REVIEW

Effectiveness of Physiotherapy on Freezing of Gait in Parkinson's Disease: A Systematic Review and Meta-Analyses

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ABSTRACT: Freezing of gait is considered one of the most disabling gait disorders in patients with PD. An effective treatment for freezing of gait is missing, thus current management requires a multidisciplinary approach. Among treatment options, physiotherapy is acknowledged to be crucial; however, a systematic review that demonstrates its efficacy is missing. This review aims at examining the short- and long-term effects of physiotherapy in improving freezing of gait in PD patients. Five electronic databases were searched for English-language full-text articles, and only randomized controlled trials were considered. The freezing of gait questionnaire was selected as the primary outcome measure because it is the only validated measure used to evaluate the severity and impact of freezing of gait on patients' daily life. From 1,130 trials, 19 relevant studies, including 913 patients, were selected. The included studies varied for sample size, methodology, and type of intervention. None of the studies had a low risk of bias, but the majority of randomized control trials presented a low risk for at least 6 of 13 biases. Our findings provide evidence for short-term effectiveness of physiotherapy in improving freezing of gait (physiotherapy vs. no treatment: effect size = –0.28 [–0.45, –0.11], P = 0.001; physiotherapy vs. control: effect size = 0.43 [–0.65, –0.21], P < 0.0001), particularly when tailored interventions are applied. These results seem to be maintained at the follow-up examinations (effect size = –0.52 [–0.78, –0.26]; P = 0.001). Promising findings on the potential benefits of physiotherapy in improving freezing of gait were found, although further randomized control trial studies are still needed. Questions remain on the type and duration of intervention that best fits for treating freezing of gait symptom in PD. © 2019 International Parkinson and Movement Disorder Society

Key Words: freezing of gait; Parkinson disease; physiotherapy; randomized controlled trial; review

Freezing of gait (FOG) is defined as "a brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk."[1] In patients with Parkinson's disease (PD), FOG is considered one of the most disabling gait disorders. It is a major cause of falls and injuries that in turn contributes to immobility, loss of independence, and reduced quality of life.[2,3] In the early stages of the disease, approximately 1 in 4 PD patients report FOG episodes and its occurrence increases to up 90% in the advanced stages.[4]

Clinical features and different patterns of FOG are well known.[5] FOG episodes may occur as motor block (i.e., feet are stuck to the floor), leg trembling in place (i.e., fast alternated leg movements mimic a tremor), or shuffling forward steps (i.e., short, crawling, and fast steps). Most commonly, each episode lasts a couple of seconds, but it can be longer (>10 seconds).[6] Despite its relationship with disease severity, FOG symptoms do not correlate with the cardinal features of PD, such as tremor, bradykinesia, or rigidity,[7,8] whereas FOG severity correlates with falls, postural instability,[7] and

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executive dysfunction, especially with set-shifting and conflict resolution.[9,10] Furthermore, in PD patients with FOG, gait is also characterized by high step-time variability,[11] altered bilateral limb coordination,[11,12] small stride amplitude,[13] and also by an increase of cadence, especially during turning.[14]

Even though FOG is widely studied, it is still considered a "mysterious phenomenon" because its pathophysiology is complex and poorly understood.[15]

An effective treatment for FOG is missing, thus current management requires a multidisciplinary approach. Optimizing dopaminergic medication or DBS are considered as potential therapeutic options,[16] whereas physiotherapy and occupational therapy are inserted as valid nonpharmacological treatments.[17]

Regarding physiotherapy intervention, in recent decades, several approaches have been developed in order to improve the management of FOG in PD subjects. Behavioral strategies, such as cueing and self-instructions, have been extensively applied.[18] These approaches are based on teaching patients to shift the control of gait from an "habitual" control to a "goal-directed" one,[19] with the aim to reduce and overcome FOG episodes. Gait training, including dual task situations or environmental factors (e.g., narrow doorways), have been also developed for improving patients' ability to manage complex situations that often trigger FOG.[20] In addition, motor learning-based strategies, such as action observation and motor imagery, have been tested to promote long-lasting effect of physiotherapy intervention. Finally, the advent of new technologies[21-23] (robotics, wearable sensors, and virtual reality) and portable neurostimulation devices[24,25] (transcranial current stimulation) paved the way for the development of new physiotherapy approaches that aim to increase the efficacy of the current interventions.

The overall results suggest that physiotherapy intervention has a positive impact on FOG severity; however, to date, a systematic review that demonstrated its efficacy is missing. Hence, we performed a systematic review and meta-analysis with three main objectives. The first was to evaluate the effectiveness of physiotherapy intervention on FOG symptoms. To this aim, we examined the effect of physiotherapy versus no treatment (meta-analysis 1) or versus control training interventions (meta-analysis 2). The second was to evaluate the strength of the evidence of different category of intervention when trials were grouped together according to the common theoretical basis of the rehabilitative treatment (meta-analysis 3 and 4). Finally, the third objective was to evaluate the impact of rehabilitative interventions over the long term (meta-analysis 5).

Our findings will shed light on extant knowledge of the effectiveness of physiotherapy interventions on FOG, thus providing useful information for clinical practice and directing future investigations for improving FOG symptoms in subjects with PD.

Methods

Protocol Registration

This systematic review was performed according to the Cochrane group recommendations[26] and according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[27] Protocol and details of this systematic review were registered into the International Prospective Register of Systematic Reviews—PROSPERO (https://www.crd.york.ac.uk/prospero/; register number CRD42017076546 and are publicly available (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=128693).

Search Strategy and Selection Criteria

A comprehensive literature search was conducted to examine the effect of physiotherapy intervention on FOG symptoms in subjects with idiopathic PD. The search was performed to find English-language articles published across five electronic databases (Pubmed, PEDro, Scopus, Cochrane, and Web of Science) from inception to March 2019. The following combination of keywords was used: ("physiotherapy" OR "physical therapy" OR "rehabilitation" OR "treatment") AND ("Parkinson's Disease" OR "Parkinson" OR "PD") AND ("Freezing of Gait" OR "FOG") AND ((random* OR control*). A manual search was also performed in the reference list of included articles and previously published reviews, in order to retrieve articles not covered by the databases search.

Eligibility Criteria

Inclusion criteria for study selection were: (1) randomized controlled trials (RCTs; parallel or crossover design) and (2) feasibility and pilot RCT studies, that assess the effectiveness of physiotherapy intervention compared to other intervention or no intervention on FOG symptoms in subjects with idiopathic PD; and (3) provided the FOG questionnaire (FOG-Q)[24,25] or new FOG (nFOG-Q) questionnaire[28] data, available in the article or upon request. Exclusion criteria were: (1) single-session interventions, (2) nonphysiotherapy interventions (e.g., dance, tai-chi), (3) noninvasive brain stimulation or the use of external devices not associated with physiotherapy, and (4) abstract and conference proceedings.

