy		16 individual sessions of 60 min; 2 times a week for 8 weeks	–	12	65.5 ± 8.2	2.1 ± 0.4	5.4 ± 4.2	
Myers et al., 2020	Intervention	Vinyasa Yoga	Active	20 to 24 sessions in groups of 7 to 9 participants by two certified Yoga instructors; twice a week	Introduction with relaxation and guided meditation, gentle spinal movements, standing poses (Warrior I and II, Crescent Lunge, Downward Dog, and Tree), cool down, and rest and relaxation	13	70.5 ± 8.7	2 [2; 3]	–	12
	Comparator (control)	Usual daily routines		–	–	13	65.0 ± 8.7	2 [2; 3]	–	
Gandolfi et al., 2019	Intervention	Trunk-specific rehabilitation	Active	30 individual sessions of 60 min; 5 days a week for 4 weeks by PT	(1) Active self-correction exercises with visual feedback (i.e. mirror), with proprioceptive feedback (i.e. EMG feed-back), and without any feedback (2) Trunk stabilization exercises (3) Functional tasks were used as the element of "distraction" (i.e. dual-task exercises) that engaged the patient's attention and induced them to maintain unconsciousness of the self-correction and trunk stabilization and reduce functional impairment	19	72.4 ± 6.4	3 [1.5; 3]	8.01 ± 5.9	4 (+ follow-up 4)
	Comparator (another intervention)	Passive mobilisation		30 individual sessions of 60 min; 5 days a week for 4 weeks by PT.	Joint mobilization, muscle strengthening and stretching, overground gait training and balance exercises	18	70.7 ± 6.6	2 [1.4; 3]	6.6 ± 4.3	
Atan et al., 2019	Intervention	Body Weight Support Treadmill Training (BWSTT) with reduction of body weight of 20%	Active	30 individual sessions of 60 min; 5 days a week by PT	Half a session for rehabilitation and the other half for BWSTT	10	68.6 ± 8.2	2.6 ± 0.7	5.6 ± 5.3	6
		10% BWSTT				10	72.2 ± 7.9	2.8 ± 0.6	9.8 ± 9.0	
	Comparator (sham)	0% BWSTT (patients are on the treadmill)				10	69.7 ± 8.0	2.7 ± 0.7	7.6 ± 6.4	

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Table 2 (*Continued*)

Authors	Group[a]	Name of intervention	Active or passive intervention	Planning of intervention	Description of intervention	Sample size by group (*n*)	Age (year) mean ± SD; [Range]	H&Y mean ± SD; [Range]	Disease duration (year) mean ± SD; [Range]	Study duration (weeks)
Exercises										
Paolucci et al., 2017	Intervention	Meziere Rehabilitation	Active	10 sessions of 60 min; twice a week for 5 weeks by a PT trained for this technique	Three postures: (1) The patient was placed in the supine position; (2) The patient was placed in the supine position, with the upper limbs abducted to 120°; (3) The patient was placed in the supine position, with the lower extremities elevated at more than 90° of flexion of the hips and the knees extended or flexed, resting on a wall or supported by the PT, if the patient was unable to reach this position with the knees extended	17	66.0 ± 18.5	1.5 ± 0.8 for all the sample without statistically significant differences between the two groups	3 ± 1.2	5 (+ follow-up 8)
	Comparator (another intervention)	Home exercise		1 educational session of 60 min and a booklet of exercises to do: 10 sessions of 60 min of exercises (twice a week for 5 weeks) at home + Each patient was contacted by telephone every 2 weeks to monitor his/her adherence to the rehabilitation program	Each exercise was proposed for three sets of ten repetitions with a rest period of at least two minutes between sets. Exercises were getting more difficult through the weeks	17	67.0 ± 11.0			
Reuter et al., 2011	Intervention	Nordic Walking (NW)	Active	72 sessions of 70 min; three times a week for 24 weeks by NW instructors	One session per week was dedicated to practising NW technique, the other sessions focused on endurance training	30	62 ± 3.2	2.53 ± 0.5	64.1 ± 48.7	24
		Walking			The training session consisted of technique training, endurance training and a cooling down. One session per week included walking uphill to improve muscle strength	30	63 ± 3.1	2.5 ± 0.5	71.9 ± 50.6	
	Comparator (another intervention)	Flexibility and relaxation		72 sessions of 70 min; three times a week for 24 weeks by PT	The training focused on stretching, improving balance and range of movements. The flexibility and relaxation programme did not include aerobic exercises	30	62.1 ± 2.5	2.5 ± 0.5	62.3 ± 38.2	
Schmitz-Hübsch et al., 2006	Intervention	Qigong	Active	16 sessions of 60 min; once a week in two courses of 8 weeks with an 8-week pause in-between; by an experienced teacher	Three opening exercises, three exercises from the syllabus "Frolic of the crane," all eight exercises from the syllabus "The eight brocades (in sitting position)," and closing exercises	30	64 ± 8	–	6.0 ± 5.5	24 (+ follow-up 28)
	Comparator (control)	Usual care		–	–	19	63 ± 8	–	5.6 ± 3.8	

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Table 2 (*Continued*)

