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Reporting and methodological quality of clinical trials on exercise therapy for Parkinson's disease

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ABSTRACT

Background: Exercise therapy is becoming extremely relevant as a new efficacious intervention in multiple medical fields. Although several clinical trials have reported benefits of exercise therapy for Parkinson's disease (PD), recommendations and prescriptions for its use in clinical practice remain limited.

Objectives: To evaluate the methodological quality and publication rate of clinical trials on exercise therapy for PD.

Methods: We analyzed all clinical trials assessing exercise therapy for PD registered in the WHO International Clinical Trials Registry Platform and the ClinicalTrials.gov registries, from 2000 to 2017. We evaluated the methodological quality of trials using the Cochrane Risk of Bias criteria.

Results: A total of 236 clinical trials were identified. Only 70 (29.7%) trials reported their findings, and 61 (25.8%) had results published in scientific journals. Most trials had an unclear risk of bias concerning incomplete and selective outcome reporting and lacked data on the randomization process, allocation concealment, blinding of participants and personnel, and outcomes assessors. Aerobic capacity was the most frequent type of exercise intervention.

Conclusions: Although a large number of trials on exercise are registered in international portals, the quality of reporting remains suboptimal and only a quarter of trials have their results published in scientific journals. These two factors, in addition to the heterogeneity of the interventions tested and the unsatisfactory reported methodological quality of most trials, compromise the interpretation of study results. Therefore, higher quality clinical trials reports are needed to establish exercise as part of the PD armamentarium.

1. Introduction

Parkinson's disease (PD) is one of the most common age-related neurodegenerative disorders. According to The Global Burden of Disease Study, there are nearly 6.2 million people with PD worldwide and it is expected that this number will double over the next 25 years [1,2].

Although there is still no cure or any treatment that delays disease progression, several pharmacological and surgical therapies were proven to improve symptoms [3]. In recent years, non-pharmacological treatments [4] received increasing attention due to positive results demonstrating an improvement in symptoms compared to available medicines that failed to demonstrate such an effect. Non-pharmacological treatments for PD encompass diverse modalities, such as physiotherapy, speech therapy, occupational therapy, exercise, cognitive training, and nutrition, etc. [5,6].

Despite having different meanings, the terms “exercise” and “physical activity” are often used interchangeably in research findings. Physical activity consists of any bodily movement produced by skeletal muscles that requires energy expenditure. Exercise therapy is a structured, planned and repetitive physical-activity program, prescribed by a doctor or rehabilitation specialist. Such therapy includes voluntary

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muscle contraction and/or body movement with the purpose of relieving symptoms or improving the function and health of the patient, while taking into account his/her current medical condition or disease [7,8]. Several trials and meta-analyses have shown that exercise contributes positively to motor and non-motor (behavior, mood, cognition) symptoms of PD, particularly in mild to moderate stages [9–12].

In the present study, we systematically reviewed the clinical trials available in trial registries and published in the literature regarding exercise therapy for PD. We sought to determine the rate of studies that publish their results in the scientific literature and assess their methodological quality. We also aimed to describe the trends of clinical trials on exercise therapy for PD and understand whether the characteristics of trials impact their publication rate.

2. Materials and methods

2.1. Literature search

We identified interventional clinical trials, registered between 2000 and 2017 on the International Clinical Trials Registry Platform (ICTRP) and the ClinicalTrials.gov clinical trials registries using the term "Parkinson". To retrieve articles linked with the identified trials (including publications of study protocols), we also searched MEDLINE, from its inception to September 2019, using the registries' identification numbers and combinations of the terms "Parkinson", "trial", "exercise", "physiotherapy" and "physical activity". In addition, we hand-searched medical journals for additional reports and attempted to contact the principal investigators (PI) of the studies. Results available in the trial registries or accessible through the indexed manuscript publications were used to classify trial results as positive or negative, based on whether the primary outcomes were statistically significant or not.

2.2. Study selection

All clinical trials evaluating exercise or physical activity for the treatment of PD were included. Trials that simultaneously evaluated both exercise and dietary supplements, drugs, behavior interventions, or passive movements were excluded. Trials that simultaneously evaluated exercise for both PD and other diseases were also excluded. Trials with incomplete data were not excluded. No restrictions were made regarding the phase of the study, study design or recruiting status.