Study Selection and Data Extraction

After removing duplicates, article selection and data extraction were performed by two independent reviewers in accord with an a priori elaborated data extraction checklist. All discrepancies were discussed and addressed by consensus or by a third reviewer inclusion, when there was any disagreement. Steps of the studies selection are detailed in a PRISMA flow diagram (Fig. 1). Data and results from the included studies were extracted using a standard data-recording spreadsheet including: demographic characteristics, H & Y stage, sample size, eligibility criteria, intervention type (experimental and control), intervention characteristics (number, duration, and frequency of physiotherapy sessions), timing of follow-up assessments, and outcome measures.

Data Synthesis and Analysis

The primary outcome measures were determined before the analysis and comprised (1) the FOG-Q and (2) the nFOG-Q, which provide a global measure of the severity and impact of FOG on patients' daily life. To date, the FOG and nFOG questionnaires are considered the only validated and reliable available clinical tests to subjectively assess FOG in patients with PD.[29,30] It is important to notice that the first and the new version of the FOG questionnaires provide an identical total score (n = 24), but differ only for one question (named PART 1) that was inserted in the newest version of the questionnaire to distinguish freezer and nonfreezer patients.

If data were presented as median and interquartile range, median was assimilated to mean and standard deviation (SD) was calculated considering that interquartile range = $1.35 \times$ SD.[26] Studies with a crossover design were analyzed as parallel group RCT, by calculating effects before the point of crossover. First, we determined the overall effect of physiotherapy versus no treatment and physiotherapy versus control interventions by two distinct meta-analyses. Second, in order to evaluate the strength of the evidence for category of intervention, data pooling was performed only when at least two studies were included in a treatment category. Studies were grouped together according to the key components of the physiotherapy interventions. The following categories were identified: (1) cueing training, (2) exercises program (postural and balance exercises), (3) home-based exercises, (4) action observation training, (5) aquatic training, and (6) treadmill training.

The standardized mean difference (SMD; Hedges' g) was calculated for all meta-analyses using a random-effects model to acknowledge the clinical and methodological diversity among trials. Hedges' g is a variation of Cohen's d that corrects for biases attributed to small

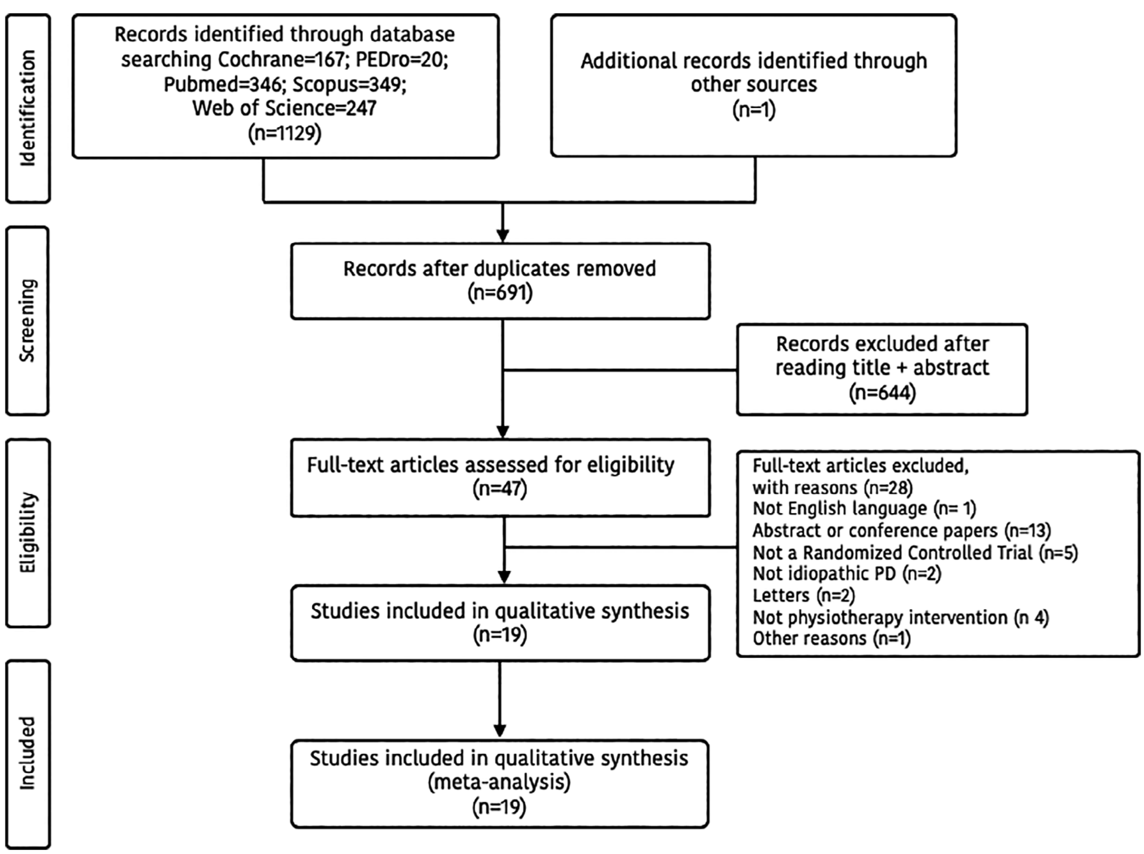

FIG. 1. Flow diagram based on PRISMA statement (www.prisma-statement.org).

sample sizes.[31] The effect size (ES) is expressed as Hedges' *g* with 95% confidence interval (CI). ES ranges from 0.2 to 0.49 were considered to be small, a value of 0.5 to 0.79 was considered to be moderate, and a value of 0.8 or above was considered to be large.[32] Study heterogeneity was assessed using the inconsistency test (I^2), in which I^2 values could be interpreted as follows: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity*; 50% to 90%: may represent substantial heterogeneity*; and 75% to 100%: considerable heterogeneity*.[26]

Finally, to rate the overall quality of evidence and strength of recommendations of each category of intervention, the Grades of Recommendation, Assessment, Development and Evaluation (GRADE)[33,34] approach was applied. In addition, the methodological quality of the included clinical trials was also evaluated with the PEDRO scale (see Supporting Information).

Meta-analytical findings were calculated using Review Manager 5.2 (The Nordic Cochrane Centre, Copenhagen, Denmark). Alpha level was set at 0.05 to test for overall effect.

Risk of Bias

The internal validity of the included studies was assessed using the 13-item tool based on the updated version[35] of the Cochrane Collaboration's Tool for assessing Risk of Bias in RCTs.[28] This tool uses 13 items to assess six different domains of bias: selection bias (criteria 1, 2, and 9), performance bias (criteria 3, 4, 10, and 11), attrition bias (criteria 6 and 7), detection bias (criteria 5 and 12), reporting bias (criterion 8), and "other" (criteria 13) to appraise any type of bias not included in previous items. Each domain was deemed as "low risk of bias" ("green"), "high risk of bias" ("red"), or "unclear risk of bias" ("yellow"). As for study selection, quality assessment was performed by two independent reviewers.

