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Non-Pharmacological Treatments in Lewy Body Disease: A Systematic Review

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Keywords
Lewy body disease · Dementia with lewy bodies · Parkinson's disease dementia · Rehabilitation treatments · Non-pharmacological treatments

Abstract

Introduction: Lewy body disease (LBD) is the second most common neurodegenerative disorder in patients older than 65 years. LBD is characterized by heterogeneous symptoms like fluctuation in attention, visual hallucinations, Parkinsonism, and REM sleep behaviour disorders. Considering the relevant social impact of the disease, identifying effective non-pharmacological treatments is becoming a priority. The aim of this systematic review was to provide an up-to-date literature review of the most effective non-pharmacological treatments in patients with LBD, focussing on evidence-based interventions. ***Methods:*** Following PRISMA criteria, we carried out a systematic search through three databases (PubMed, Cochrane Libraries, and PEDro) including physical therapy (PT), cognitive rehabilitation (CR), light therapy (LT), transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), deep brain stimulation (DBS). All studies were qualitatively assessed using standardized tools (CARE and EPHPP). ***Results:*** We obtained a total of 1,220 studies of which 23 original articles met eligibility criteria for inclusion. The total number of LBD patients included was 231; mean age was 69.98, predominantly men (68%). Some PT studies highlighted improvements in motor deficits. CR produced significant improvements in mood, cognition, and patient's quality of life and satisfaction. LT outlined a partial trend of improvements in mood and sleep quality. DBS, ECT, and TMS showed some partial improvements mainly on neuropsychiatric symptoms, whereas tDCS provided partial improvements in attention. ***Conclusion:*** This review highlights the efficacy of some evidence-based rehabilitation studies in LBD; however, further randomized controlled trials with larger samples are needed to provide definitive recommendations.

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Introduction

Lewy body disease (LBD) is a neurodegenerative disorder characterized by a clinical spectrum in which dementia with Lewy bodies (DLB) and Parkinson's

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disease dementia (PDD) represent different points of the disease continuum [1, 2]. Both DLB and PDD share common clinical manifestations like motor symptoms, cognitive impairments (mainly attentional, executive, and visuoperceptual deficits), sleep disorders, and neuropsychiatric symptoms [3]. Despite these similarities, the timing of the clinical presentation could differentiate the two syndromes according to the 1-year rule recommended by the international consensus of the Dementia with Lewy Bodies Consortium. DLB should be diagnosed when dementia occurs before or concurrently with Parkinsonism, whereas PDD should be diagnosed when dementia occurs in the context of well-established Parkinson's disease [4].

The prevalence rate of LBD is considerable, being the second most common neurodegenerative disease in older people, although diagnoses of DLB and PDD are often delayed and could be under-recognized [5, 6]. Clinical manifestations of LBD may be very heterogeneous in terms of symptomatology and timing of presentation across individuals, making the treatment management difficult. For instance, DLB and PDD might respond differently to the same treatments, underlining the importance of an accurate diagnosis [3]. Furthermore, pharmacological interventions may present the intrinsic risks of improving one symptom but worsening another (e.g., a pharmacological intervention addressing neuropsychiatric symptoms may exacerbate motor symptoms and vice versa) [7].

In this perspective, identifying effective non-pharmacological treatments to slow down the worsening of the disease, thus improving both patients and caregivers' quality of life should be a priority. In recent years, there have been a growing number of non-pharmacological trials involving LBD patients, although no definitive recommendations are provided. In a previous systematic review, Inskip and colleagues [8] collected all physical therapy (PT) interventions for LBD patients presented in the literature, and they concluded that these treatments showed some improvements in gait speed, although the quality of the studies was low and with a restricted number of participants. Other two systematic reviews focused on non-pharmacological interventions in LBD and presented a very heterogeneous range of treatments [9, 10]. Both reviews identified possible benefits of non-pharmacological interventions, although the studies highlighted several limitations due to the small sample sizes and the low quality of the study designs. The aim of the present systematic review was to provide an up-to-date literature review of the most effective non-pharmacological treatments in patients with Lewy body disease, focussing on evidence-based interventions.

Methods

The systematic review was conducted according to the PRISMA guidelines [11].