We classified trials into one of three clusters: those for which we could only access the protocol; those with protocol and results; and finally, studies with protocol, results and publication.

2.3. Data extraction and analysis

The following data were manually extracted and recorded in an electronic database: the official title of the trial and its phase, year, sponsor, funder, identification number, intervention type, registration, status, start and estimated end dates, type of study, number of participants, length of treatment intervention (days), location, inclusion criteria, allocation, primary and secondary outcomes, endpoints classification, intervention model, masking, frequency (times *per* week or other), complexity and intensity of exercise (duration of each exercise session, in minutes), and study arms (experimental, placebo, active comparator). Trials with an "unknown" phase were classified by the authors of this study, based on Messier et al.'s [13] classification, adapted to non-pharmacological studies.

In addition, for each trial, exercise was classified into the following types, according to Mak et al. [14] and Baker et al. [15].: muscle strength, aerobic capacity, balance, gait, cueing strategies (external cues provided to facilitate movement initiation and/or continuation, such as lines or markers on the ground and treadmill, music at a preset frequency, among others), complementary exercises (including Tai Chi and dance) and "multimodal" exercise (defined as the use of three or more combined exercise modalities, including flexibility, strength, balance, coordination and/or aerobic training).

Two authors (CMS, AMT) independently performed the selection of trials and the extraction of data. Disagreements among the authors were resolved by consensus or by a third author (JJF).

2.4. Methodological quality and assessment of risk of bias

We used the Cochrane Risk of Bias Tool to assess the methodological quality of each trial [16,17]. This tool evaluates the potential risk of bias in five domains: selection (including randomization and allocation concealment [the steps taken to guarantee strict implementation of the sequence of random assignment and prevent the foreknowledge of the forthcoming allocations]), performance (including blinding of the participants and personnel), detection (including blinding of the outcome assessment), attrition (including incomplete outcome data), and reporting (including selective reporting of results, i.e., the selection of a subset of the original variables recorded, based on the results, for inclusion in publication of trials). Each of the five domains was rated as having a low, unclear, or high risk of bias.

2.5. Statistical analysis

A descriptive statistical analysis was performed to characterize the studies. Standard deviation (SD) and interquartile range were used to evaluate data dispersion. The software Cochrane Review Manager Version 5.3 was used for the risk of bias assessment [18].

3. Results

A total of 446 potentially relevant trials were identified using our search strategy and, after preliminary review, we included 236 clinical trials registered between 2000 and 2017 (Fig. 1). Trials were performed in 27 countries worldwide, mainly Brazil (n = 49, 20.8%), the United States [US] (n = 45, 19.1%), Australia (n = 18, 7.6%), and Italy (n = 18, 7.6%). Most trials were funded exclusively by hospitals, universities, governmental agencies and other public organizations (n = 234, 99.2%). Only two trials (n = 2, 0.8%) were funded by non-public sources.

3.1. Trial registry and dissemination of results

3.1.1. Publication rate in scientific journals

Seventy-seven (32.6%) of the 236 clinical trials evaluated had their study protocol published: 16 (6.8%) trials published the study protocol and no results; 10 (4.2%) trials published the study protocol and shared the results in another publication; 51 (21.6%) trials published the study protocol and results in the same publication. The study protocols were published mainly in the following journals: BMC Neurology (n = 14 of 77, 18.2%, impact factor [IF] 2.233); Pilot and Feasibility Studies (n = 3, 3.9%, source normalized impact per paper [SNIP] 0.877).

Overall, only 61 (25.8%) of the registered trials had their results published in scientific journals: 52 (85.2%) of 61 publications had positive findings and nine (14.8%) had negative results. The majority of publications came from Brazil (n = 11 of 61, 18.0%), the US (n = 10, 16.4%), the United Kingdom [UK] (n = 8, 13.1%), Australia (n = 7, 11.5%) and Italy (n = 6, 9.8%).