Results

Study Selection and Characteristics

The literature search identified a total of 1,130 results, among which 439 duplicates were removed and 644 studies were rejected according to title and abstract. A total of 47 unique full-text articles were assessed for eligibility. At the end of the screening phase, 28 studies were excluded (reasons for exclusion are reported in Fig. 1), and then 19 studies were included in systematic review (Fig. 1). The total number of subjects in all of the studies combined is sufficiently high (n = 913), but diversity among the studies was high (range, 16–231 participants). Two reviewers (C.C., M.B.) independently reviewed titles and abstracts to identify articles of interest. The Kappa statistic (κ) was used for assessing the inter-rater reliability for the article selection, and results showed a significant level of consensus between the reviewers (κ = 0.85; $P < 0.0001$).

Studies Characteristics

A comprehensive summary of the trials and participants' characteristics is reported in the Supporting Information (Supporting Information Tables S1 and S2). All the 19 studies included were randomized, three[36-38] (16%) were crossover, and 16[39-54] (84%) had a parallel design. Nine trials[36-38,42,43,47-49,53] (47%) had no active treatment as comparator (Supporting Information Table S1), and 10 trials[39-41,44-46,50-52,54] (58%) had an active control group (Supporting Information Table S2). Eleven studies[37,40,41,44-48,50-52] (63%) had follow-up assessment including 506 participants (number of subjects at follow-up: experimental group 220 of 459: 50%; control group 223 of 454: 50%) with the same dropout rate (experimental group 8 of 459: 2%; control group 8 of 454: 2%). Timing of follow-up assessments ranged from 4 to 24 weeks.

The sample size per study was 48.1 ± 54.2 (mean ± SD) with a total of 913 PD participants (age, 69.6 ± 3.4 years; disease duration: 9.4 ± 2.3 years; H & Y: 2.5 ± 0.4, stage; FOG-Q = 11.1 ± 4.3, score). Eleven studies[36,38-41,44-46,48,52,54] (58%) were specifically focused on improving FOG symptoms, whereas eight[37,42,43,47,49-51,53] (42%) evaluated the effect of physiotherapy intervention on PD patients reporting FOG-Q as a secondary outcome measure.

Type of treatment tested in the 19 selected trials was varied: action observation (n = 4),[40,41,45,52] aquatic therapy (n = 3),[39,43,44] cueing (n = 4),[36,37,50,51] exercises program (n = 3),[42,47,48] home-based exercises (n = 3),[38,49,53] and treadmill (n = 2).[46,54] Total number of intervention sessions for each trial differed significantly among the studies (range, 6–72) with a mean ± SD of 22.1 ± 19.3, whereas intensity of training (i.e., number of sessions × week) was quite similar in most of the studies (range, 2–7; mean × week: 3.3 ± 1.5 SD). In 16[36-41,43-48,50-52,54] of the 19 studies, treatment effects were evaluated when patients were in the *on* phase (approximately 30 minutes after having taken the medication), and in the three RCTs left[42,49,53] this information was not reported.

Outcome Measures

Sixteen studies[36,37,39,42-54] used the FOG questionnaire and three[38,40,41] the nFOG questionnaire. In 4[39-41,46] of 19 trials, the FOG questionnaire was the primary outcome measure of the study. Furthermore, all RCTs assessed additional outcome measures which are known to be associated with FOG. Balance and mobility were assessed with Berg Balance Scale in seven studies,[39-41,44,45,52] with the Timed Up & Go test in nine RCTs[37,39-41,44,46,50-52] and with Repeated Chair Stand test in two works.[49,53] Seven RCTs tested gait performance with the 10-m walking test[37,45,47,52] and with the 6-minute walking test.[39,40,54] Fear of falling was measured with the Fall Efficacy Scale International in five RCTs.[37,42,48,49,53] Finally, quality of life, which is strongly associated with the presence of FOG,[55] was evaluated in seven studies with the Parkinson's Disease Questionnaire-39.[37,43,45-47,52,53] Please note that the FOG and nFOG questionnaires were the primary outcome measure of interest for the analysis in this review, regardless if it was declared as primary outcome. Details of outcome measures are reported in the Supporting Information (Supporting Information Tables S1 and S2).

Risk of Bias

Risk of bias graph is reported in Figure 2. None of the studies had a low risk of bias for all 13 methodological items. Briefly, all the RCTs presented a low risk of bias for selective reporting (criterion 8), cointervention (criterion 10), and timing of outcome assessments (criterion 12). Most of the studies (over 90%) had a low risk of bias for random sequence generation (criterion 1), incomplete outcome data (criterion 6), compliance (criterion 11), and other bias (criterion 13). Regarding blinding, all studies were judged at high risk of bias for blinding of personnel (criterion 4), whereas 16 of 19 trials presented a high risk of bias related to the participants (criterion 3) and outcome assessors (criterion 5). For the blinding of outcome assessment, we judged the risk as "high" because, here, patients were identified as the "assessors" given that the primary outcome considered are self-reported questionnaires (FOG-Q and nFOG-Q). Finally, it must be reported that 12 of 19 studies (63%) were not registered on a clinical trial register. Details of the results for each included study are reported in the Supporting Information (Supporting Information Fig. S1).

Effectiveness of Physiotherapy Interventions Versus No Treatment

Overall Effect of Physiotherapy Interventions Versus No Treatment

Nine[36-38,42,43,47,48,53,56] of nineteen RCTs were included in this meta-analysis, with 573 participants (Supporting Information Table S1). Six studies[42,43,47-49,53] had a parallel design, and three trials[36-38] were designed as crossover. All the trials, except one[38] that used nFOG-Q, evaluated FOG severity by means of the FOG-Q. In all the studies, FOG-Q was used as a secondary outcome. The mean number of sessions ± SD was of 28 ± 27.7 (range, 6–72): Training