Eligibility Criteria

For the selection of the studies, PICOS inclusion criteria were followed: population, intervention, comparison, outcome measures, and study design. Only original articles written in English language were included.

The target population was patients with a diagnosis of DLB [4] or PDD [12], both pathologies included under the umbrella term Lewy body disease. Therefore, individuals with different age, gender, and ethnicity with a clinical diagnosis of DLB or PDD were included. Studies that explored the efficacy of non-pharmacological interventions without separately reporting outcomes for LBD were not included. For the purpose of the present review, we included non-pharmacological interventions concerning the following domains: PT, cognitive rehabilitation (CR), light therapy (LT), transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), deep brain stimulation (DBS). Studies reporting any other non-evidence-based treatments, such as musical therapy or psychoeducational interventions, were not included. All selected studies contained quantitative and/or qualitative outcome measures as indicators of the treatment's efficacy.

Search Strategy

A systematic search was conducted in March 2022 through the following three free databases: PubMed, Cochrane libraries, and PEDro (Physiotherapy Evidence Database). All selected terms (MeSH terms) were written combining appropriate syntax for each database (see online suppl. material at www.karger.com/doi/10.1159/000529256). No filters were applied to the search nor to the records extracted from databases.

Study Selection

Two independent reviewers (L.G. and M.M.) performed separately the study selection to guarantee the consistency of the results. The first step, after extracting all records from the three databases, was to remove all duplicates using Python software (https://www.python.org/). The second step was reading the titles and the abstracts of the studies and excluding those presenting unrelated topics. After this preliminary screening process, a final pool of articles was read in full and those that followed the eligibility criteria were included in the review.

Quality Assessment

The quality of the studies included was also assessed independently by two reviewers (LG and MM) using standardized tools for case reporting: "CARE criteria checklist" [13] and the "Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies" [14]. Any disagreements between reviewers were resolved through discussion.

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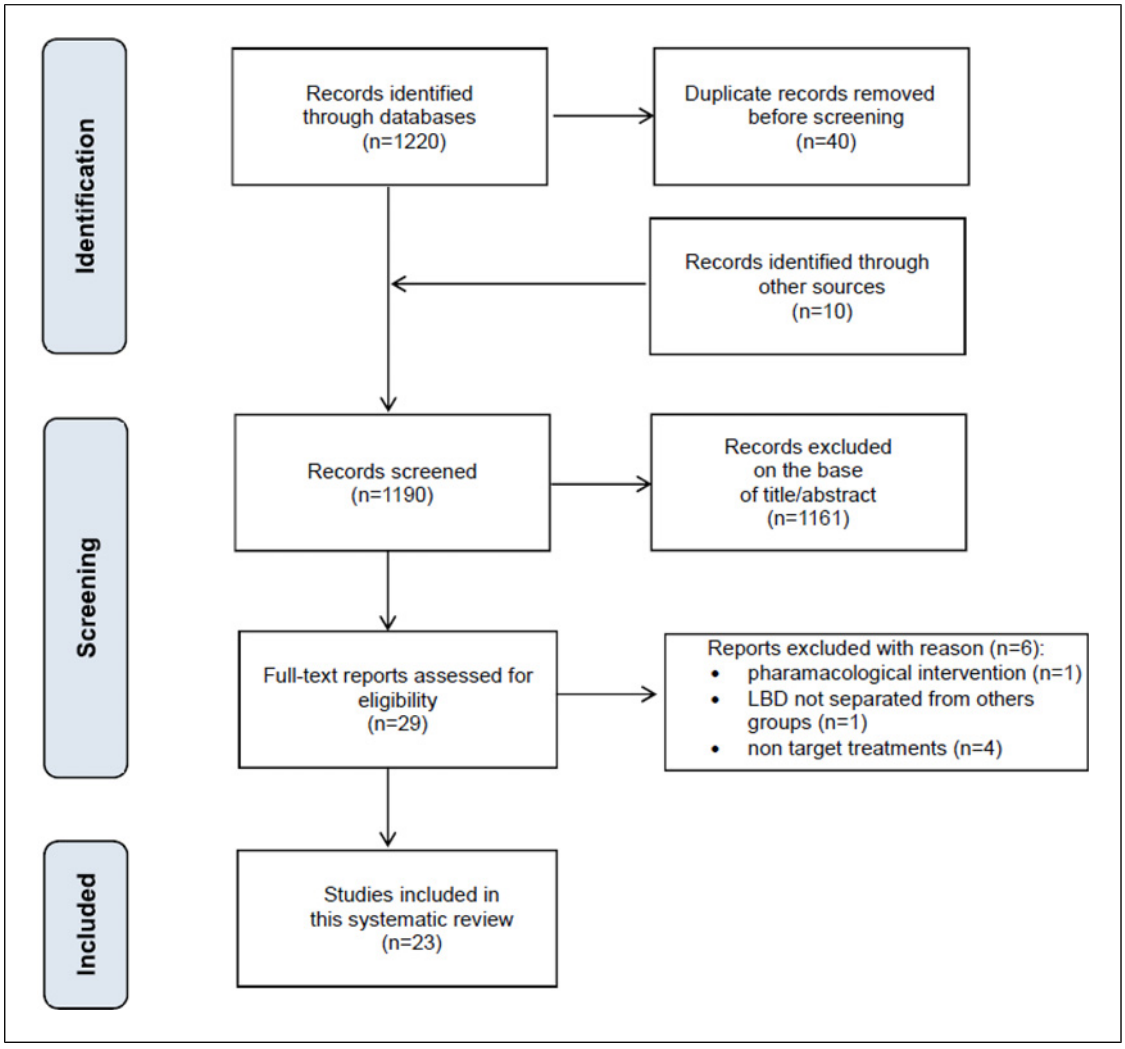

