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Physical interventions for people with Parkinson's disease: a systematic review and network meta-analysis (Protocol).
Cochrane Database of Systematic Reviews 2021, Issue 2. Art. No.: CD013856.
DOI: 10.1002/14651858.CD013856.

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[Intervention Protocol]

Physical interventions for people with Parkinson's disease: a systematic review and network meta-analysis

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Editorial group: Cochrane Movement Disorders Group.
Publication status and date: New, published in Issue 2, 2021.

Citation: Roheger M, Ernst M, Folkerts A-K, Krohm F, Liebermann-Jordanidis H, Chakraverty D, Droz M, Adams A, Eggers C, Monsef I, Hounsome J, Dresen A, Skoetz N, Kalbe E. Physical interventions for people with Parkinson's disease: a systematic review and network meta-analysis (Protocol). *Cochrane Database of Systematic Reviews* 2021, Issue 2. Art. No.: CD013856. DOI: 10.1002/14651858.CD013856.

ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To compare effects of different physical interventions in adult participants with Parkinson's disease on the improvement of motor functions and QoL and the reduction of adverse events.

To generate a clinically meaningful treatment ranking of physical interventions for Parkinson's disease using a network meta-analysis.

BACKGROUND

Description of the condition

Parkinson's disease is the second most common neurodegenerative disease for people over 60 years of age (De Lau 2006).

Parkinson's disease is associated with loss of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies (Damier 1999). The precise mechanisms of neurodegeneration are unclear but most likely involve both genetic and environmental factors (Ascherio 2016).

Parkinson's disease is primarily characterized by progressive motor symptoms, including bradykinesia, muscular rigidity, rest tremor, and postural instability (Hughes 1992). These features affect various aspects of mobility, such as gait, transfers, balance, and posture (Keus 2007). Furthermore, non-motor symptoms frequently occur in Parkinson's disease patients, such as anxiety, depression, fatigue, sleep disturbance, and sensory symptoms (Shulman 2001), as well as cognitive dysfunctions ranging from mild cognitive impairment to Parkinson's disease dementia (Muslimović 2005). Motor and non-motor symptoms cause substantial functional limitations and a reduction of the quality of life (QoL) of the patients and their caregivers (Martinez-Martin 2011).

Parkinson's disease remains a clinical diagnosis typically based on the presence of a combination of cardinal motor features, associated and exclusionary symptoms, and response to dopaminergic treatment (Rao 2003; Rizek 2016).

Incidence rates of Parkinson's disease based on prospective population-based studies range from 8 to 18 per 100,000 person-years. Incidence of Parkinson's disease is rare before 50 years of age and increases sharply after 60 years of age (De Lau 2006).

Most but not all epidemiological studies suggest that men have a higher risk than women to develop Parkinson's disease (De Lau 2006; Moisan 2016; Pringsheim 2014). Life expectancy is reduced in people with Parkinson's disease (De Lau 2006).

With approximately 6.1 million people with Parkinson's disease worldwide, the global burden of Parkinson's disease has more than doubled over the past generation, and it is likely to increase further due to demographic change (Dorsey 2018).

Description of the intervention

Pharmacological agents, such as levodopa, dopamine agonists, and monoamine oxidase B inhibitors, have been central to the treatment of motor symptoms in Parkinson's disease (Rizek 2016). Surgical treatment, such as deep brain stimulation, is another widely investigated intervention that may be useful for some Parkinson's disease patients (Aum 2018).

Recently, an increasing number of studies has been investigating the potential of non-pharmacological and non-surgical interventions, such as exercise and physical interventions, in managing motor and non-motor symptoms in Parkinson's disease.

In systematic reviews and clinical guidelines, physical interventions for people with Parkinson's disease are defined as interventions that focus on the enhancement of muscle strength, aerobic capacity, balance, gait, and functional mobility by means of cueing, cognitive movement strategies, and physical exercises (e.g. Keus 2014; Tomlinson 2013).

Positive effects of several physical interventions in people with Parkinson's disease have been observed in recent systematic reviews, such as short-term benefits of physiotherapy on motor symptoms and activities of daily living (Tomlinson 2013), positive effects of Nordic walking on motor and non-motor symptoms (Bombieri 2017), and improved balance and well-being through tai chi training (Ćwiękała-Lewis 2017). Physical activity was found to have a positive impact on physical and functional capacities but only moderate effects on Parkinson's disease-specific symptoms and psychosocial aspects (Lauzé 2016).
Furthermore, physical activity was found to have a positive impact on the global burden of non-motor symptoms, including depression, apathy, fatigue, daytime sleepiness, sleep, and cognition (Cusso 2016).