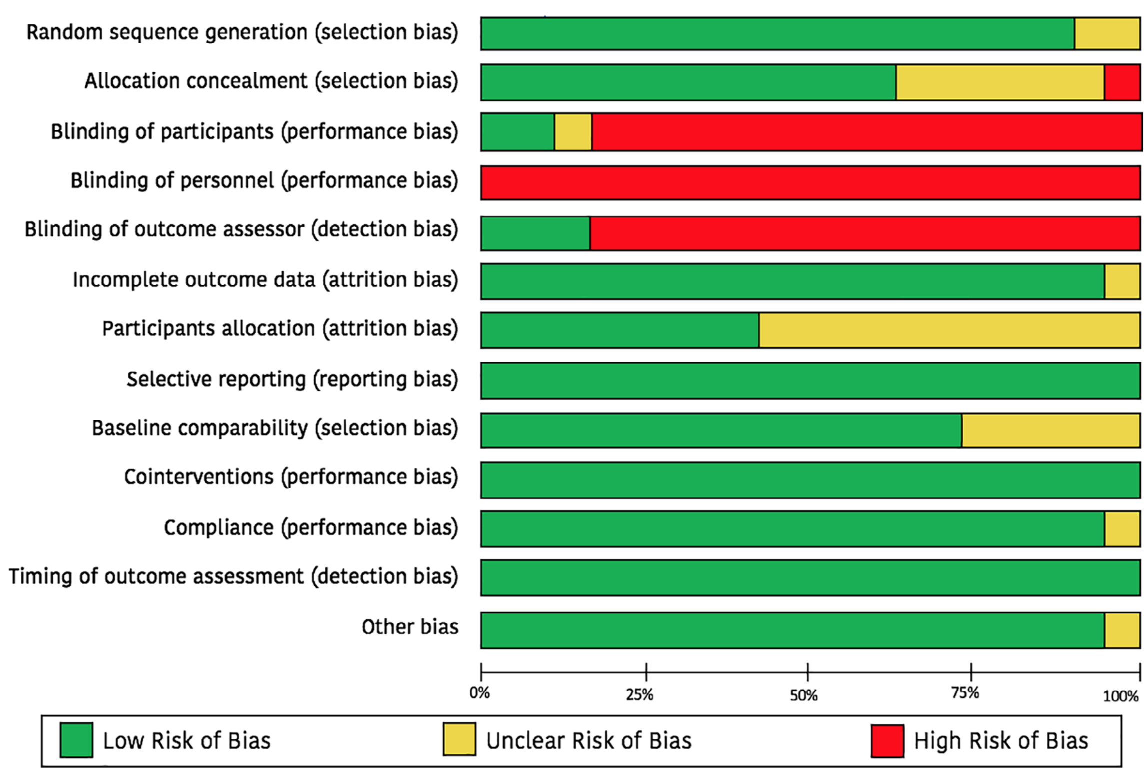

FIG. 2. Risk of bias graph: review authors judgments about each risk of bias item presented as percentages across all included studies. [Color figure can be viewed at wileyonlinelibrary.com]

intensity was sufficiently equal (range, 2–3; mean × week: 3 ± 0.5 SD) whereas session duration varied between 23 and 60 minutes (mean 44 ± 14.2 SD).

Effect of physiotherapy was evaluated by pooling postintervention data, and pooled estimate of the ES showed significant effect in favor of physiotherapy intervention (ES = –0.29 [–0.45, –0,12]; P = 0.0006). Level of heterogeneity was low and not significant (I^2= 0%; P = 0.68). Results are reported in Figure 3A.

Subgroup Analysis

Eight[36-38,42,47-49,53] of nine RCTs, evaluating the effect of physiotherapy interventions versus no treatment, were included in this subgroup analysis, with 552 participants. One study[43] was excluded because it was the unique trial applying aquatic training, and data pooling was performed only when at least two studies were included in each category. Results are reported in Figure 3B. Based on type of treatment, studies were grouped in three main categories: cueing strategies (n = 2),[36,37] exercises program (n = 3),[42,47,48] and home-based exercises (n = 3).[38,49,53] The mean number of sessions for each category was 7.5 ± 2.1 for cueing, 72 for exercises program, and 17.3 ± 6.1 for home-based exercises. Training intensity was similar among categories (around three sessions *per* week) whereas duration of session was, on average, 30 minutes for cueing, 50 minutes for home-based, and varied from 23 to 60 minutes in the exercise program category. Details are reported in the Supporting Information (Supporting Information Table S1).

Subgroups analysis revealed that the ES was significant only for home-based category (ES = –0.30 [–0.53, –0.07]; P = 0.010). The ES of trials applying cueing strategies and exercises program did not show significant results (P always >0.05). The GRADE level for the home-based category was judged as low, whereas for cueing and exercises-based categories it was rated as very low (Table 1).

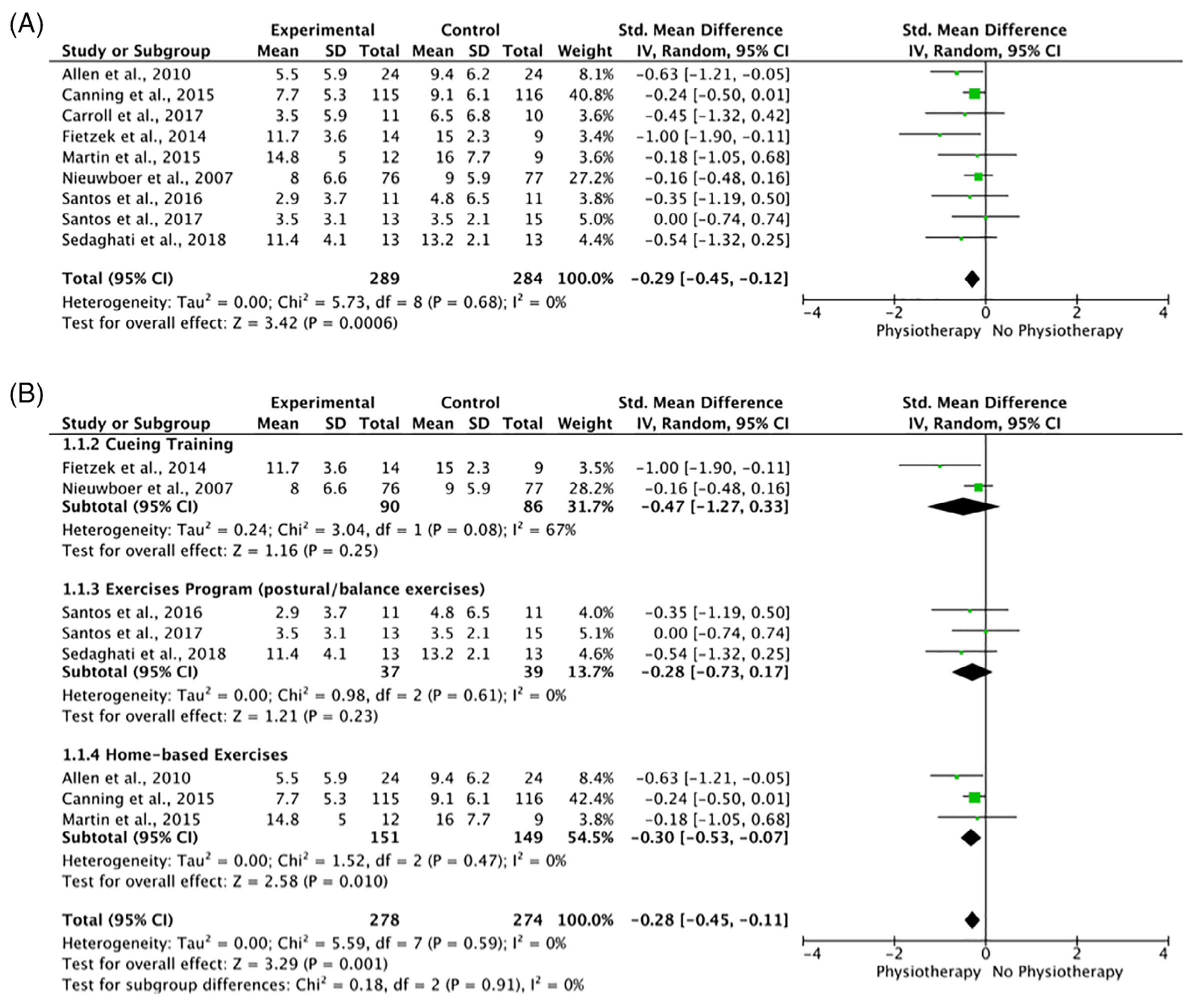

FIG. 3. Forest plots of studies comparing physiotherapy to no treatment. (**A**) Overall effect of physiotherapy vs no treatment. (**B**) Subgroup analysis (category of intervention) comparing the effect of physiotherapy vs no treatment. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1. Quality of evidence for each category of intervention based on GRADE system