Trial results were published mainly as original articles in the following journals: Archives of Physical Medicine and Rehabilitation (n = 7, 11.5%, IF 2.697); Journal of Neurology, Neurosurgery & Psychiatry Research (n = 4, 6.6%, IF 8.272); Journal of NeuroEngineering and Rehabilitation (n = 3, 4.9%, IF 3.582); Parkinson's Disease (n = 3, 4.9%, IF 2.051).

3.1.2. Trial registries

The number of exercise studies registered increased over the years,

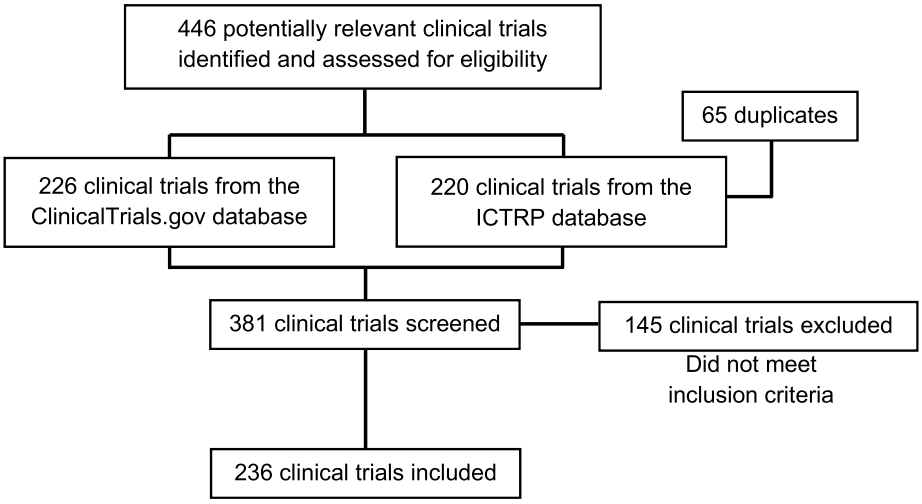

Fig. 1. Flowchart summarizing the stages of research.

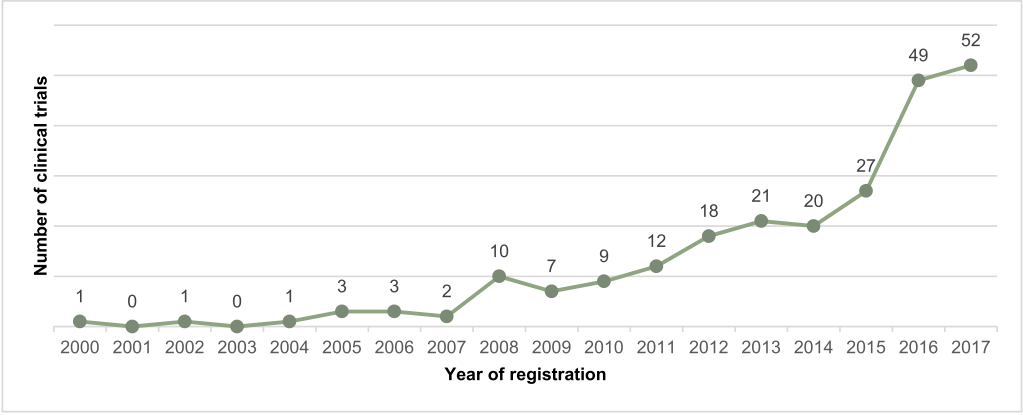

Fig. 2. Distribution of PD clinical trials (with the Intervention "Exercise") by year of registration.