Investigations of the long-term effects of exercise and physical therapy interventions (including, multi-modal physical therapy, progressive resistance training, aerobic training, gait and balance training, tai chi, and dance) found that these interventions modify long-term motor symptoms and physical functioning in people with Parkinson's Disease, with balance training having the longest carry-over effects, followed by gait and tai chi training (Mak 2017).

Physical interventions appear to be relatively safe. Although data on adverse events were rare in most studies included in previous systematic reviews on physical interventions for Parkinson's disease, studies that provided data on this outcome reported either none, or no serious adverse events (Bombieri 2017; Ćwiękała-Lewis 2017; Tomlinson 2013).

A review of long-term effects of exercise and physical activity for Parkinson's disease that included 46 studies, reported that adverse events were published in 25 studies, of which 10 reported injuries that were sustained during training, and 28 studies noted falls and minor injuries that did not require medical attention. Further adverse events reported were hypotension, lightheadedness or dizziness, joint pain or muscle soreness, injury-induced shoulder pain, fatigue, and discomfort due to devices (i.e. due to the harness of a robotic gait trainer in one study). Given the total number of participants in the 25 studies (n = 792), the authors regarded the overall risk of adverse events as low and the interventions as safe and well tolerated (Mak 2017).

Nevertheless, it has to be noted that adverse events may have occurred in studies without being recorded or reported, potentially leading to an underestimation of the safety of physical interventions.

How the intervention might work

There is a vast amount of evidence that physical interventions substantially induce neuroplasticity and enhance brain health in both motor and cognitive circuits in Parkinson's disease. Neuroplasticity is the brain's ability to modify existing neural networks by adding or reorganizing synapses. However, evidence on structural and functional brain changes in participants is lacking yet, and one can deduce Parkinson's disease-specific effects of physical interventions only from animal studies. In rodent models

of Parkinson's disease, forced or voluntary physical exercises have neuroprotective effects as the release of neurotrophic factors (e.g. brain-derived neurotrophic factor, glial-derived neurotrophic factor) increases (Cohen 2003). These animal models also showed compensatory changes in dopaminergic neurons of the basal ganglia. For example, dopamine neurotransmission increases through enhanced vesicular release and decreasing dopamine clearance in the synaptic cleft due to reduced dopamine reuptake (Petzinger 2007). Furthermore, the efficacy of neurotransmission increases because of enhanced dopamine D2 receptor expression in remaining dopaminergic neurons and their targets (Yin 2009).

Why it is important to do this review

The increasing number of trials assessing physical interventions demonstrates the growing interest in non-pharmacological and non-surgical interventions for the treatment of Parkinson's disease.There are several systematic reviews and meta-analyses focusing on one type (e.g. Bombieri 2017; Ćwiękała-Lewis 2017; Dockx 2016; Dos Santos 2017), and there are some that focus on several types (e.g. Tomlinson 2013; Tomlinson 2014).

However, the relative benefit of these interventions in improving motor functions, QoL, and reducing adverse events remains unclear.
Therefore, we want to conduct a comprehensive systematic review comparing all types of physical intervention in a network meta-analysis combining direct and indirect evidence.

When the methodological assumptions are met, network meta-analysis allows the estimation of metrics for all possible comparisons in the same model and enables analyses of direct and indirect evidence simultaneously. Such analyses would enable ranking of different treatments for specific outcomes. Such ranking could be highly relevant for participants and clinicians when making clinical decisions on non-pharmacological and non-surgical Parkinson's disease treatment, or when participants wish to integrate more physical training in their daily life.

OBJECTIVES

To compare effects of different physical interventions in adult participants with Parkinson's disease on the improvement of motor functions and QoL and the reduction of adverse events.

To generate a clinically meaningful treatment ranking of physical interventions for Parkinson's disease using a network meta-analysis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs). We will include both full-text and abstract publications if sufficient information on study design, characteristics of participants, and interventions are provided. We will include trials with participants receiving physical interventions in at least one treatment arm. In the case of cross-over trials, we will analyse only the first period of the trial. There will be no limitations with respect to length of follow-up.