Authors	Group[a]	Name of intervention	Active or passive intervention	Planning of intervention	Description of intervention	Sample size by group (*n*)	Age (year) mean ± SD; [Range]	H&Y mean ± SD; [Range]	Disease duration (year) mean ± SD; [Range]	Study duration (weeks)
Exercises										
Balneotherapy										
Pérez-de la Cruz et al., 2017	Intervention	Ai Chi Aquatic physiotherapy	Active	20 group sessions of 45 min; twice a week for 10 weeks by PT expert on Ai Chi	The sessions were designed with a gradual increase in difficulty: warm up activity followed by 35 minutes dedicated to practicing the Ai Chi program at the end of the session there was a calming down activity	15	66.8 ± 5.3	2.8 ± 0.2	6.2 ± 2.5	10 (+ follow-up 4)
	Comparator (sham)	Dry physiotherapy		20 group sessions of 45 min twice a week for 10 weeks	Functional exercises based on activities of daily living, balance exercises, facial muscle exercises, proprioceptive exercises, muscle relaxation and stretching. During each session, emphasis was placed on training the trunk and lower limbs with the goal of improving the overall posture	15	67.5 ± 9.9	2.7 ± 1.0	6.7 ± 3.2	
Volpe et al., 2017	Intervention	Intensive physiotherapy in water	Active	40 sessions of 60 min; 5 days a week for 8 weeks by a trained PT	Warm up with relaxing exercises, exercises for postural realignment, cooling down and relaxation exercises	13	70.6 ± 7.8	2.6 ± 0.5	9 ± 7.0	8 (+ follow-up 8)
	Comparator (sham)	Physiotherapy			Exercises designed for postural deformities as much as possible similar to those used in the hydrotherapy programme	11	70 ± 7.8	2.7 ± 0.5	9.4 ± 7.5	
Pérez-de la Cruz et al., 2019	Intervention	Ai Chi Aquatic physiotherapy	Active	20 group sessions of 45 min twice a week by PT expert on Ai Chi	The sessions were designed with a gradual increase in difficulty: warm up activity followed by 35 minutes dedicated to practicing the Ai Chi program at the end of the session there was a calming down activity	15	64.4 ± 5.1	2.8 ± 0.2	7.1 ± 2.0	10 (+ follow-up 4)
	Comparator (sham)	Dry physiotherapy		20 group sessions of 45 min twice a week by a PT	Functional exercises based on activities of daily living, balance exercises, facial muscle exercises, proprioceptive exercises, muscle relaxation and stretching. During each session, emphasis was placed on training the trunk and lower limbs with the goal of improving the overall posture	15	65.8 ± 8.9	2.8 ± 1.0	7.7 ± 3.0	
Manual therapy										
Miyahara et al., 2018	Intervention	Therapeutic Thai Massage (TTM)	Passive	6 individual sessions of 30 min for 3 weeks by certified TTM practitioner	Kneading and pressing with moderate intensity, within patient's range of comfort, along six designated 'Sen' lines of the upper limbs (inner and outer arm)	30	66.4 ± 7.3	2.1 ± 0.3	8.5 ± 4.7	3
	Comparator (control)	Usual medical care		–	–	30	64.1 ± 10.8	2.3 ± 0.5	9.2 ± 7.8	

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Exercises										
Skogar et al., 2013	Intervention	Tactile Touch (TT) and music	Passive	10 individual interventions of 60 min; twice per week for 3 weeks and then once a week for 4 weeks. Interventions were made by licensed massage therapists	Tactile touch corresponded of stroking with intention, using soft and encompassing hands on the skin. The strokes were given with respect, empathy and sensitivity regarding the special needs of the individual. 1. Back of legs 2. The back 3. Back of the head The recipient turns over 4. Abdomen 5. Chest 6. Face, ears 7. Front of head 8. Right arm, then right hand 9. Left arm, then left hand 10. Left leg, then left foot 11. Right leg, then right foot	29	Male [50; 78] & Female [60; 79]	*Median [10th/90th percentile]*: Male 1.5 [1.0/2.5] & Female 2.5 [1.5/3.0]	–	7 (+ follow-up 26)
	Comparator (control)	Rest To Music (RTM)		10 interventions of 60 min	The music was identical for TT and RTM: "Music for well-being II – Letting go of stress", LC6607 Fönix Music®, Sweden. All patients were asked to indicate the most comfortable volume before the intervention	15–	Male [50; 74] & Female [50; 74]	*Median [10th/90th percentile]*: Male 3.0 [1.5/3.0] & Female 2.0 [1.0/4.0]	–	
Acupuncture										
Lei et al., 2016	Intervention	Electro-acupuncture (EA)	Passive	3 sessions of 30 min in 3 weeks by a physician who had more than 5 years of experience in acupuncture and was certified	All the EA points were stimulated at the same time with frequency of 100 Hz or 4 Hz. Eleven points were selected: Foot motor Sensory Area, Balance Area, GV 20, GV 14, LI4, GB34, BL40, SP6, KI3, LR3	10	69.8 ± 4.5	3.0 ± 1.0	6.2 ± 5.9	3
	Comparator (sham)	Sham EA		3 sessions of 30 min in 3 weeks by a physician who had more than 5 years of experience in acupuncture and was certified	The Sham EA was performed for the control group with insertion of needles less than 4 mm, just under the skin at non-acupuncture points The electric stimulation in sham EA was performed in a similar fashion to the real EA but with intensity equal to zero	5	71.0 ± 11.7	2.9 ± 0.7	5.2 ± 4.7	
Toosizadeh et al., 2015	Intervention	EA	Passive	3 sessions of 30 min in 3 weeks by a physician who had more than 5 years of experience in acupuncture and was certified	All the EA points were stimulated at the same time with frequency of 100 Hz or 4 Hz. Eleven points were selected: Foot motor Sensory Area, Balance Area, GV 20, GV 14, LI4, GB34, BL40, SP6, KI3, LR3	10	71.2 ± 6.3	–	3.0 ± 1.0	3
	Comparator (sham)	Sham EA		3 sessions of 30 min in 3 weeks by a physician who had more than 5 years of experience in acupuncture and was certified	The Sham EA was performed for the control group with insertion of needles less than 4 mm, just under the skin at non-acupuncture points The electric stimulation in sham EA was performed in a similar fashion to the real EA but with intensity equal to zero	5	74.6 ± 6.5	–	2.9 ± 0.7	