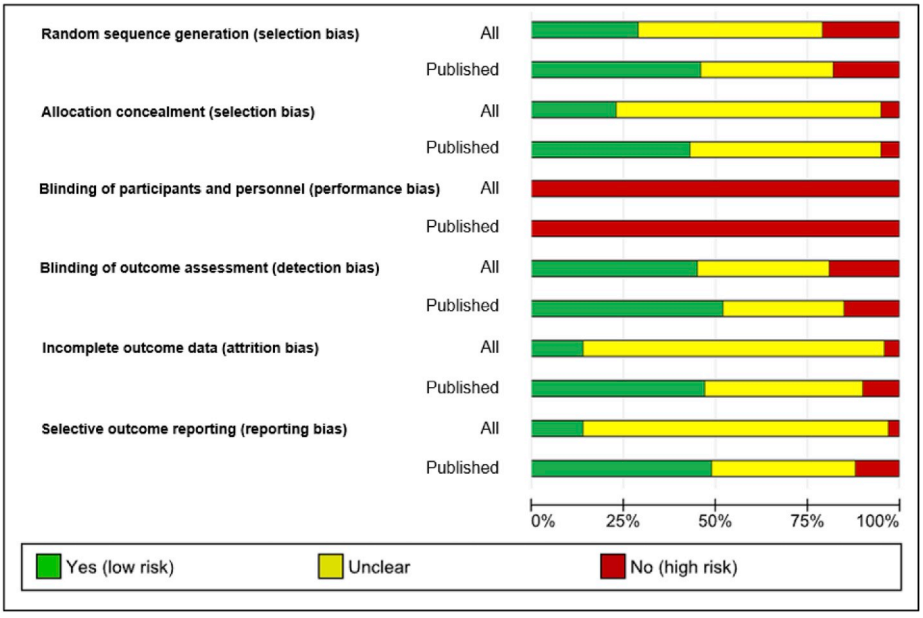

Fig. 3. Review author's judgement about each bias item (based on the Cochrane Handbook for Systematic Reviews of Interventions), presented as percentages across all included studies and published studies.

with the great majority of trials being registered between 2010 and 2017 (n = 208, 88.1%, Fig. 2). Most were accessible on the ClinicalTrials.gov database (n = 145, 61.4%). The distribution of trials according to the phase of development revealed: seven pilot studies (3.0%), 124 phase 1 trials (52.5%), 101 phase 2 trials (42.8%), four phase 3 trials (1.7%) and no phase 4 trials. One hundred and thirty-six trials (57.6%) were classified as completed, 52 (22.0%) as recruiting, 15 (6.4%) as unknown status, 10 (4.2%) as active but not recruiting, and 13 (5.5%) as not yet recruiting. The others were either enrolling by invitation (n = 3, 1.3%), pending (n = 3, 1.3%), terminated for funding reasons (n = 3, 1.3%), or withdrawn (n = 1, 0.4%).

3.1.3. Reporting of results

Of the 236 clinical trials, only 70 (29.7%) reported their results (Fig. S5, Suppl Mat). Overall, 54 (22.9%) trials reported their results directly in trial registries (n = 9, 3.8%) or the link to the publication of results was automatically indexed to the trial registry (n = 45, 19.1%); 16 (6.8%) trials reported the results through publications not yet indexed to the trial registry.

Fifty-five (78.6%) of the 70 trials reported positive results and a total of 15 (21.4%) reported negative findings. The remaining studies (n = 166, 70.3%) did not report their results. By contacting the PI of the studies, we ascertained that one of the 166 studies had positive results (not yet shared in a trial registry, nor published).

3.2. Methodological quality assessment

The analysis of methodological data was not uniform across trial reports and several quality indicators were not discussed in all of them (Fig. 3). Only 117 trials (49.6%) clearly described the process of random sequence generation; of these, 48 trials (20.3%) had a high risk of bias. The remaining 119 (50.4%) were found to have an unclear risk of bias for this criterion. Only 54 trials (22.9%) described the allocation concealment process, whereas the remaining studies had a high risk (n = 11, 4.7%) or unclear risk (n = 171, 72.4%) of bias, since it was impossible to understand the procedures adopted. Regarding blinding of participants and personnel, all studies (n = 236, 100%) were classified as having a high risk of bias, given that it is not possible to effectively blind participants to exercise therapy. Blinding of outcome assessment was performed in almost half of the trials (n = 107, 45.3%); 84 trials (35.6%) had an unclear risk and 45 (19.1%) had a high risk of bias. Only a few trials (n = 34, 14.4%) explained the reasons for missing data, thus being classified as having a low risk of bias for this criterion; in the remaining trials, there was an unclear (n = 193, 81.8%) or high risk of bias (n = 9, 3.8%). Regarding selective outcome reporting, most of the trials had an unclear risk of bias (n = 196, 83%).