Outcome	SMD [95% CI]	No. of Subjects (Studies)	Quality of the Evidence	Comments
FOG: posttreatment Cueing training	SDM –0.47 [–1.27, 0.33]	176 (2 RCTs)	⊕○○○ Very Low	- Downgraded by one level for inconsistency (I^2=67%) - Downgraded by one level for risk of bias - Downgraded by one level for imprecision[b]
FOG: posttreatment Exercises program (postural/balance exercises)	SDM –0.28 [–0.73, 0.17]	76 (3 RCTs)	⊕○○○ Very low	- Downgraded by two levels for risk of bias - Downgraded by one level for imprecision[a]
FOG: posttreatment Home-based exercises	SDM –0.30 [–0.53, –0.07]	300 (3 RCTs)	⊕⊕○○ Low	- Downgraded by two levels for risk of bias
FOG: long-term effect Exercises program (postural/balance exercises)	SDM –0.02 [–0.58, 0.53]	50 (2 RCTs)	⊕○○○ Very Low	- Downgraded by two levels for risk of bias - Downgraded by two levels for imprecision[a,b]
FOG: posttreatment effect Action observation training	SDM –0.40 [–0.76, –0.05]	131 (4 RCTs)	⊕⊕⊕○ Moderate	- Downgraded by one level for risk of bias
FOG: posttreatment effect Aquatic training	SDM –0.48 [–1.24, 0.27]	106 (2 RCTs)	⊕○○○ Very Low	- Downgraded by one level for inconsistency (I^2 = 72%) - Downgraded by one level for risk of bias - Downgraded by one level imprecision[b]
FOG: posttreatment effect Cueing training	SDM –0.32 [–1.10, 0.47]	39 (2 RCTs)	⊕○○○ Very Low	- Downgraded by two levels for risk of bias - Downgraded by one level for imprecision[a]
FOG: posttreatment effect Treadmill training	SDM –0.58 [–1.08, –0.07]	64 (2 RCTs)	⊕○○○ Very Low	- Downgraded by two levels for risk of bias - Downgraded by two levels for imprecision[a,b]
FOG: long-term effect Action observation training	SDM –0.56 [–0.91, –0.21]	131 (4 RCTs)	⊕⊕⊕○ Moderate	- Downgraded by one level for risk of bias
FOG: long-term effect Cueing training	SDM –0.45 [–1.10, –0.20]	39 (2 RCTs)	⊕○○○ Very Low	- Downgraded by two levels for risk of bias - Downgraded by two levels for imprecision[a.b]

Imprecision: **a** = total sample size population small (<100), **b** = wide confidence intervals.
GRADE Working Group grades of evidence.
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Effectiveness of Physiotherapy Interventions Versus Control Interventions

Overall Effect of Physiotherapy Interventions Versus Control Interventions

Ten[39-41,44-46,50-52,54] of 19 RCTs involving 340 participants were included in this meta-analysis. Details of studies are described in the Supporting Information (Supporting Information Table S2). Briefly, FOG-Q was used in eight trials,[39,44-46,50-52,54] and the nFOG-Q was used in two studies.[40,41] In four studies,[39-41,46] FOG-Q or nFOG-Q were declared to be the primary outcome measure, in five studies[44,45,50,52,54] primary and secondary outcome measures were not clearly specified, and in one study[51] FOG-Q was considered as a secondary outcome measure. The total number of sessions (mean ± SD: 17 ± 7.4; range, 10–30) and training intensity, calculated as sessions × week, varied among trials (mean ± SD: 4 ± 1.7; range, 2–7). Duration of each session was similar, except for one study[39] which provided a combination of different exercise programs lasting around 3 hours × day.

The meta-analysis results showed that the ES was statistically significant in favor of the intervention when compared to control treatment (ES = –0.43 [–0.65, –0.21]; $P < 0.0001$). No significant results were found for heterogeneity (I^2= 0 %; P = 0.46). Results are reported in Figure 4A.

Subgroup Analysis

All the 10 RCTs were included in the subgroup analysis. Based on type of treatment, studies were grouped in four main categories: action observation training (n = 4),[40,41,45,52] aquatic training (n = 2),[39,44] cueing training (n = 2),[50,51] and treadmill training (n = 2).[46,54] The mean number of sessions (mean ± SD) varied among categories with a range from 12.5 ± 2.5 in the action observation group to 27 ± 4.2 in the aquatic-based training group. Frequency (sessions per week) was similar in the action observation (mean ± SD: 2.5 ± 0.6) and in cueing studies (mean ± SD: 2.7 ± 0.4) whereas it was higher in the aquatic (mean ± SD: 5.5 ± 0.7) and treadmill training