We will exclude cluster RCTs, non-randomized trials, case reports, and clinical observations.

Types of participants

We will include trials involving adult participants (≥ 18 years of age) with a confirmed diagnosis of idiopathic Parkinson's disease (at least 90% with idiopathic Parkinson's disease of the sample). We will include participants of all cognitive stages (without cognitive impairment, with mild cognitive impairment, with dementia). We will not impose any restriction regarding sex or educational level of the participants.

We will exclude trials involving participants with atypical parkinsonism (e.g. drug-induced parkinsonism, vascular parkinsonism).

We assume that participants who fulfil the inclusion criteria are equally eligible to be randomized to any of the interventions we plan to compare.

Types of interventions

We will include trials comparing different physical interventions according to an adapted version of the ProFaNE taxonomy (a naming and classification system developed for falls-prevention interventions (Lamb 2011), with each other or with a control group.

We will include trials involving physical training, exercise, or motor training as one main component of the intervention. Interventions need to comprise structured exercise. Interventions may include various training contents, be delivered in various environments, and incorporate diverse training devices (e.g. treadmill, physiotherapy, aerobic exercises, boxing, qigong, karate, bicycle exercises, strength training, Lee Silverman Voice Training BIG (LSVT BIG), Nordic walking, virtual reality exercises, dance therapy, balance training, gait training, aqua therapy, yoga, tai chi). We will include interventions that are conducted in either a group or an individual setting, lasting for at least five sessions under supervision, interventions consisting of either continuous training or interval training, and combined interventions only if physical training is the main component of the intervention. Concomitant supportive treatment should not differ between study arms.

We will group similar interventions based on an adaptation of the ProFaNE taxonomy (Lamb 2011). As recommended by authors of a Cochrane Review who applied the taxonomy to categorize exercise interventions for falls prevention (Sherrington 2019), we will provide information on our operationalization of the system.

Our decision set will include all interventions that use structured exercise and may be categorized using the following categories:

- gait, balance, and functional training;
- strength and resistance;
- flexibility;
- 3D - dance;
- 3D - mind-body;
- 3D - aqua;
- endurance;
- virtual reality (VR);
- LSVT BIG;
- multiple components.

We expect that many studies will use an active or a passive control group as comparators against the interventions included in

our decision set and, therefore, improve inferences among these when included in the network. Therefore, we will include these interventions in our supplementary set.

We define 'active control groups' as groups receiving a structured, supervised, non-physical intervention (i.e. that may be not be categorized using the abovementioned categories, e.g. handwriting training, communication training).

We define 'passive control groups' as groups not receiving a structured, supervised intervention (e.g. waiting list, no treatment, treatment-as-usual, advice only, unstructured general activity).

Should no direct evidence from RCTs exist and the trials be considered sufficiently similar with respect to the participant population, to ensure the transitivity assumption of network meta-analysis, we will obtain indirect estimates of intervention effectsvia the network calculations.

Types of outcome measures

We will include all trials fulfilling our inclusion criteria, irrespective of whether or not the outcomes of interest listed in the following section are reported.

We will estimate the relative ranking of the competing interventions according to the outcomes described in the following section. We will produce network plots for each outcome displaying the amount of evidence.

We will consider only outcomes measured using validated instruments.
When multiple outcome measures are reported, we will give preference according to the order in which they are listed in the following section.

Primary outcomes

- Clinician-rated impairment and disability (measured, e.g., with the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS III, motor score) (Goetz 2008); the Unified Parkinson's Disease Rating Scale (UPDRS III, motor score, designed to assess motor impairment and disability in Parkinson's disease) (Fahn 1987); the Hoehn & Yahr scale (used to describe how symptoms of Parkinson's disease progress) (Hoehn 1967), the Webster Rating Scale (assessment of severity of disease and clinical impairment against 10 items) (Webster 1968), the Columbia University Rating Scale (assessment of motor impairment and activities of daily living against 13 items) (Yahr 1969), etc.).
- Patient-rated QoL (measured, e.g., with the Parkinson's Disease Questionnaire 39 (PDQ-39, a Parkinson's disease-specific health-related QoL questionnaire containing 39 items divided among eight domains) (Jenkinson 1997; Peto 1995),Parkinson's Disease Questionnaire 8 - short-form of the PDQ-39 (Jenkinson 1997aa), EuroQol (EQ-5D) - generic QoL questionnaire containing five items (EuroQol Group 1990), etc).