Overall, comparing published with unpublished trials, the methodological quality was better in the first group (Table S6, Suppl Mat).

3.3. Trials characteristics

3.3.1. Study design and comparators

Most trials had a parallel-group design (n = 174, 73.7%). Of these, 158 (90.8%) were randomized and 70 (40.2%) were randomized and had a “usual care” control arm.

A total of 148 (62.7%) clinical trials had a comparator group: of these trials, 72 (48.6%) had a usual care comparator, 62 (41.9%) had an active comparator and 14 (9.5%) had a non-intervention comparator (Table S7, Suppl Mat). The most used active comparator was “treadmill gait training”. The comparator was not specified for 42 (17.8%) trials. A total of 46 (19.5%) clinical trials had no comparator group.

3.3.2. Sample

All trials reported information on the number of participants (estimated or actual enrolment). One hundred and sixty-four trials (69.5%) reported the actual enrolment; the median of participants was 40. One hundred and seventy-four trials (73.7%) reported the estimated enrolment, and the median of participants was 50. Data on the mean age of participants enrolled in each trial and the number of dropouts and withdrawals were not found in trial records.

Regarding the characteristics of the published trials: the mean sample size was 90.6 (SD 137.5) [range 6–762] participants, with a median of 40. The most common age group categories of participants were adults and seniors (mainly from 50 to 75 years old). The average dropout rate was 11%.

3.3.3. Eligibility criteria

The criteria for selecting the participants were described in the majority of trials (n = 187, 79.2%). The main diagnostic criteria were the UK PD Society Brain Bank Clinical Diagnostic Criteria (n = 54, 22.9%) and clinical diagnosis of PD by movement disorders experts (n = 34, 14.4%). The Hoehn and Yahr scale was used in the majority of trials (n = 128, 54.2%) to classify disease stage, and trials included mainly PD patients between stages 1 and 3. Other important criteria were: no severe cognitive impairments (score of 24 or higher on the Mini Mental State Examination – MMSE); adequate vision and hearing; ability to walk independently with or without an assistive device; stable medication regimen.

3.3.4. Intervention

The most common frequency of exercise was twice a week (n = 65, 27.5%), followed by three times a week (n = 60, 25.4%). The mean duration of each exercise session was 55 min (SD = 19.6). Overall, 51 distinct types of interventions were assessed. Thirty-six trials (15.3%) assessed aerobic exercise (the most frequently evaluated type of exercise), 26 trials (11.1%) assessed multimodal exercise, 21 (8.9%) evaluated balance and 17 focused on dance (7.2%), corresponding to almost half of the trials. Fig. 4 shows the six most frequent interventions evaluated in trials. The mean length of interventions was 89 days (SD = 107.9). The mean follow-up period foreseen was 4.9 months (SD 4.6).

For the published trials, the mean follow-up period was 5.3 months (SD 5.4). Thirty-nine (63.9%) of the 61 trials published had a follow-up period below 6 months.

3.3.5. Outcomes and assessment tools

Altogether, outcome measures were very different among studies. We focused on the primary outcomes, given their relevance for the methodological quality of studies. The most cited primary outcomes included: change in motor symptoms (n = 20, 8.5%), frequency of falls between baseline and post-intervention (n = 17, 7.2%), improvement in quality of life (n = 16, 6.8%) and change in cognitive performance from baseline to study completion (n = 14, 5.9%). The definition of primary outcomes was unclear in 17 (7.2%) of the clinical trials.

For primary outcome assessment, the most applied tools were: the Unified Parkinson's Disease Rating Scale (UPDRS) (n = 26, 11.1%) – total score (n = 15, 6.4%) or only part III (n = 11, 4.7%), followed by the Berg Balance Scale (n = 20, 8.5%) and the Timed Up and Go Test (n = 18, 7.6%). Other tools included: the Parkinson's Disease Questionnaire (PDQ-39) (n = 12, 5.1%), the Mini-Balance Evaluation Systems test (Mini-BESTest) (n = 12, 5.1%), etc (Table S9, Suppl Mat).

Regarding secondary outcomes, some of the most mentioned included: change in functional endurance (through the 6-min walking test) and change in falls self-efficacy.