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Authors	Group[a]	Name of intervention	Active or passive intervention	Planning of intervention	Description of intervention	Sample size by group (*n*)	Age (year) mean ± SD; [Range]	H&Y mean ± SD; [Range]	Disease duration (year) mean ± SD; [Range]	Study duration (weeks)
Exercises										
Botanical preparation										
Chua et al., 2017	Intervention	Active herbal treatment Jiawei Liujunzi Tang (JLT)	Passive	2 doses per day, 11 g each time (a dosage equivalent to 55 g of herbs)	Patients were instructed to take the granules orally, at least two hours apart from taking any routine Western medication	45	63.5 ± 9.7	2.1 ± 0.6	6.4 ± 4.2	32 (+ follow-up 6)
	Comparator (sham)	Placebo pill			Composition of the placebo pill: caramel, gardenia yellow pigment, sunset yellow, permicol egg yellow, cocoa brown, citric acid, sodium cyclamate, dextrin, and broadleaf holly leaf; with the same instruction as the intervention group	46	63.3 ± 8.2	2.0 ± 0.6	5.4 ± 3.8	
Carroll et al., 2004	Intervention	Active cannador capsule	Passive	Medication was taken twice daily for 10 weeks. The dose of cannabis extract or placebo administered was based on body weight, with a maximum possible dose of 0.25 mg/kg of THC per day	Capsules of cannador, an ethanolic extract of Cannabis sativa standardized to 2.5 mg of 9-THC and 1.25 mg of cannabidiol per capsule	9	67 [51; 78]	3.0 [2.5; 4]	14 [4; 32]	10
	Comparator (sham)	Placebo pill		Medication was taken twice daily for 10 weeks	Synthetic oil vehicle	8				

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Table 2 (*Continued*)

Authors	Group[a]	Name of intervention	Active or passive intervention	Planning of intervention	Description of intervention	Sample size by group (*n*)	Age (year) mean ± SD; [Range]	H&Y mean ± SD; [Range]	Disease duration (year) mean ± SD; [Range]	Study duration (weeks)
Exercises										
Body-psychological practice										
Pickut et al., 2015	Intervention	Mind-Based Intervention	Active	8 sessions of 150 min meetings on 8 consecutive weeks without the one-time full-day session in the sixth week of practice by two experienced mindfulness teachers	Audio recordings containing 45 min guided mindfulness exercises (meditation, yoga, and the body scan) were given with instructions for daily home practice corresponding to the course sequence. Time spent in mindfulness practices, as reported by the participants, was recorded weekly for each participant	14	61.4 ± 11.3	2.1 ± 0.3	–	8
	Comparator (control)	Usual care		–	–	13	62.2 ± 6.6	2.2 ± 0.5	–	
Electromagnetic methods										
Li et al., 2020	Intervention	High-frequency repetitive Transcranial Magnetic Stimulation (HF rTMS)	Passive	5 consecutive daily sessions of 20 min	The investigators used a handheld 7-cm figure- 8 coil. The coil was centered over the scalp above the hand area of the M1 contralateral to where the participant reported feeling pain. If the patient reported bilateral or diffuse pain, then the coil was placed over the left M1. The coil was oriented at a 45° angle relative to the midsagittal plane The rTMS protocol involved applying a train of 100 rTMS pulses at 20 Hz once per minute for 20 min. Each train's intensity was set at 80% of the participant's resting motor threshold	24	61.7 ± 6.9	1.9 ± 0.6	5.5 ± 3.7	1 (+ follow-up 4)
	Comparator (sham)	Sham HF rTMS			The sham protocol was similar to the rTMS protocol, but the coil was oriented at a 90° angle relative to the midsagittal plane to partly reproduce the subjective sensations associated with rTMS while not inducing currents within the brain	24	61.5 ± 8.4	1.8 ± 0.6	6.5 ± 5.2	

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Table 2 (*Continued*)

Authors	Group[a]	Name of intervention	Active or passive intervention	Planning of intervention	Description of intervention	Sample size by group (*n*)	Age (year) mean ± SD; [Range]	H&Y mean ± SD; [Range]	Disease duration (year) mean ± SD; [Range]	Study duration (weeks)
Exercises										
Multi-professional care										
Gage et al., 2014	Intervention	Specialist rehabilitation intervention: Multidisciplinary Team care (MDT)	Active & passive	The rehabilitation intervention was coordinated by the Parkinson's nurse specialist, and involved specialist input from each professional, over a period of six weeks. The team met face-to-face four times in each six-week cycle to discuss patients' plans and progress, and communicated by email and telephone at other times. Two hospital consultants (neurologist and geriatrician), both with a special interest in movement disorders, could be called upon by the MDT for medication changes or advice	90	72.9 ± 8.6	2.4	–	6 (+ follow-up 30)	
		MDT + Ongoing support		About one hour per week per patient was allowed for ongoing support, and contact was through a mix of home visits and telephone, through which the care assistant monitored progress in implementation of the agreed care plan and reported back to the MDT	90	74.0 ± 8.2	2.4	–	24 (+ follow-up 12)	
	Comparator (control)	Usual care		No coordinated team care planning or ongoing support	90	71.6 ± 7.9	2.2	–	6 (+ follow-up 30)	

PT: physiotherapist; H&Y: Hoehn and Yahr; 'Sen' lines correspond to energy lines, in the traditional Thai massage.

[a] Groups are defined as the Intervention group or the Comparator group. For the comparator group, "control" corresponds to a comparison without any standard intervention or treatment (that is usual routine care); "sham" is defined as an intervention with the same time and type of interaction with the patient but without a supposed specific effect; and "another intervention" stands for another intervention modality (e.g. another medication, therapeutic education, physical activity program etc.).

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Table 3 – NPIs and management of pain.