Secondary outcomes

- Freezing of gait (measured with the Freezing of Gait Questionnaire (measures the freezing of gait in people with Parkinson's disease)).
- Functional mobility and balance (measured with the Timed Up & Go (measures time taken in seconds for a person to get up from a chair, walk a certain distance (usually three meters), turn around, and walk back to the chair and sit down) (Podsiadlo 1991)).
- Adverse events (number of participants with any adverse event).

Timing of outcome assessment

We will evaluate outcomes assessed shortly (≤ six weeks) after the intervention. If multiple assessments within this interval are reported, we will evaluate the assessment closest to the end of the intervention.

We will evaluate adverse events measured at any time up to six weeks after the intervention.

Search methods for identification of studies

Electronic searches

We will adapt search strategies as suggested in Chapter 4 of the Cochrane Handbook for Systematic Reviews of Interventions (Lefebvre 2020). We will apply no language restrictions to reduce language bias. We will use medical subject headings (MeSH) or equivalent and text word terms.

We will conduct searches tailored to each of the following databases and trial registries:

- CENTRAL (via The Cochrane register of Studies Online)
- MEDLINE (via OvidSP; for a preliminary version of the search strategy, see Appendix 1)
- Embase (via OvidSP)
- CINAHL (via EBSCO)
- SPORTDiscus (via EBSCO)
- AMED (Allied and Complementary Medicine; via OvidSP)
- REHABDATA (www.naric.com/?q=en/rehabdata)
- PEDro (Physiotherapy Evidence Database; www.pedro.org.au)
- EU Clinical Trials Register (www.clinicaltrialsregister.eu/ctr-search/search)
- World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp/search/en)
- ClinicalTrials.gov (www.clinicaltrials.gov)
- ISRCTN registry (www.isrctn.com)

This search which will be complemented by a handsearch of the most recent conferences if not already included, will cover the following conferences:

- International Congress of Parkinson's Disease & Movement Disorders (from 2010)
- American Academy of Neurology (from 2008)
- European Academy of Neurology (from 2015)
- International Association of Parkinsonism and Related Disorders (from 2009)

Searching other resources

Furthermore, we will handsearch references of all identified trials, relevant review articles, and current treatment guidelines for further literature. We will contact authors of relevant studies and

study groups who are known to be active in the field of physical interventions in Parkinson's disease for unpublished material or further information on ongoing studies.

Data collection and analysis

Selection of studies

One review author [ME] will screen the results and remove titles that clearly do not satisfy the inclusion criteria. Following this initial screening, two review authors [ME, AF] will independently screen the remaining results for eligibility by reading the abstracts and obtain full-text copies of potentially eligible studies. In the case of disagreement or if it is unclear whether we should include an abstract or not, we will assess the full-text publication for further discussion. If still no consensus can be reached, a third author [MR] will adjudicate.

Two review authors [ME, AF] will read the studies independently to select relevant studies, and in the event of disagreement, a third author [MR] will adjudicate.

We will not anonymize the studies before assessment. We will include a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart in the full review that will show the status of identified studies (Moher 2009), as recommended in Part 1, Chapter III of the *Cochrane Handbook for Systematic Reviews of Interventions* (Page 2020a). We will report the review in accordance with the PRISMA extension for network meta-analysis (Hutton 2015).

We will include studies in the 'Characteristics of included studies' irrespective of whether measured outcome data are reported in a 'usable' way. There will be no language restrictions, and articles will be translated if not published in English language. We will record excluded studies in the 'Characteristics of excluded studies'.

Data extraction and management

Two review authors [ME, AF] will extract data using a standardized data extraction form. If the authors are unable to reach a consensus, we will consult a third review author [MR] for the final decision. If required, we will contact the authors of specific studies for supplementary information (Li 2020). After we have reached agreement, we will enter data into Review Manager 5 (RevMan 2014).