4. Discussion

We included a total of 236 clinical trials assessing exercise therapy in PD patients; the majority were conducted in Brazil and in the US. Overall, only 70 (29.7%) trials reported their findings, while 61 (25.8%) trials had their results published in scientific journals. The main journals with publications were: Archives of Physical Medicine

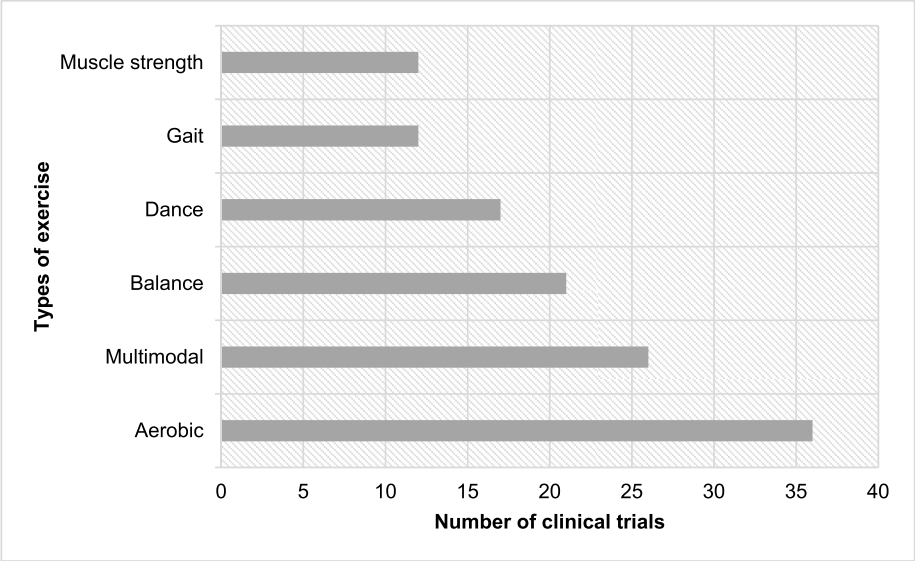

Fig. 4. Ranking of most frequently evaluated interventions.

and Rehabilitation (IF 2.697) and Journal of Neurology, Neurosurgery & Psychiatry Research (IF 8.272). The amount of missing data in the registries (such as trial phase and status, study arms and results) was considerably high.

4.1. Reporting analysis

In our review, only 70 (29.7%) of the 236 clinical trials reported their results; 54 (22.9%) of these were posted in trial registries. This means that nearly 70% of studies did not report their findings. Given that data should be shared instead of remaining unpublished or unreported [19], this percentage is very low and alarming.

As for scientific journals, only 61 (25.8%) of the 236 registered clinical trials had their results published. Eighty-five percent had positive results, supporting the fact that positive results are more likely to get published [20].

We found a publication rate of nearly 26%. In the field of neurology, the overall publication rate was 47.8% [21]. A similar rate was found for other medical areas [22]. A publication rate of 48.4% was also found for drug-evaluating clinical trials approved by a general hospital [23]. These values are significantly higher than ours, which highlights that there is still a huge lack of dissemination of trial results and a significant non-publication rate of trials concerning exercise therapy on PD.

4.2. Methodological quality assessment

The methodological details available in registries were not adequate to perform a complete and detailed evaluation, as some trials didn't describe several quality indicators. The most important issues with methodological quality rely on the fact that many studies fail to report all the results (both negative and positive), do not describe the study protocol and do not fulfil all the criteria for randomization, allocation concealment and blinding. Of note, poor and/or selective reporting can hamper judgments of risk of bias and contribute to the poor methodological quality of the trials, since records in the registries frequently lack information and are incomplete. Therefore, only a complete and detailed reporting of a trial's design, conduct, analysis and results allows its accurate assessment by the readers [24].

Published trials had better methodological quality and significantly lower risk of bias compared to unpublished trials. Methodological quality was also higher in studies where the trial protocol was published. This could be explained by the fact that relevant methodological data included in the study protocol publication are often missing in the trial registry.