Fig. 1. PRISMA flow diagram of the systematic review.

Results

Study Selection

The systematic search identified a total of 1,220 records from the three databases (PubMed, Cochrane Libraries, and PEDro) of which 1,180 were unique and 40 duplicates. Other 10 additional studies were identified through the reference list of the selected papers and previous reviews on this topic. After excluding articles unrelated to our topic, 29 studies were read in full, and a final number of 23 studies met the eligibility criteria, shown in the flowchart (see Fig. 1). The included studies were 8 randomized controlled trials, 7 uncontrolled trials, and 8 case studies.

Quality Assessment

All following trials (n = 15) were evaluated with EPHPP quality assessment tool [14]: three received strong global rating, other three a moderate global rating, and the majority (n = 9) received a weak global rating. Most frequently, these studies failed to control for confounders (n = 8), blinding condition (n = 7) and others do not provide a control group (n = 10). All case studies (n = 8), evaluated with CARE checklist [13], did not provide a patient's history organized as a timeline. Furthermore, due to the intrinsic nature of case studies, some biases are clearly present (e.g., selection bias, confounders, and blinding).

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Table 1. Characteristics of LBD patients included in this systematic review

Citation	Study design	Number of participants	Age of participants mean (SD)	Gender	Reported diagnosis	Medications during treatment
PT						
Tabak et al. [20] 2013	Case study	1	61	1 M	PDD	Carbidopa + levodopa
Dawley et al. [19] 2015	Case study	1	57	1 M	LBD	Carbidopa/levodopa; antidepressant; antipsychotic
Telenius et al. [18] 2015	Randomized controlled trial	4	84 (10)	1 M; 3 F	PDD	NR
Longhurst et al. [17] 2020	Uncontrolled trial	35	77 (6)	24 M; 11 F	DLB	NR
Kegelmeyer et al. [21] 2021	Uncontrolled trial	8	83.57 (6.58)	4 M; 4 F	LBD	NR
CR						
Hindle et al. [22] 2018	Randomized controlled trial	29	76.34 (6.42)	23 M; 6 F	25 PDD; 4 DLB	Levodopa (all patients) + cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists (9/29)
LT						
Sekiguchi et al. [15] 2017	Uncontrolled trial	5	74.4 (7.3)	3 M; 2 F	DLB	Aripiprazole (1/5); tiapride (1/5); sodium valproate (1/5); rivastigmine (1/5); galantamine (1/5); quietapine (3/5)
Akkaoui et al. [23] 2019	Case study	1	63	1 M	DLB	Verapamil
tDCS and TMS						
Elder et al. [26] 2016 tDCS	Uncontrolled trial	13	64.81 (7.9)	10 M; 3 F	8 PDD; 5 DLB	Cholinesterase inhibitors (1/13); antidepressants (3/13); levodopa (all patients)
Elder et al. [27] 2017 tDCS	Randomized controlled trial	38	66.63 (8.39)	27 M; 11 F	PDD	Cholinesterase inhibitors + levodopa (all patients)