Authors	Intervention	Blind	Evaluation of pain	Assessment in ON or OFF[a] state	TiDIER list completion	Adverse event (AE)	Results
Exercises							
Schaible et al., 2021	Lee Silverman Voice Treatment (LSVT)-BIG training Intensive physiotherapy with an individual training plan Regular physiotherapy	Open	Miscellany subscale of the Non-Motor Symptom Scale (NMSS)	ON	8/8	None	Only the INTENSIVE group had a significant different change in NMSS total compared to the Regular physiotherapy group ($P = 0.03$) and a significant amelioration of NMSS miscellany subscore ($P = 0.036$) after 8 weeks, but between groups changes were not significant ($P = 0.593$)
Myers et al., 2020	Vinyasa Yoga Usual daily routines	Open	Revised Oswestry Disability Index (RODI)	ON	7/8	–	No intergroup statistic. Decrease of pain only in the yoga group ($P = 0.03$)
Gandolfi et al., 2019	Trunk-specific rehabilitation Passive mobilisation	Single-blind (assessor)	Numeric Rating Scale (NRS)	ON	7/8	None	No significant differences between the two groups from T0[b] and T1 ($P = 0.87$) and from T0 and T2 ($P = 0.25$). Significant reduction of pain in both groups from T0 to T2 intervention group: $P = 0.001$; Control Group: $P < 0.001$
Atan et al., 2019	Body Weight Support Treadmill Training (BWSTT) with reduction of body weight of 20% 10% BWSTT 0% BWSTT	Double-blind (assessor & patients)	Nottingham Health Profile (NHP) Pain subscore	ON	8/8	Few adverse events such as muscle or joint pain	Decrease of pain only in the intervention groups (10% or 20% BWSTT) while pain increased in the control group ($P < 0.05$) with an intergroup effect ($P = 0.013$)
Paolucci et al., 2017	Meziere Rehabilitation Home exercise	Single-blind (assessor)	Visual Analog Scale (VAS)	ON	7/8	None	No significant intergroup differences ($P = 0.2$ at T1[c] and $P = 0.8$ at T2). Significant improvement of pain only in the intervention group ($P < 0.001$)
Reuter et al., 2011	Nordic Walking (NW) Walking Flexibility and relaxation	Single-blind (assessor)	VAS for several regions of the body	–	7/8	Cardiovascular side effects (hypotension and injuries, caused by fall or overuse)	Reduction of pain of the neck, the hip and the sacroiliac joint in all groups; while higher amelioration of pain in the back ($P < 0.001$), hands ($P < 0.001$) and legs ($P < 0.002$) for both Walking groups in comparison with control group. In the Nordic walking group up to 30% of patients became free of pain after the training
Schmitz-Hübsch et al., 2006	Qigong Usual care	Open	Semi-structured interviews & consumption of antalgic drugs	ON	7/8	–	No intergroup statistic realised. No significant differences within groups, even if pain complaints tended to reduce only in the treatment group

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Table 3 (*Continued*)

Authors	Intervention	Blind	Evaluation of pain	Assessment in ON or OFF[a] state	TiDIER list completion	Adverse event (AE)	Results
Exercises							
Balneotherapy							
Pérez-de la Cruz et al., 2017	Ai Chi Aquatic Physiotherapy Dry physiotherapy	Single-blind (assessor)	VAS (Primary Outcome)	OFF	8/8	None	No intergroup statistic presented. Improvement in each group on the VAS pain scale (treatment × time interaction effect $P = 0.005$)
Volpe et al., 2017	Intensive physiotherapy in water Physiotherapy	Single-blind (assessor)	VAS	ON	6/8	Orthostatic hypotension, pulmonary disease –	No significant differences between groups. No intragroup statistic realised
Pérez-de la Cruz et al., 2019	Ai Chi Aquatic Physiotherapy Dry physiotherapy	Single-blind (assessor)	VAS	OFF	7/8	None	No intergroup statistic presented. Improvement in each group on the VAS pain scale (treatment × time interaction effect $P = 0.005$)
Manual therapy							
Miyahara et al., 2018	Therapeutic Thai Massage (TTM) Usual medical care	Single-blind (assessor)	VAS	ON	7/8	None	Intergroup statistics showed an improvement of pain with a significant effect of the intervention group ($P < 0.001$)
Skogar et al., 2013	Tactile Touch (TT) and music Rest To Music (RTM)	Open	Patient's Evaluation Analysis (PEA), VAS of maximum pain, Pain-O-Meter (POM) (Primary Outcome)	–	8/8	–	There were no significant differences of pain evolution between groups. Only at short-term (week 3), emotional and physical expression of pain improved significantly only in the TT group ($P = 0.03$)
Acupuncture							
Lei et al., 2016	Electro-acupuncture (EA) Sham EA	Double-blind (assessor & patients)	VAS	OFF	7/8	Transient light-headedness None	No intergroup statistic realised. No significant pain improvement ($P = 0.26$ in the EA group)
Toosizadeh et al., 2015	EA Sham EA	Double-blind (assessor & patients)	VAS	OFF	7/8	Transient light-headedness None	No intergroup statistic realised. Reduction of VAS in both groups but changes were not significant ($P = 0.26$ in the EA group)
Botanical preparation							
Chua et al., 2017	Active herbal treatment Jiawei Liujunzi Tang (JLT) Placebo pill	Double-blind (assessor & patients)	MDS-UPDRS I – question 9 about pain	ON	8/8	Abdominal pain, dyspepsia, diarrhoea, dizziness, back pain and joint pain	No significant differences between groups ($P = 0.3$). No intragroup statistic realised
Carroll et al., 2004	Active cannador capsule Placebo pill	Crossover study double-blind (assessor & patients)	McGill Pain Questionnaire (MPQ)	ON	8/8	A similar spectrum of adverse events was recorded in both treatment and placebo groups during the RCT, although more common in the treatment group ($n = 37$ vs. $n = 15$)	No significant differences between groups ($P = 0.4$). No intragroup statistic realised

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NEUROL 2823 1–21

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REVUE NEUROLOGIQUE XXX (2023) XXX–XXX

Table 3 (*Continued*)