We will extract the following information:

- general information: author, title, source, publication date, country, language, duplicate publication;
- quality assessment: sequence generation, allocation concealment, blinding (participants, personnel, outcome assessors), incomplete outcome data, selective outcome reporting, other sources of bias;
- study characteristics: trial design, setting, source of participants, statistical methods (power calculations, subgroup analysis), treatment cross-overs, compliance with assigned treatment, discontinuation, time point of randomization, length of follow-up;
- participant characteristics: participant details (baseline demographics such as age, sex), number of participants recruited, allocated, or evaluated, participants lost to follow-up, disease severity, cognitive stage, physical capability;
- intervention: type, frequency, setting, supervision;
- outcomes: motor outcomes (clinician-rated impairment and disability, freezing of gait, functional mobility and balance), patient-rated QoL, adverse events;
- notes: sponsorship or funding for trial and notable conflicts of interest of authors, trial registry record information (e.g. NCT numbers).

We will collate multiple reports of the same study, so that each study rather than each report is the unit of interest in the review. We will collect characteristics of the included studies in sufficient detail to populate a table of 'Characteristics of included studies' in the full review. For the outcomes, if both effect sizes with SDs or SEs and raw data are reported, we will collect the effect sizes with SDs or SEs originally reported by the authors of the trial. We will evaluate the impact of potential effect modifiers in the context of the transitivity assumption (see Subgroup analysis and investigation of heterogeneity section).

Assessment of risk of bias in included studies

We will use the Risk of Bias tool (RoB 2.0) to assess risk of bias for all outcomes included in the 'Summary of findings' table (Sterne 2019).

We will assess the effect of assignment to intervention (the intention-to-treat effect).

The tool implements signalling questions for each domain leading to low, high, or some concern for risk of bias.

We will make the answers to these signalling questions available in the appendix.

Two review authors [ME, AF] will independently assess risk of bias for each outcome, and if they are unable to reach a consensus, we will consult a third review author [MR] for a final decision.

We will address the following domains covering all types of bias that can affect results of randomized trials:

- bias arising from the randomization process;
- bias due to deviations from intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome;
- bias in selection of the reported result.

Measures of treatment effect

Relative treatment effects

We will use intention-to-treat data to calculate treatment effects. For continuous outcomes, we will calculate mean differences (MDs), including 95% confidence intervals (CIs), when assessed with the same instrument; otherwise we will calculate standardized mean differences (SMDs), including 95% CIs. We will convert SMDs back to MDs on the most frequently reported scale and interpret findings with respect to a minimum clinically important difference on the respective scale (e.g. 2.5 points (95% CI 2.3 to 2.7) on the UPDRS III, motor score (Shulman 2001)).

For binary outcomes, we will extract number of participants and number of events per arm and calculate risk ratios (RRs) with 95% CIs for each trial.

Relative treatment ranking

We will obtain a treatment hierarchy using P values (Rücker 2015). P values allow ranking treatments on a continuous 0 to 1 scale in a frequentist network meta-analysis. Since ranking according to P values is a probability ranking, we will report not only P values but also network estimates along with corresponding 95% CIs.

Unit of analysis issues

Studies with multiple treatment groups

As recommended in Chapter 23.3.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020), for studies with multiple treatment groups, we will combine arms as long as they can be regarded as subtypes of the same intervention. When arms cannot be pooled this way, we will include multi-arm trials using a network meta-analysis approach that accounts for the within-study correlation between the effect sizes by reweighting all comparisons of each multi-arm study (Rücker 2012; Rücker 2014). For pairwise meta-analysis, we will treat multi-arm studies as multiple independent comparisons and will not combine these data in any analysis.

Dealing with missing data

As suggested in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2020), we will take the following steps to deal with missing data. Whenever possible, we will contact the original investigators to request relevant missing data. If the number of participants evaluated for a given outcome is not reported, we will use the number of participants randomized per treatment arm as the denominator. If only percentages but no absolute number of events are reported for binary outcomes, we will calculate numerators using percentages. If estimates for means and SDs are missing, we will calculate these statistics from reported data whenever possible, using approaches described in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2020). If SDs are missing and we are not able to calculate them from reported data, we will calculate values according to a validated imputation method (Furukawa 2006). If data are not reported numerically but graphically, we will estimate missing data from figures. We will perform sensitivity analyses to assess how sensitive results are to imputing data in some way. We will address in the Discussion section the potential impact of missing data on findings of the review.