Elder et al. [25] 2019 tDCS	Randomized controlled trial	36	75.09 (7.97)	27 M; 9 F	13 PDD; 23 DLB	Levodopa + cholinesterase inhibitors (all patients)
Wang et al. [24] 2021 tDCS	Randomized controlled trial	11	77.08	NR	DLB	NR
Takahashi et al. [28] 2009[a] TMS	Uncontrolled trial	6	61.9 (9.2)	3 M; 3 F	DLB	NR
ECT						
Kung et al. [31] 2002	Case study	1	60	1 F	DLB	Sertraline + citalopram
Rasmussen et al. [29] 2003	Uncontrolled trial	7	73.57 (10.56)	2 M; 5 F	DLB	Antidepressants, antipsychotics, mood stabilisers (all patients), cholinesterase inhibitors (5/7); carbidopa/levodopa (2/7)
Takahashi et al. [28] 2009[a]	Uncontrolled trial	8	71.6 (7.3)	1 M; 7 F	DLB	Antidepressant
Izuhara et al. [30] 2020	Case study	1	69	1 F	DLB	Suvorexant
DBS						
Loher et al. [39] 2002	Case study	1	75	1 M	PDD	Levodopa + carbidopa + paroxetine
Freund et al. [36] 2009	Case study	1	71	1 M	PDD	Levodopa

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Table 1 (continued)

Citation	Study design	Number of participants	Age of participants mean (SD)	Gender	Reported diagnosis	Medications during treatment
Ricciardi et al. [16] 2015	Case study	1	69	1 M	PDD	Levodopa
Kim et al. [35] 2017	Uncontrolled trial	5	66 (1.8)	3 M; 2 F	PDD	Levodopa (all patients)
Gratwicke et al. [33] 2018	Randomized controlled trial	6	65.2 (10.7)	6 M	PDD	Cholinesterase inhibitors + levodopa (all patients)
Gratwicke et al. [34] 2020	Randomized controlled trial	6	71.33; (3.67)	5 M; 1 F	DLB	Cholinesterase inhibitors (all patients) + levodopa (5/6)
Maltête et al. [32] 2021	Randomized controlled trial	6	62.2 (7.8)	6 M	LBD	Cholinesterase inhibitors (all patients)

PDD, Parkinson's disease dementia; LBD, Lewy body disease; DLB, dementia with Lewy bodies; NR, not reported. [a]Same study.

Participants

The total number of participants included in the present review was 231. Of these, 113 patients were reported with a diagnosis of DLB, 103 with PDD, and 15 described as LBD. The mean age of the participants was 69.98 years (range 54.4–94) and although information about gender was not reported in 1 study, participants were clearly predominantly men (68%) (Table 1). Cognitive profiles were tested at baseline in most cases, and participants varied from those with severe dementia [15] to very mild dementia [16]. Information about medications was present in almost all studies (n = 19/23 studies), and drug intake remained stable for the entire duration of the treatments except for ECT (Table 1). Patients were recruited from neurological and movement disorders clinics (n = 7 studies), psychiatric departments (n = 4 studies), general hospitals (n = 2 studies), nursing home (n = 1 study), and n = 9 studies did not report patients' provenience.