Authors	Intervention	Blind	Evaluation of pain	Assessment in ON or OFF[a] state	TiDIER list completion	Adverse event (AE)	Results
Exercises							
Body-psychological practice							
Pickut et al., 2015	Mind-Based Intervention Usual care	Single-blind (assessor)	VAS	–	5/8	Acute back pain –	A marginal significant interaction effect between groups ($P = 0.07$). No intragroup statistic realised
Electromagnetic methods							
Li et al., 2020	High-frequency repetitive Transcranial Magnetic Stimulation (HF rTMS) Sham HF rTMS	Double-blind (assessor & patients)	NRS (Primary Outcome)	ON	7/8	Headaches, dizziness, tinnitus, transient aggravation of gait disturbances (all acute) Headaches, dizziness, tinnitus (all acute)	A significant difference between groups ($P < 0.001$) was observed, with only the HF rTMS group exhibiting improvements in NRS scores at each follow-up time points (after the fifth intervention, 2-weeks and 4-weeks after) compared to baseline
Multi-professional care							
Gage et al., 2014	Specialist rehabilitation intervention: Multidisciplinary Team care (MDT) Ongoing support Usual care	Single-blind (assessor)	VAS	ON and OFF	8/8	Falls, infections (chest, gastric, urinary), worsening symptoms and minor surgery (but not requiring hospital admission overnight) There were sixty-nine serious adverse events (involving hospital stays or death) recorded for people with Parkinson's disease, and two for carers. These serious adverse events were judged expected by teams and there were no differences between groups	Some significant changes (degradation) in the MDT group between baseline and week 24 or 36, and in the control group between baseline and week 6, but globally no significant difference of pain evolution between groups ($P > 0.05$)

[a] OFF state is 12 h after medication withdrawal.
[b] Gandolfi et al., 2019: T0 = before the treatment; T1 = two days after the end of the treatment; T2 = one-month follow-up after the end of the treatment;
[c] Paolucci et al., 2017: T1 = at the end of the rehabilitative program; T2 = at 12-week follow-up.

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a book [39]): exercise, balneotherapy, manual therapy, acupuncture, botanical preparation, body-psychological practice, and electromagnetic methods. Moreover, it was decided to add the multi-professional care category as an NPI. A qualitative analysis by type of intervention was then conducted to achieve the objectives of the review. The results were then discussed in terms of their scientific and medical relevance. Quantitative data is presented either with the mean ± standard error of the mean (SEM) or with the median, range and percentile according to studies available information.

3.6. *Quality criteria: risk of bias (RoB)*

To assess the risk of bias, the RoB2 tool for RCTs [40] was used. The same two authors (M.H. and M.B.) independently evaluated each study for the five domains of the RoB2 using the specified designed RoB2 tool either for parallel or crossover RCTs. Any conflict was resolved by discussion as recommended in the Cochrane handbook.

4. Results

4.1. *Description of the flow chart*

Search terms submitted to the databases led us to 711 records that two independent authors (M.H. and M.B.) investigated between January 2022 and March 2022. After deleting duplications, these records were firstly selected by their title in accordance to our eligibility criteria described in the method section. From the remaining 76 records, we excluded 57 after reading the abstracts. The selection was made following the PICO criteria and the majority of excluded articles were uncontrolled clinical trials (comparison) and/or without pain assessment (outcome). Then we added 32 titles that we considered relevant based on the references of the screened records, as well as seven articles identified from the supplementary research about neuromodulation. Finally, we read 58 full-text articles leading to the inclusion of 19 RCTs in our review.

4.2. *Studies characteristics*

The characteristics of the selected studies are presented in the Table 2. The studies were published between 2004 to 2021. Our review gathered data from 976 subjects, age range 50 to 79 years, and mean Hoehn and Yahr score between 1.5 and 3.0. The number of patients by study ranged from 15 to 270 subjects. All clinical trials were randomised and controlled with parallel groups except one that used a crossover design.

Study duration was from three weeks to one year including follow-up, which was the case for eleven studies (follow-up from four weeks to thirty weeks after the last intervention).

Two studies verified that all the patients had chronic pain either by including pain duration greater than three months as an inclusion criteria [41] or by only evaluating patients with musculoskeletal pain. This means that pain assessment in the other studies was probably made both in patients with and without chronic pain.

To make sure PD patients were naive to the interventions, three studies noted whether the patient had experienced the intervention in a recent past (practice of Qigong in the last month [42] and history of receiving any kind of repetitive transcranial magnetic stimulation [rTMS] [43]) or at the present time (current yoga practice [44]) as an exclusion criteria.

Because description of the intervention is very important to be transferable into clinical practice, we assessed the reproducibility of these interventions using the TIDieR checklist [37]. Of the 19 RCTs, seven of them validated all items of the TIDieR checklist, ten missed one item and two missed more than one item.

4.3. *Outcomes and pain assessment*

Only three studies assessed pain as their primary outcome: one on Ai Chi aquatic physiotherapy [45], one on tactile touch [41] and one on high-frequency repetitive transcranial magnetic stimulation (HF rTMS) [43]. In the remaining studies, primary outcomes were mostly motor scores.

Three studies did not describe the time of the measurements while eleven assessed patients in the ON state, four in the OFF state and one in both ON and OFF states.

Twelve studies (63%) assessed pain with a unidimensional scale: a VAS in ten studies and a numeric rating scale (NRS) in two studies. For the others studies, a wide range of multidimensional pain assessments was used: either specialised pain questionnaires (McGill pain questionnaire [MPQ]) or non-specialised instruments such as the revised Oswestry disability index (RODI) or one item of the non-motor symptoms scale (NMSS). Finally, one study used both a qualitative (semi-structured interview) and a quantitative assessment (consumption of antalgic drugs [42]).

Except for two studies assessing musculoskeletal pain [43,46], the other RCTs did not mention the type of pain.

4.4. *Non-pharmacological interventions (NPI)*

Active therapy accounted for the majority of interventions (53%) performed by either a health specialist (physical therapist) or a non-health care specialist (Nordic walk or Qigong studies).

The following paragraphs present the global overview of the results, details are presented in Table 3.

4.4.1. *Physical exercises*

In this category, seven different NPIs were found: each in a single investigation (there were no replication studies of these NPIs).

First, there were specific rehabilitation techniques, performed by qualified physical therapists: Lee Silverman voice treatment-BIG (LSVT-BIG); specific trunk rehabilitation; and the Meziere rehabilitation (Table 2 presents the characteristics of the interventions). None of these NPIs showed significant intergroup difference. However, in the LSVT-BIG study, the group that participated in the intensive physiotherapy – which was not the main intervention and consisted of an intensified

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and personalised physiotherapy – showed a significant improvement in the overall NMSS score compared to the control group. In the intragroup analyses, a decrease of pain was observed in both active and passive trunk rehabilitation groups as well as an improvement of pain in the Meziere rehabilitation group without improvement in the control group.