Assessment of heterogeneity

Assessment of clinical and methodological heterogeneity within treatment comparisons

To evaluate the presence of clinical heterogeneity, we will generate summary statistics for the important clinical and methodological characteristics across all included studies. Within each pairwise comparison, we will assess the presence of clinical heterogeneity by visually inspecting the similarity of these characteristics.

Assessment of transitivity across treatment comparisons

To infer about the assumption of transitivity, we will assess whether the included interventions are similar when they are evaluated in RCTs with different designs. Furthermore, we will compare the distribution of the potential effect modifiers across the different pairwise comparisons. For each set of studies, grouped by treatment comparison, we will create a table of important clinical and methodological characteristics (e.g. age, sex, and cognitive stage of participants, length of intervention, disease duration, disease severity, physical capability). We will visually inspect the similarity of these factors, including the inclusion and exclusion criteria of every trial in the network. Yet, due to our research question, there is a high diversity of the investigated interventions in the network. However, because of the narrow inclusion criteria, we expect transitivity across our treatment comparisons.

Assessment of statistical heterogeneity and inconsistency

- To evaluate the presence of heterogeneity and inconsistency in the entire network, we will give the generalised heterogeneity statistic Q_{total} and the generalised I^2 statistic as described in Schwarzer 2015. We will use the decomp.design command in the R package netmeta version 1.0-1 or decomposition of the heterogeneity statistic into a Q statistic for assessing the heterogeneity between studies with the same design (R Core Team 2019; Rücker 2019), and a Q statistic for assessing the designs inconsistency to identify the amount of heterogeneity or inconsistency within as well as between designs. To evaluate the presence of inconsistency locally, we will compare direct and indirect treatment estimates of each treatment comparison. This can serve as a check for consistency of a network meta-analysis (Dias 2010). For this purpose, we will use the netsplit function in the R package netmeta version 1.0-1, which enables us to split the network evidence into direct and indirect contributions (R Core Team 2019; Rücker 2019). For each treatment comparison, we will present direct and indirect treatment estimates plus the network estimate using forest plots. In addition, for each comparison, we will give the Z value and P value of test for disagreement (direct versus indirect). It should be noted that in a network of evidence there may be many loops, and with multiple testing there is an increased likelihood that we might find an inconsistent loop by chance. Therefore, we will be cautious when deriving conclusions from this approach.

If we find substantive heterogeneity, inconsistency, or both, we will explore possible sources by performing prespecified sensitivity and subgroup analyses (Subgroup analysis and investigation of heterogeneity). In addition, we will review the evidence base, reconsider inclusion criteria, and discuss the potential role of unmeasured effect modifiers to identify further sources.

We will interpret I^2 values according to Chapter 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2020) as follows:

- 0% to 40% might not be important;
- 30% to 60% may represent moderate heterogeneity;
- 50% to 90% may represent substantial heterogeneity;
- 75% to 100% represents considerable heterogeneity.

We will use the P value of the Chi^2 test only for describing the extent of heterogeneity and not for determining statistical significance. In addition, we will report Tau^2, the between-study variance in random-effects meta-analysis. In the event of excessive heterogeneity that is unexplained by subgroup analyses, we will not report outcome results as the pooled effect estimate of the network meta-analysis but provide a narrative description of the results of each study.

Assessment of reporting biases

In pairwise comparisons with at least 10 trials, we will examine the presence of small-study effects graphically by generating funnel plots. We will use linear regression tests to test for funnel plot asymmetry (Egger 1997). We will consider a P value < 0.1 significant for this test (Page 2020b). We will additionally consider comparison-adjusted funnel plots and the accompanying regression test to assess selection bias. We will examine the presence of small-study effects for the primary outcome only. Moreover, we will search study registries to identify completed, but not published trials.

Data synthesis

Methods for direct treatment comparisons

Pairwise comparisons are part of the network meta-analysis, thus we do not plan to perform additional pairwise meta-analyses. To outline available direct evidence, we will provide forest plots for pairwise comparisons without giving an overall estimate. Only when there are insufficient data to be combined in a network meta-analysis (e.g. in the case of inconsistency), we will perform pairwise meta-analyses according to recommendations provided in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2020). We will use random-effects models. We will use the R package meta for statistical analyses. (R Core Team 2019; Schwarzer 2007). When trials are clinically too heterogenous to be combined, we will perform only subgroup analyses, without calculating an overall estimate.