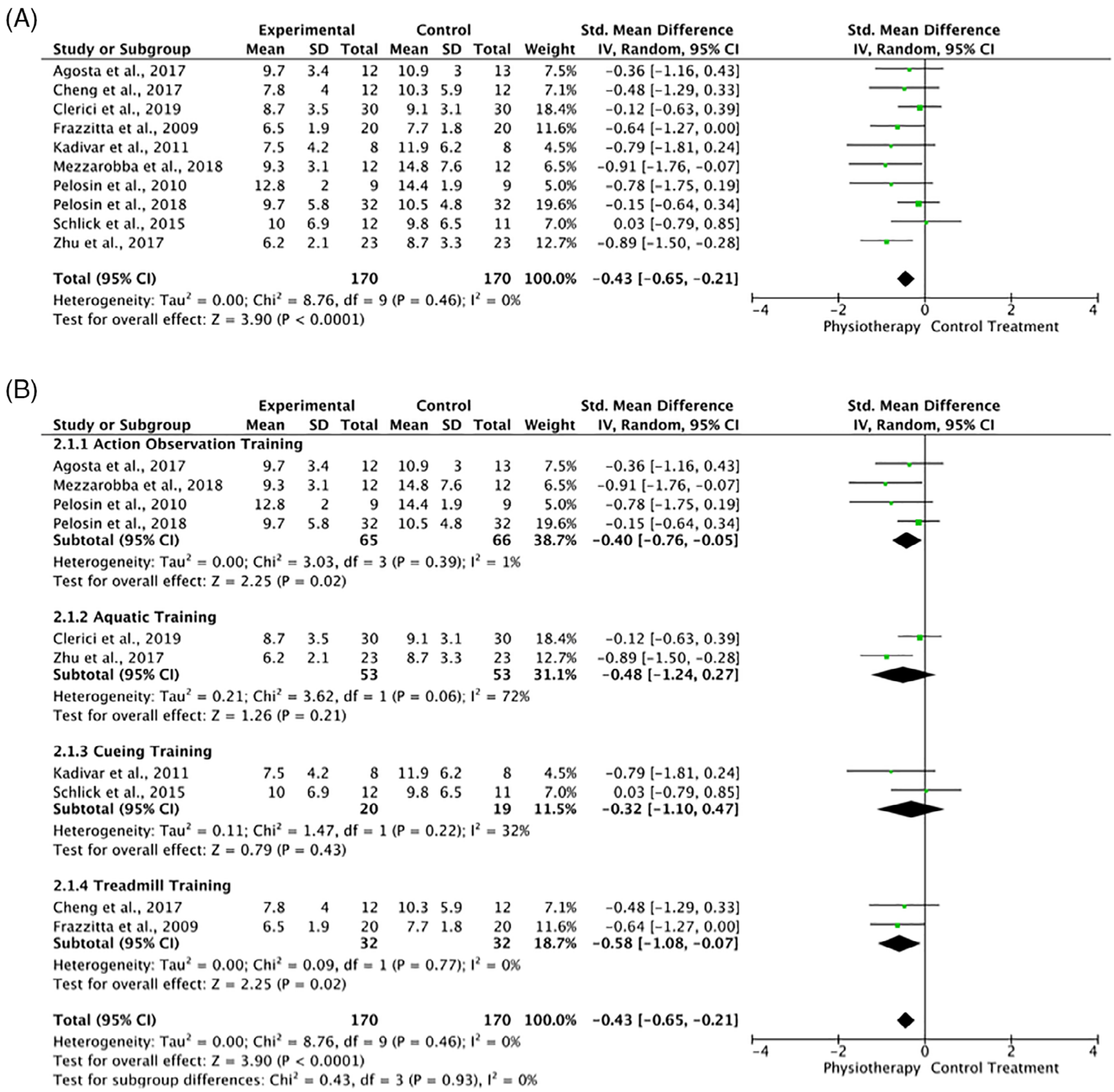

FIG. 4. Forest plots of studies comparing physiotherapy interventions versus control interventions. (**A**) Overall effect of physiotherapy interventions versus control interventions. (**B**) Subgroup analysis (category of intervention) comparing the effect of physiotherapy interventions versus control interventions. [Color figure can be viewed at wileyonlinelibrary.com]

(mean ± SD: 6 ± 1.4) categories. Finally, the duration of the training session (mean ± SD) was quite similar among the overall categories (45 ± 15 minutes × session), except for one study.[39] Details are reported in the Supporting Information (Supporting Information Table S2).

Subgroups analysis for each category of intervention revealed that the ES was significant for action observation therapy (ES = –0.40 [–0.76, –0.05]; P = 0.02) and treadmill training (ES = –0.58 [–1.08, –0.07]; P = 0.02). The GRADE level for studies action observation training was rated as moderate, whereas for treadmill training it was judged as very low (Table 1). The ES for aquatic and cueing training did not show any significant results (P always >0.05). The GRADE level for both categories of intervention was rated as very low (Table 1).

Long-Term Effectiveness of Physiotherapy

In all, 10 RCTs[40,41,44-48,50-52] reported follow-up assessments. Two[47,48] of these 10 trials compared physiotherapy intervention to no treatment, and the remaining eight[40,41,44-46,50-52] evaluated long-term effectiveness of physiotherapy when treatment was compared to a control intervention; therefore, two separate analyses were performed.

Overall Long-Term Effect of Physiotherapy Interventions Versus No Treatment

The first meta-analysis, which involved 50 participants, included only two studies,[47,48] belonging to the exercises program category. None of these studies used the FOG questionnaire as a primary outcome. The study evaluating the effect of cueing[37] was excluded because of the crossover design. The timing of follow-up examination was 4 weeks in both RCTs. Details are reported in the Supporting Information (Supporting Information Table S1).

The analysis for this category of intervention revealed a small ES, and the statistical analysis was not significant (ES = –0.02 [–0.58, 0.53]; *P* = 0.93). The GRADE level for the exercises program category was rated as very low. Results are reported in Figure 5A.

Overall Long-Term Effect of Physiotherapy Interventions Versus Control Interventions

The second analysis was performed on eight studies involving 240 participants. Six trials[39,44,45,50-52] evaluated FOG severity by means of FOG-Q, and two studies[40,41] used the nFOG-Q. In three studies, FOG-Q or nFOG-Q[40,41,46] were reported as the primary outcome measure, whereas in the remaining five RCTs[44,45,50-52] it was considered as a secondary outcome measure.

Timing of follow-up ranged from 4 to 24 weeks. Precisely, four studies[41,45,46,52] evaluated the effect of treatment at 4 weeks, one study[50] at 8 weeks, one at 1, 4, and 8 weeks, one study[40] at 4 and 12 weeks, and one[44] at 24 weeks after the end of the training protocol.

Results of the meta-analysis revealed that the effect was statistically significant in favor of the intervention (ES = –0.52 [–0.78, –0.26]; *P* = 0.0001). Heterogeneity among studies was low and not significant (I^2= 0%; *P* = 0.63). Results are reported in Figure 5.

Subgroup Analysis

Two studies[44,46] were excluded from subgroup analysis because they were unique trials applying treadmill and aquatic training. The subgroup analysis was performed on the following two categories: action observation training (n = 4 studies)[40,41,45,52] and cueing training (n = 2 studies).[50,51] In the cueing category, the follow-up examination was set at 8 weeks in all the trials included, whereas in the action observation category three of four studies collected data 4 weeks after the end of the training, whereas one study scheduled the last follow-up at 12 weeks over. Details are reported in the Supporting Information (Supporting Information Table S2).

Subgroups analysis revealed that the ES was significant for the action observation category and lasted for 6 ± 4 weeks (ES = –0.56 [–0.92, –0.21]; *P* = 0.002). The GRADE level for this category was rated as moderate. Conversely, for the cueing training category, results revealed that the effect size was small and the statistical analysis was not significant (ES = –0.09 [–0.73,0.55]; *P* = 0.78). The GRADE level for this category was rated as very low. Results are reported in Figure 5C.

Discussion

Summary of Evidence

To the best of our knowledge, this is the first systematic review with meta-analysis of randomized controlled trials evaluating the effectiveness of physiotherapy interventions on FOG in subjects with PD.

Nineteen studies, including 913 participants, were included in the analyses: Nine studies[36-38,42,43,47-49,53] compared the physiotherapy intervention versus no treatment (meta-analysis 1), and 10 trials[39-41,44-46,50-52,54] 52,54 compared physiotherapy with an active control condition (meta-analysis 2). Furthermore, the trials were grouped into six categories according to the common scientific underpinnings of each study, and the strength of the evidence was evaluated for category of interventions (meta-analysis 3 and 4). Finally, 10[40,41,44-48,50-52] of 19 studies reported data for follow-up examinations (290 participants) and were analyzed to investigate long-term effects on FOG symptoms: Two trials[37,47,48] compared physiotherapy to no treatment, and eight[40,41,44-46,50-52] compared physiotherapy versus control intervention (meta-analysis 5).