Regarding the other physical activities, for body weight supported treadmill training (BWSTT), intergroup comparison showed a significant decrease of pain for the two intervention groups (10% and 20% of body supports). In the same way, inside the groups, pain decreased only in both intervention groups while it increased in the control group (0% of body support).

Concerning Nordic walking, researchers found an improvement of pain in the back, hands and legs for both walking groups (Nordic walking and walking training) compared to the stretching and relaxation control group. Moreover, in the Nordic walking group up to 30% of the patients became free of pain after the training.

The Qigong intervention did not show any intergroup difference on pain compared to usual care, ''although pain complaints tended to decrease only in the treatment group''. No intergroup comparison was presented for the yoga intervention, while intragroup analyses showed a decrease of pain only in the intervention group compared to the usual routine.

4.4.2. *Balneotherapy*

Three studies focused on the effect of balneotherapy versus dry physical therapy but only intragroup analyses were presented. Two studies found a significant decrease of pain in both groups, while the most recent study did not find significant difference in any groups.

4.4.3. *Manual therapy*

Two studies investigated manual therapy. Regarding the intergroup analysis, Thai massage seemed to provide a significant beneficial effect on pain in the intervention group in comparison with usual medical care. Conversely, therapeutic touch did not show significant long-term differences (34 weeks post-intervention) between the intervention and control groups, despite an emotional and physical improvement of pain at short-term (three weeks post-intervention) only in the intervention group through intragroup analyses.

4.4.4. *Acupuncture*

Electro-acupuncture (EA) was evaluated in two studies in comparison with placebo acupuncture, but intergroup analysis was not presented. In both studies, intragroup analyses did not find any significant improvement of pain in either group.

4.4.5. *Botanical preparation*

Two types of herbal preparations were evaluated in the literature: a cannabis-based preparation and a mixture called Jiawei Liujunzi Tang (JLT). Importantly, these two studies were the only ones to be conducted in a double-blind design. Both studies did not show any significant difference between the intervention and control groups on pain assessment. Intragroup analyses were not presented.

4.4.6. *Body-psychological practice*

A research studied the effect of a mind-based intervention (MBI) described as guided mindfulness exercises (meditation, yoga and body scan) to do at home. Intergroup analysis showed a tendency of beneficial effect on pain with the MBI. Intragroup analyses were not presented.

4.4.7. *Electromagnetic methods*

A research studied the effect of HF rTMS over the primary motor cortex in PD patients with musculoskeletal pain, compared to a sham intervention. Intergroup analysis showed a significant difference between groups: only the rTMS group had an improvement of pain after the intervention that persisted after follow-up.

4.4.8. *Multi-professional care*

A national study investigated the multidisciplinary follow-up of PD patients under a request from the English government. Patients were followed in hospital and at home with nursing, rehabilitation (physiotherapy, speech therapy), social support, and medical care. This study did not show any significant changes in pain between groups (intergroup analysis). However, they observed some significant changes (augmentation of pain) in the multidisciplinary team (MDT) group between baseline evaluation and evaluation at week 24 and 36, and in the control group from baseline to week 6 (intragroup analyses) in ON state. No significant difference in pain were found in OFF state.

4.5. *Adverse events*

In this wide range of interventions, reported adverse events were rare. Of the ten studies (52%) that mentioned adverse events, only one described serious adverse events involving hospital stays or death [47]. These serious adverse events were expected by the clinical research team regarding the number of participants and the study duration (250 PD patients followed for 36 weeks) and no difference was found between groups (intervention and control groups). The main minor adverse events were pain (muscle pain following exercise or abdominal pain), hypotension, transient headaches or dizziness, transient light-headedness and falls.

4.6. *Quality of studies: risk of bias*

To assess the risk of bias, the RoB2 tool of the Cochrane collaboration for RCT was used.

As can be seen in the Figs. 2 and 3, a large proportion of articles are considered to be at high risk of bias in the 'outcome measurement' domain (D4). In fact, in a large majority of studies (74%), the assessor (who was the patient for self-reported pain) was not blinded, which is considered as a high risk of bias.

5. Discussion

This review explores the benefits (effectiveness and safety) of NPIs for PD pain management, in a holistic approach. More precisely, studies were RCTs with pain assessment as a primary or secondary outcome.

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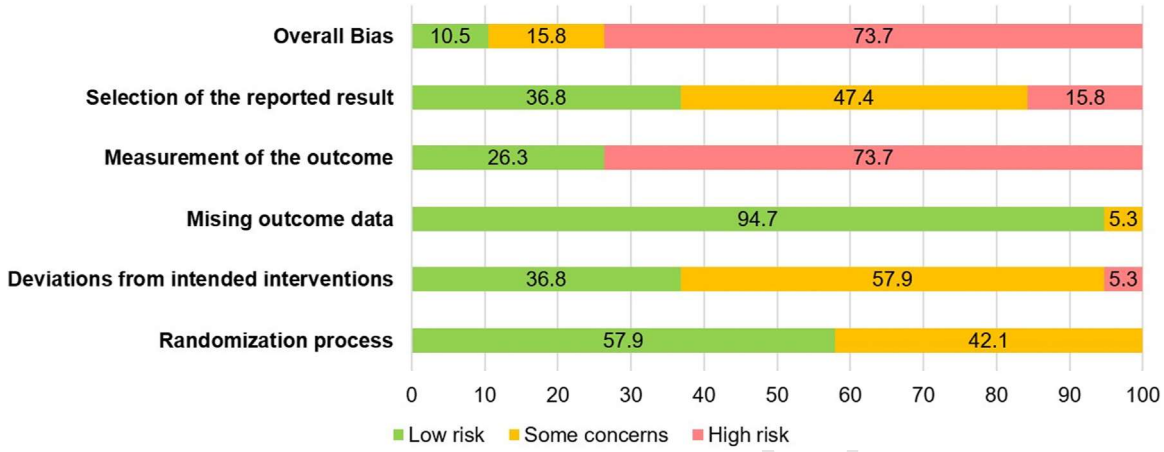

Fig. 2 – Risk of bias as percentage (all studies included).