4.3. Trends in clinical trials of exercise for PD

The majority of trials we analyzed were registered between 2010 and 2017 (n = 208, 88.1%), indicating an increase in the number of registered trials over the years. Most registered clinical trials were sponsored by public organizations; only two received industry sponsorship [25].

Overall, interventions were very different, including mainly aerobic, multimodal and balance training, which can be justified by the complexity of defining and classifying the distinct types of exercise. The main characteristics of the exercise programs from the included trials were the frequency of exercise (mainly 2 or 3 times a week), the mean duration of each exercise session (55 min) and the mean length of treatment (89 days, i.e. almost 12 weeks). A review by Bhalsing et al. [26] recognized that the sedentary lifestyle of most PD patients could compromise the adherence to these exercise programs, so it is important to keep in mind that exercise levels should be tailored to the patients' capacities.

Primary outcomes were very heterogeneous among studies, which limits the possibility to summarize the evidence of exercise for PD and, consequently, the creation of guidelines and consensus statements. The future definition and validation of a standard set of core outcome measurements for exercise in PD is important to establish comparability.

The mean follow-up period according to trials registries was 4.9 months. For the published trials, it was 5.3 months and 63.9% of the trials published had a follow-up period below the mean. These data suggest the need to conduct studies with a higher duration to clarify the long-term effects of exercise interventions.

4.4. Implications of exercise prescription for PD clinical practice and research

There is a growing interest in exercise as a management strategy for PD, but only a small number of conducted studies report their results in registries or journal publications. There continues to be a significant lack of standardization of the interventions tested and not enough evidence about the most adequate comparators and outcomes that should be used to measure the efficacy of exercise. These data suggest that well-designed and large-scale clinical trials are warranted to

further define the role of exercise in the treatment of PD and provide robust recommendations about the best type, frequency, and intensity of exercise regimens.

In order to improve the reporting and methodological quality of trials on exercise for PD, we suggest the following recommendations: (1) study protocols should be written according to the international standards for interventional trials (e.g. SPIRIT) [27]; (2) participants should be randomly assigned to one of the comparison groups; (3) trials should include a sham-controlled procedure or at least a blind-rater for the primary outcome; (4) trials should have powered samples and explicit sample size calculations; (5) the duration of intervention and follow-up period should be explicit and adequate to the type of interventions and therapeutic indication; (6) the primary outcome should be explicit; (7) the hierarchy of outcomes should be defined *a priori*; (8) drop-outs should be accounted for and described; (9) unsuccessful trials should report their results, even if negative.

4.5. Study limitations

This systematic review has some limitations. First, data were limited to trials registered in the ICTRP and the ClinicalTrials.gov portals and accessible in the MEDLINE database. Some trials may also be ongoing, but not yet registered or published. Second, trial registries are updated periodically, and the reported stage may not correspond to the current status. Third, there is a variable lag between the study end and publication. In our work, we are foreseeing the publication rate from a period of at least 2 years and it can underestimate the intent to report in the cases where manuscripts have been submitted to journals. Fourth, there is a significant amount of missing or unsubmitted data in registries, which compromises the quality of analysis and the interpretation of results. In addition, it is also possible that relevant manuscripts are published in databases other than MEDLINE, underestimating the publication rate.

5. Conclusions

To our best knowledge, this is the first systematic review focusing on clinical trials on exercise registered in international portals for trial registries. Some conclusions emerge from our study: 1) the publication rate is low; 2) the methodological quality of study reports is unsatisfactory; 3) there is a high heterogeneity of interventions and outcomes; 4) most of clinical trials lack a long-term follow-up post-intervention.

Currently, further high-quality clinical trial reports, whose results lead to a standardized and evidence-based exercise prescription for PD, are required. Similarly, a higher publication rate is also mandatory.

Contributors

CS contributed to the study concept and design, acquisition, analysis and interpretation of data; wrote the first draft and critically revised the manuscript and gave final approval of the submitted manuscript. AT contributed to the data acquisition, analysis and interpretation; critically revised the manuscript and gave final approval of the submitted manuscript. RBM contributed to the data acquisition and gave final approval of the submitted manuscript. DC and JJF contributed to the concept and design, interpretation of data; critically revised the manuscript and gave final approval of the submitted manuscript.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.11.011.

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