Our results provide evidence that physiotherapy is effective in improving FOG in the short term when compared with no intervention. Furthermore, meta-analysis yielded a greater standardized ES on FOG for the effect of interventions tailored for PD subjects when compared to conventional treatments. Finally, although long-term effect was explored in a small sample, a significant ES was found, suggesting that physiotherapy might impact on FOG symptoms for a time of at least 4 weeks from the end of the intervention.

Effectiveness of Physiotherapy Versus No Treatment on FOG

In this first analysis, nine trials[36-38,42,43,47-49,53] were included with a total of 573 participants. The type of intervention used in these studies was heterogeneous. Trials differed for the total duration of the treatment and for delivery forms (e.g., one-to-one, group- or home-based). Conversely, interventions were similar for the number of sessions per week and for the duration of each single session (around 45–60 minutes). Only in three studies[36,37,48] the duration of each single session ranged from 20 to 30 minutes.

In all, our results demonstrated that the effect provided by physiotherapy was superior to no treatment, suggesting that different types of interventions can succeed in reducing FOG symptoms in subjects with PD. It is noteworthy to observe that some studies[36,49,53] contributed to the ES significantly more than other studies. Indeed, when we separately analyzed the ES for each category of intervention, prolonged home-based interventions (i.e., around 4 months), which include

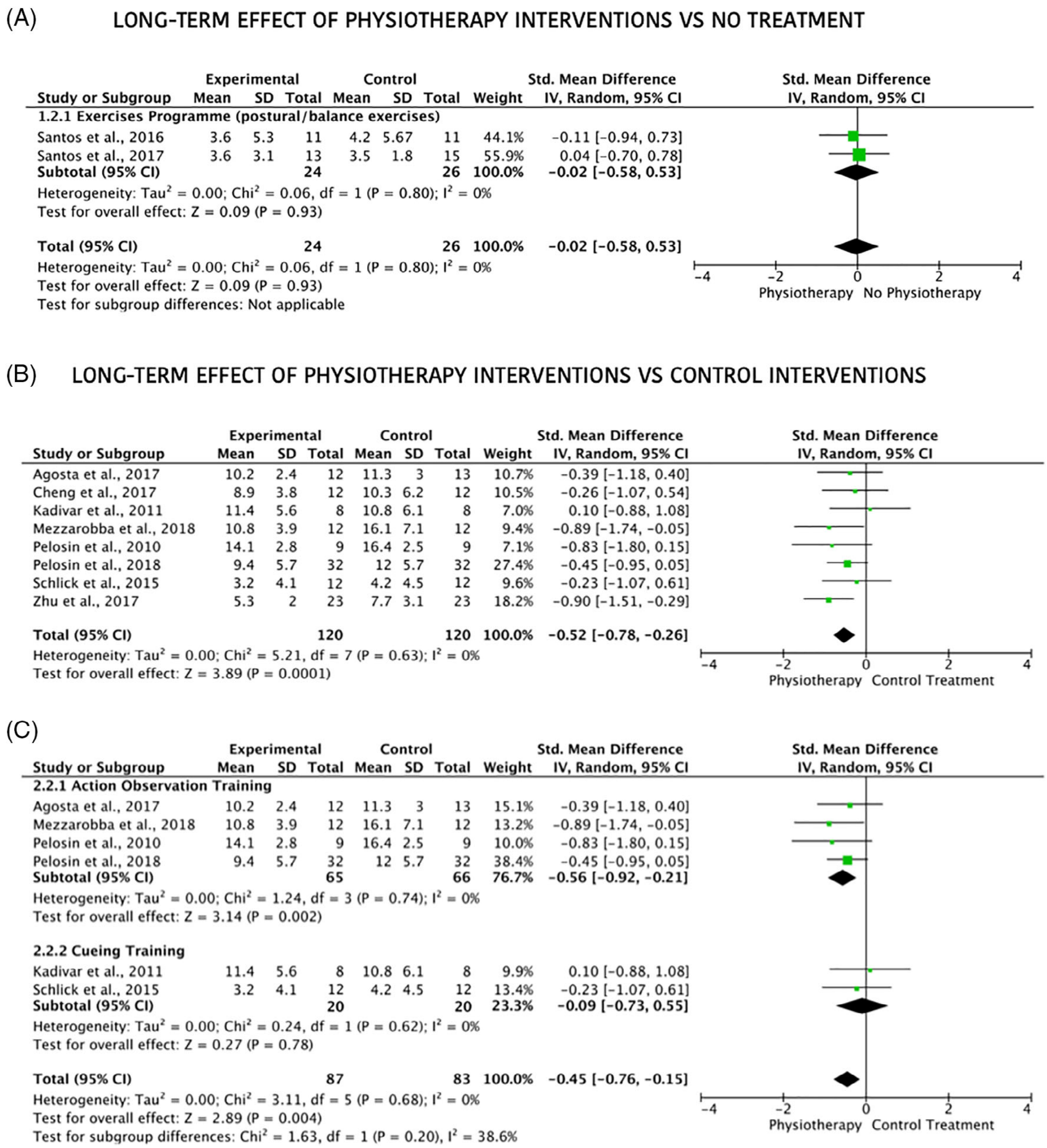

FIG. 5. Forest plot of studies comparing long-term effectiveness of physiotherapy. (**A**) Long-term effect of physiotherapy versus no treatment. (**B**) Overall long-term effect of physiotherapy interventions versus control interventions. (**C**) Subgroup analysis (category of intervention) comparing the long-term effect of physiotherapy interventions versus control interventions. [Color figure can be viewed at wileyonlinelibrary.com]

exercises for balance and gait and cueing, showed a more prominent ES. In contrast, the effect of shorter exercise program, including balance and postural exercises and cueing training, was not significant. This finding might suggest that, in order to impact FOG to a greater extent, an extensive intervention based on teaching behavioral strategies in a variety of environmental situations, which includes gait training and cueing, might be required.

Evidence for a superior effectiveness of physiotherapy compared to no treatment in improving FOG has also been consistently reported in a wide number of previous pilot or not randomized studies. In addition, previous narrative reviews[17,57,58] highlighted that a multidisciplinary approach, which include pharmacological, surgical, and nonpharmacological (i.e., physiotherapy, occupational-therapy, and cognitive-emotional interventions) therapies, is essential for a successful positive impact on FOG symptoms. Nevertheless, the quality of current literature remains low. Indeed, the majority of the published studies do not have a randomized-controlled design and varied for sample size and outcome measures. Therefore, a formal comparison among different physiotherapy approaches cannot yet be performed.

Effectiveness of Physiotherapy Versus Control Interventions on FOG

In this second analysis, we reviewed 10 studies[39-41,44-46,50-52,54] including 340 subjects with PD. The interventions applied were various (i.e., action observation, aquatic, cueing, and treadmill training), but quite similar for treatment period, duration, and frequency of training sessions. Only in one study[39] the time per day dedicated to training (around 3.5 hours) was significantly higher compared to the other trials (on average, 45 minutes). Finally, in three[39,44,54] of 10 studies, the total number of sessions (on average, ~n = 25) was different with respect to the other trials (on average, ~n = 13).