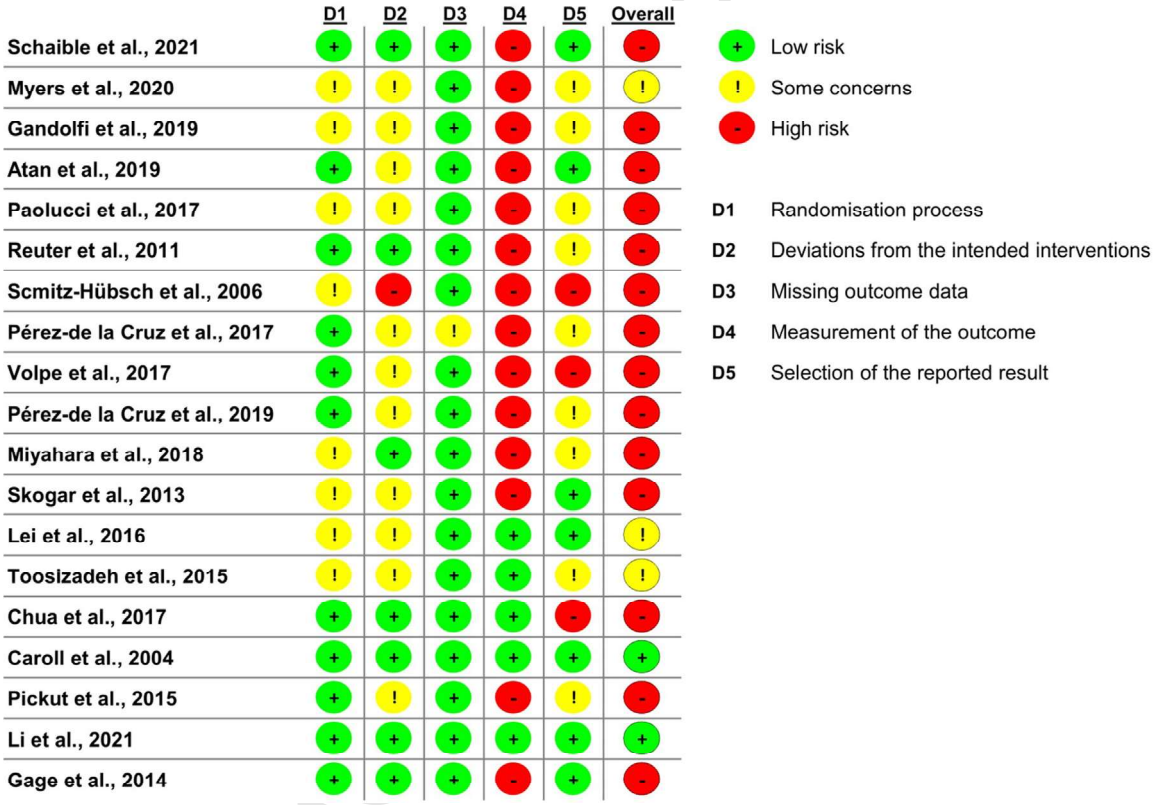

Fig. 3 – Risk of bias for each study. D: domain.

5.1. *Effectiveness of non-pharmacological interventions*

Results have shown that NPIs had a low-to-moderate level of evidence for PD pain management, with favourable or inconclusive results. This could be due to the small sample size of the studies or to the choice of assessment methods, which were probably not specific or sensitive enough to assess changes in PD pain. These results must be considered with great caution because of the arguments outlined below.

In our review, the effects of NPIs can be summarized into four categories:

- NPIs ($n = 5$) that have shown a significant effect on PD pain compared to their control group (intergroup analyses). This is the case for Thai massage, Nordic walking, BWSTT, MBI and HF rTMS;
- NPIs ($n = 5$) that did not show intergroup differences (absence of statistical analyses or non-significant results)

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but where an improvement of pain was only observed within the intervention group (and not in the control group). This is the case for tactile touch, Qigong, yoga, the Meziere rehabilitation and trunk-specific rehabilitation;

- NPIs ($n = 4$) whose results did not allow to conclude on their effect on PD pain management: both the intervention and control groups showed significant changes in the same direction but without significant intergroup comparison. This is the case for aquatic Ai Chi ($n = 2$) (both the control and intervention groups showed improvements of pain), electro-acupuncture, and for the multidisciplinary management (aggravation of pain was observed in both groups);
- NPIs ($n = 5$) that did not show any significant differences either in inter- or intra-groups comparisons. This is the case for intensive physiotherapy in water, LSVT-BIG technique, electro-acupuncture, JLT and cannabis.

Regarding these previous categories, it seems that NPIs where the patient was active (exercises and body-psychological practice from the NPIS classification [39]: three studies out of five that showed a significant effect on PD pain compared to their control group) had a more significant impact to decrease PD pain than NPIs where the patient was passive. These benefits could be explained by the effect of physical activity on neuroplasticity, neuro-restoration and improvement of dopamine neurotransmission, as shown on animal models of PD [48]. These findings support the hypothesis that the benefits of NPIs emerge through a process of patient empowerment, active problem solving, realistic goal setting, and a functional/rehabilitative perspective [31].

According to our results, NPIs resulting from passive interventions, such as vitamins, herbs, cannabis, or acupuncture, seem to be less effective on pain, except for Thai massage and HF rTMS.

5.2. *Evaluation of pain*

Pain is a complex construct to assess because it is a multimodal sensation, with biopsychosocial dimensions: sensory-discriminative, affective-emotional, cognitive and behavioural. Pain questionnaires are rarely validated for PD pain, despite a recommended list of specific questionnaires to assess PD pain [49]. Through the seven questionnaires recommended with caution, only four were used in this review (MPQ, NRS, VAS, pain-o-meter). However, even when they are, their results are often not comparable because they do not assess the same type and dimension of pain.