Methods for indirect and mixed comparisons

Should the data be considered sufficiently similar to be combined, we will perform a network meta-analysis using the frequentist weighted least- squares approach described by Rücker 2012. We will use a random-effects model, taking into account the correlated treatment effects in multi-arm studies. We will assume a common estimate for the heterogeneity variance across the different comparisons. To evaluate the extent to which treatments are connected, we will give a network plot for our primary and secondary outcomes. For each comparison, we will give the estimated treatment effect along with its 95% CI. We will graphically present the results using forest plots, with passive control as reference treatment. We will use the R package netmeta version 1.0-1 for statistical analyses (R Core Team 2019; Rücker 2019).

Subgroup analysis and investigation of heterogeneity

We will consider performing subgroup analyses using the following characteristics, which might have an effect on the outcomes:

- age (< 50 years, ≥ 50 years);
- sex (male, female);
- cognitive stage (participants without cognitive impairment, participants with cognitive impairment);
- length of intervention (< 12 weeks, ≥ 12 weeks).

Sensitivity analysis

We will perform sensitivity analyses to test the robustness of our results by analysing trial results at low overall risk of bias, as judged by using the RoB 2 tool only (Sterne 2019).

Summary of findings and assessment of the certainty of the evidence

Confidence in the evidence

Two review authors [ME, AF] will independently rate the confidence in the evidence in the results of the network meta analyses using the Confidence in Network Meta-Analysis (CINeMA) approach (Nikolakopoulou 2020).

CINeMA considers six domains to be judged:

- within-study bias
- reporting bias
- indirectness
- imprecision
- heterogeneity
- incoherence

'Summary of findings' table

We will include a 'Summary of findings' table to present the main findings in a transparent and simple tabular format. In particular, we will include key information concerning the confidence in the evidence, the magnitude of effect of the interventions examined, and the sum of available data on the following outcomes:

- clinician-rated impairment and disability;
- patient-rated QoL;
- adverse events.

ACKNOWLEDGEMENTS

We would like to thank the members of the editorial team of the Cochrane Movement Disorders Group as well as the Methods Support Unit for their support. We would especially like to thank Gonçalo S Duarte and Kerry Dwan for their helpful comments on the protocol of this review.

This project is funded by the German Ministry for Education and Research (grant no 01KG1902).

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APPENDICES

Appendix 1. MEDLINE search strategy (preliminary)

Medline (via OvidSP)

#	Searches
1	exp PARKINSON DISEASE/
2	parkinson*.tw,kf.
3	or/1-2
4	exp SOFTWARE/
5	software.mp.
6	game.mp.
7	gaming.mp.
8	play*.mp.
9	simulation*.mp.
10	program*.mp.
11	techni*.mp.
12	video.mp.
13	VIRTUAL REALITY EXPOSURE THERAPY/
14	user-computer interface.mp.
15	interactive.mp.
16	virtual*.mp.
17	vr.mp.
18	augmented.mp.
19	exergam*.mp.
20	kinect.mp.
21	nintendo wii.mp.
22	microsoft xbox.mp.

(Continued)

23	or/4-22
24	biofeedback.mp.
25	exp MOVEMENT/
26	movement.mp.
27	exp PHYSICAL THERAPY MODALITIES/
28	exp PHYSICAL FITNESS/
29	fitness.mp.
30	exp MUSCLE STRENGTH/
31	strength.mp.
32	muscle.mp.
33	locomot*.mp.
34	exp BODY WEIGHT/
35	(weight* adj1 body*).mp.
36	(weight* adj2 training*).mp.
37	motor activity.mp.
38	or/24-37
39	exp EXERCISE/
40	exercise*.mp.
41	activit*.mp.
42	sport*.mp.
43	train*.mp.
44	intervention*.mp.
45	condition*.mp.
46	exp PHYSICAL ENDURANCE/
47	endurance.mp.
48	exp GAIT/
49	gait*.mp.
50	postural balance.mp.