Overall, our results demonstrated that physiotherapy interventions tailored for PD led to greater improvement on FOG severity with a significant reduction in the FOG-Q score when compared to conventional treatment. Furthermore, subgroup analysis revealed that some categories of intervention reported a superior effect on FOG symptoms compared to others. Indeed, both trials based on action observation and treadmill training were able to significantly reduce FOG-Q scores. Vice versa, interventions based on aquatic and cueing training failed in inducing significant changes on FOG.

Previous reviews[59] suggested that action observation training could represent a new therapeutic technique to improve motor performance and promote motor learning in PD subjects. Action observation combined with a training program can enhance the effect of physiotherapy by recruiting cortical and subcortical circuits (i.e., the mirror neurons system) together with peripheral circuits activated by one's own execution of the movements.[60] Our results provide evidence that action observation training might be a potentially effective approach to reduce FOG when exercises are focused on teaching specific motor skills, such as strategies to circumvent freezing episodes.

For treadmill training, several RCTs demonstrated that this type of intervention is effective in improving gait, balance, and significantly reduced falls in PD subjects. This meta-analysis suggests that treadmill training could also be considered a useful approach for improving FOG symptoms. Although this result should be interpreted with caution because of the small number of studies, one possible explanation is that the treadmill-induced changes on gait parameters (i.e., speed and stride length) might indirectly reduce FOG episodes. Another hypothetical explanation could be that both studies included in this analysis were specifically designed to improve FOG symptoms and did not apply a "conventional" treadmill training. In one study,[54] treadmill training was associated with auditory and visual cues, whereas Cheng and colleagues[46] used a turning-based treadmill as a tailored intervention for improving a specific task (i.e., turning) that is known to be a motor action that can often trigger freezing.

Unexpectedly, our results revealed that the ES for cueing training was not significant in improving FOG. This finding is in conflict with those summarized in a recent narrative review by Ginis and colleagues,[18] who suggested that interventions based on cueing are effective in improving FOG symptoms. Noteworthy in the present meta-analysis, we included only two RCT studies, even if we are aware that the majority of studies assessing the effect of cueing training on FOG symptoms are not controlled studies. Further RCTs studies are needed to better clarify the effectiveness of cueing training in improving FOG symptom.

Long-Term Effectiveness of Physiotherapy on FOG

Regarding the long-term effect of interventions, we performed two separate meta-analysis, including two[47,48] and eight studies[40,41,44-46,50-52] respectively. The ES of the first analysis, in which we compared physiotherapy versus no treatment, was not significant, revealing that the positive results obtained immediately after the exercise program training vanished after a period of 4 weeks. Nevertheless, it should be noticed that the number of studies included in this analysis is very small; thus, caution should be taken when interpreting this result.

The second analysis included eight studies, comparing the long-term effect of physiotherapy interventions versus control interventions. The overall results showed a significant and a large effect in favor of physiotherapy compared to general exercise, suggesting that improvements in FOG can be maintained over time (around 6 weeks; range, 4–12) when a tailored training is applied. Longer effect was noted in only one study, based on intensive aquatic training[44] (30 sessions), where positive results on FOG were retained up to 6 months. Furthermore, subgroup analysis revealed that interventions based on action observation are the most effective in inducing long-lasting effects (at least for 4 weeks), whereas positive results obtained by cueing training vanished at follow-up examinations. Together, these results suggest that tailored interventions may be able to induce motor-learning processes with a positive impact on motor performance. Nevertheless, it is well known that the retention of improvements (in terms of motor performance) relies not only on the type of training, but also depends on how subjects keep practicing exercises at home.[61] The lack of this information, together with follow-up timing and intervention protocols heterogeneity, undermines a qualitative comparison among studies included.

Quality of Evidence

Based on the GRADE system, the quality of each category of intervention was classified as very low, except for action observation (moderate) and home-based categories (low). Therefore, a formal analysis of the strength of clinical recommendations was not conducted. The most frequent limitations identified were the following: lack of blinding of personnel, participants and outcome assessor, small sample size, allocation concealment, high value of confidence interval, and participants allocation. However, it is important to notice that some methodological issues detected, such as sample size and blinding of personnel, are difficult to face because they represent limitations common to physiotherapy trials in general. In addition to that, the level of the quality was downgraded for the blinding of outcome assessor because the primary outcome measure for this meta-analysis was a self-reported questionnaire. Nevertheless, encouraging results of some well-designed trials applying motor-cognitive strategies (such as action observation and treadmill combined with cueing) or prolonged home-based exercises support further exploration.

Study Strengths and Limitations

Advances in the field of physiotherapy interventions aimed at improving FOG will only occur if efficacy for treatment is demonstrated. To this aim, we designed a review where only studies with a RCT design were included and trials with a not proper number of training sessions (e.g., $n < 5$) or assessing the efficacy of recreational activities training (e.g., dancing or tai-chi) were excluded in order to provide a clearer picture of current findings on physiotherapy. Furthermore, to help in setting future directions for clinical applications and research, the included studies were categorized based upon the common theoretical basis of different interventions, and the effect of each category was also reported.

Some limitations related to this meta-analysis deserved to be discussed. First, the primary outcome measure selected for evaluating FOG is a self-reported questionnaire. We were aware about the inherent limitations of a questionnaire; however, we selected the FOG-Q because it is the only validated clinical test used to assess FOG and its impact on patients' daily-life activity.[15] Second, because of the large heterogeneity of the follow-up period, a precise estimation about the duration of the effectiveness of physiotherapy could not be granted. Third, the literature search was limited to English-language articles, as in most available meta-analyses.

Conclusions and Future Direction for Rehabilitation

This review provides evidence that physiotherapy interventions have a greater impact on freezing compared with no treatment or usual care. Furthermore, when the analysis for category of intervention was performed, it emerges that action observation, treadmill combined with cueing, and prolonged home-based exercise trainings are able to impact on FOG more than other approaches. Indeed, cueing, postural, and balance-based exercises failed in achieving superior results on FOG compared to control interventions. However, our results were based on a limited sample of trials, and none of the categories had a sufficient number of studies not to support conclusive evidence for effectiveness of a specific approach and to define specific recommendations for clinical practice. Questions remain on the type and duration of intervention that best fits for treating FOG symptoms and on the generalizability of this result across the different stages of the disease.

Nevertheless, taking together our results offer some hints of reflection. First, to achieve effective results, interventions should be FOG specific as well as intensive and prolonged (home-based) in order to foster motor learning and promote long-lasting effects. Second, the combination of different approaches, tailored on patients' abilities and needs, could be more successful in reducing FOG than conventional approaches. Third, based on recent evidence showing that executive dysfunction and mood disturbances are known to exacerbate FOG symptoms,[62,63] a multidisciplinary approach (e.g., including a cognitive behavioral intervention) should be considered.

Finally, to draw recommendation for clinical practice, further progress still needs to be achieved: (1) increase of high-quality randomized trials with larger samples of patients recruited, (2) optimizing the timing of follow-up examination, (3) upgrading of evaluation and detection of FOG episodes, and (4) identify a proper control condition, although it is well recognized that it is hard to set up a credible placebo for rehabilitation.[64,65]

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.