Furthermore, we can point out that there were only three studies in which pain was the primary outcome and all assessed pain with a unidimensional scale (either by the VAS, which was the most commonly used scale in our review's studies, or the NRS). In four studies, the assessment of pain intensity was only done in the OFF-medication state, which can be considered irrelevant as it does not represent the patients' daily life.

Finally, there are different types of PD pain [5] corresponding to different mechanisms that should be treated with specific therapy. Indeed, pain treatment should probably not be etiology-driven, but rather mechanism-based [6]: this is why the characterisation of the different subgroups of PD pain is so important [5]. Nevertheless, only two of the studies in our review defined which type of pain was assessed. In future studies, it could be interesting to specify the types of pain with the aim of adapting the management strategy as well as possible. For example, it is conceivable that NPIs modulating neuroplasticity might have a better effect on nociplastic pain.

5.3. *Quality of non-pharmacological interventions studies*

These results should be viewed with great caution due to the methodological limitations of the studies. These limitations may relate to the lack of blinding, the control group and/or the duration of the study.

Firstly, for the three studies with pain as the primary endpoint, only one was double-blind, while one was single-blind and the other was open-label. Including the other studies, only six (31%) were double-blind. Therefore, a majority of studies are rated as high risk of bias by the RoB2 tool.

The second methodological limitation is the lack of a suitable control group. It could be explained by the inherent characteristics of NPIs. Indeed, it is difficult to construct a control group that mimics the active intervention without containing its active ingredients, so the control group often constitutes another form of NPI that improves the patient's condition and reduces the magnitude of the specific effect of the NPI.

The control group may be (i) a control group (without any standard intervention or treatment); (ii) a sham intervention group (intervention with the same time and type of interaction with the patient but without a supposed specific effect); or (iii) another intervention modality (e.g., medication, therapeutic education, physical activity program). Concerning the three studies with pain as a primary objective, control groups were adequate since they properly isolated the specific NPI induced-effect and patients in both groups had the same number of sessions and duration of study. Nonetheless, we cannot exclude that these control groups constitute another form of NPI. Concerning the remaining studies, some had discrepancies between their control and intervention groups about the planning; while others used control groups too different from the intervention group to truly isolate NPI specific effect.

Thirdly, duration of the study could also be an important feature to consider when reviewing the quality of the studies.

In the three studies where pain was the primary endpoint, the interventions were conducted during five to twenty sessions. Except for the rTMS sessions which were all performed during the same week, both other interventions were carried out between seven and ten weeks, which seems to be a good length of time to study the effect of NPIs. Indeed, the literature advises a study duration of ideally twelve weeks, with a minimum of eight weeks, for chronic pain [50]. The remaining studies tended to be sufficiently long because of the median duration of twelve weeks.

Nevertheless, three studies (16%) had a duration of four weeks or less (follow-up included), which may overestimate effectiveness [50].

Finally, concerning the three studies with pain as the primary outcome [41,45], one of them [45] can be criticised

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because it was almost identical to another study in our review done by the same author [51]. This makes us question its veracity since there are some inconsistencies between the demographic data presented in the text and in the table in the second one [51].

In the same way, both studies about electro-acupuncture [52,53] present identical demographic data and results, which seems improbable.

5.4. *Safety of non-pharmacological interventions*

Some studies reported few minor transient adverse events. Only one study documented some serious adverse events probably explained by evolution of the disease through the study. Given this information, it would appear reasonable to consider NPIs as safe in PD pain management.

5.5. *Limits and strengths*

The limitations of our review result from a lack of information in the study reports, although this can easily be justified as pain was often not the primary assessment in the studies. Another limit is the absence of PD pain classification, as mentioned before, forcing us to treat all results on equal terms, while nociceptive, neuropathic or nociplastic pain could respond differently to various NPIs. NPIs effects cannot be generalised but need to be deconstructed and their specificities associated with the mechanisms underlying the therapeutic effect correlated to each type of pain.

The strength of our review is that it was made very carefully following the PRISMA recommendations and that reproducibility of NPIs were well evaluated using the TIDieR checklist.

6. Conclusion and implication for future research

Our review highlighted the clinical relevance of some NPIs in PD pain management, in particular NPIs where the patient was active (exercises and body-psychological practice), and the safety of NPIs since only a few minor transient adverse effects were reported. Hence, according to our results categorisation, we could recommend Thai massage, Nordic walking, BSWTT, MBI and HF rTMS as effective NPIs to relieve PD pain.

Nevertheless, even if we have found some interesting results, differentiating NPIs superiority was difficult because of the absence of standardised measurement procedures, the variety of outcomes, and the limited number of high-quality studies. The methodology of future studies also needs to be more robust and to include comprehensive descriptions in order to be replicated and to offer reliable and sound recommendations to clinicians.

Specifically, pain evaluation needs to be assessed with robust tools and validated PD pain classifications in order to be precise about the type of pain studied. In addition, the promising scientific evidence supporting the concept of bio-psychosocially mediated analgesia must be translated into an assessment of the biopsychosocial dimensions of pain. This new perspective on pain management should allow us to study NPIs in a new framework and to understand the mechanisms underlying their effect, to dissect their active effects and to look at the patients' profiles (responders, non-responders, personality dimensions…). This will allow clinicians to propose NPIs according to PD pain types and patient profiles, in a personalised medicine concept.

To this end, we would like to encourage future studies to be conducted in this area by addressing the following criteria to improve the reports:

- explanation of the relevance of the evaluation criteria (feasibility of their gathering, traceability, availability of information, clarity and absence of ambiguity of the criteria, margin of improvement, expected impact on the results, compliance of patients);
- adequate control group with a justification;
- evaluation performed on biopsychosocial dimensions of pain;
- adequate duration of follow-up.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurol.2023.04.010.

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