(Continued)

51	exp DANCING/
52	danc*.mp.
53	tango.mp.
54	exp MARTIAL ARTS/
55	martial art*.mp.
56	aerobic.mp.
57	(boxing or shadowboxing).mp.
58	treadmill*.mp.
59	karate.mp.
60	exp WALKING/
61	walking.mp.
62	BICYCLING/
63	bicycle*.mp.
64	or/39-63
65	MEDICINE, CHINESE TRADITIONAL/
66	traditional chinese exercise.mp.
67	or/65-66
68	exp MIND-BODY THERAPIES/
69	(mind adj1 body).mp.
70	Tai ji/
71	((chi adj1 tai) or (tai adj1 ji*) or taiji* or taichi* or t'ai chi).mp.
72	(wuqinxi or baduanjin or yijiejing).mp.
73	QIGONG/
74	(qi-gong* or qigong*).mp.
75	((qi* adj2 (gong* or kung* or chung* or gung*)) or (chi* adj2 (gong* or kung* or chung* or gung*))).mp.
76	yoga.mp.
77	(asana or pranayama or dhyana).mp.
78	pilates.mp.

(Continued)

79	or/68-78
80	exp REHABILITATION/
81	rehab*.mp.
82	exp THERAPEUTICS/
83	therap*.mp.
84	physical*.mp.
85	physiotherapy.mp.
86	exercise therapy.mp.
87	exp EXERCISE TEST/
88	exercise test.mp.
89	strengthening program*.mp.
90	progressive resistance training.mp.
91	cardiorespiratory.mp.
92	exp CARDIOVASCULAR SYSTEM/
93	cardiovascular.mp.
94	aqua*.mp.
95	hydrotherapy.mp.
96	(lsvt-big or lsvtbig).mp.
97	("Lee Silverman Voice Treatment" and big).mp.
98	periodicity.mp.
99	socio environmental.mp.
100	(whole body adj1 vibration*).mp.
101	or/80-100
102	23 or 38 or 64 or 67 or 79 or 101
103	randomized controlled trial.pt.
104	controlled clinical trial.pt.
105	randomi?ed.ab.
106	placebo.ab.

(Continued)

107	clinical trials as topic.sh.
108	randomly.ab.
109	trial.ti.
110	or/103-109
111	exp animals/ not humans/
112	110 not 111
113	3 and 102 and 112

key: exp # /: explode # MeSH subject heading, tw: text word. kf: keyword heading word mp: multiple purpose, ti: title, ab: abstract, pt: publication type, *: truncation, ?: wildcard, adj#: adjacent within # number of words
searchline #103-#112 Cochrane RCT-Filter, sensitivity- and precision-maximizing version

HISTORY

Protocol first published: Issue 1, 2021

CONTRIBUTIONS OF AUTHORS

Draft the protocol	MR, FK, ME, EK, NS
Develop and run the search strategy	IM, JH
Obtain copies of studies	FK
Select which studies to include	MR, ME, HL-J
Extract data from studies	MR, ME, HL-J
Enter data into RevMan	FK, ME
Carry out the analysis	AA, MR, ME
Interpret the analysis	MR, FK, ME, HL-J, DC, AA, EK, CE, AD, NS
Draft the final review	All authors
Update the final review	MR, FK, ME, HL-J, DC, EK, NS

DECLARATIONS OF INTEREST

MR: Award of the grant by Federal Ministry of Education and Research for the University Hospital of Cologne to perform this systematic review does not lead to a conflict of interest.

ME: Award of the grant by Federal Ministry of Education and Research for the University Hospital of Cologne to perform this systematic review does not lead to a conflict of interest.

HL-J: Award of the grant by Federal Ministry of Education and Research for the University Hospital of Cologne to perform this systematic review does not lead to a conflict of interest.

FK: None known.

MD: None known.

DC: Award of the grant by Federal Ministry of Education and Research for the University Hospital of Cologne to perform this systematic review does not lead to a conflict of interest.

AA: Award of the grant by Federal Ministry of Education and Research for the University Hospital of Cologne to perform this systematic review does not lead to a conflict of interest.

CE: None known.

IM: Award of the grant by Federal Ministry of Education and Research for the University Hospital of Cologne to perform this systematic review does not lead to a conflict of interest.

JH: None known.

AD: None known.

NS: None known.

EK: Award of the grant by Federal Ministry of Education and Research for the University Hospital of Cologne to perform this systematic review does not lead to a conflict of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- German Ministry of Education and Research (BMBF), Germany

  Grant no: 01KG1902