PT Studies

Primary outcomes mainly used to evaluate the efficacy of physical therapies were balance, gait, and cognitive performance (Table 2). Significant improvements in all motor measures were found in a recent retrospective study in which 35 DLB participants underwent a 4-week structured PT programme in a clinical setting [17]. In a randomized controlled trial [18], involving a large cohort of persons with dementia, the following measures relative to 4 PDD participants were reported separately: after 12 weeks of intensive strengthening and balance exercises, 2 PDD assigned to the exercise group improved sit-to-stand, balance, and speed measures compared to the 2 PDD assigned to the control group. In a case study, Dawley [19] reported a relatively young patient (age 57) with a diagnosis of LBD treated with a Parkinson's specific intervention called "Lee Silverman Voice Treatment-Big," a programme with intensive exercises with large amplitude movements of the body. The patient after 12 weeks of training improved in all motor scales (sit to stand, speed, risk of falls, walking, and balance), although results were not statistically significant due to the nature of the study. Another case study by Tabak and colleagues [20] reported successful 8-week PT in a PDD patient that obtained benefits in both motor functions (walking and balance) and executive functions, measured with Montreal Cognitive Assessment subtests, suggesting a causal relationship between these abilities. Finally, Kegelmeyer and colleagues [21], in a cohort study of 8 LBD patients, administered a single session of treadmill training with the goal of improving gait disorders. No significant changes in gait measures were found after a session of treadmill walking, and authors highlight the need of longer sessions to obtain significant improvements (Table 3).

CR Study

Our systematic search identified only one intervention [22] of CR for a group of 29 LBD patients that were randomly assigned to the following 3 groups: cognitive rehabilitation (CR), relaxation therapy, and treatment as usual. Primary outcomes of the study were goal attainment and satisfaction of the intervention, and secondary outcomes were quality of life, cognition, and mood (Table 2). After 8 weeks of CR consisting of planning, orientation, and memory exercises, participants assigned to CR group compared to relaxation therapy and treatment as usual groups were less depressed, more socially involved, with higher perception of self-efficacy and with higher values in

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Table 2. Treatment characteristics of the included studies

Citation	Treatment	Characteristics of the treatment	Duration of treatment	Primary outcomes	Secondary outcomes
Tabak et al. [20] 2013	PT	Aerobic exercise training on a stationary bicycle	8 weeks	Effects on executive functions	Effects on disease severity, QoL, walking
Dawley et al. [19] 2015	PT	Intensive exercises (LSVT BIG programme)	12 weeks	Efficacy of a PD treatment with a LBD patient	–
Telenius et al. [18] 2015	PT	Intensive strengthening, balance exercises	12 weeks	Effects on balance	Effects on muscle strength, mobility, ADL, QoL, and neuropsychiatric symptoms
Longhurst et al. [17] 2020	PT	Aerobic activity, strengthening, balance training	4 weeks	Effects on gait and balance	Effects on cognition
Kegelmeyer et al. [21] 2021	PT	20 min of treadmill training	1 day	Feasibility and safety of the treatment	Effects on gait, mobility, and coordination
Hindle et al. [22] 2018	CR	Orientation, planning, and memory exercises	8 weeks	Effects on goal attainment and satisfaction	Effects on cognition, mood, QoL
Sekiguchi et al. [15] 2017	LT	2,500–5,000 lux	2 weeks	Effects on different type of dementia	Effects on different severity of dementia
Akkaoui et al. [23] 2019	LT	10,000 lux	6 weeks	Effects on sleep disturbances	–
Elder et al. [26] 2016	tDCS	Anodic stimulation in left DLPFC	1 day	Feasibility of the treatment and the effects on attention	–
Elder et al. [27] 2017	tDCS	Anodic stimulation in left DLPFC	1 day	Effects on attention	–
Elder et al. [25] 2019	tDCS	Anodic stimulation in right posterior parietal cortex	4 days	Effects on frequency and severity of visual hallucinations	Effects on visual cortical excitability and visuoperceptual function
Wang et al. [24] 2021	tDCS	Anodic stimulation in left DLPFC	10 days	Effects on cognition	–
Takahashi et al. [28] 2009[a]	TMS	Bilateral DLPFC	10 days	Efficacy and safety of TMS in depressive patients	–
Kung et al. [31] 2002	ECT	Unilateral	7 sessions	Effects on mood and neuropsychiatric symptoms	–
Rasmussen et al., [29] 2003	ECT	Bitemporal stimulation (depressive symptoms) Bifrontal stimulations (cognitive symptoms)	Different treatments (4–33 sessions)	Effects on mood	–
Takahashi et al. [28] 2009[a]	ECT	Bifrontotemporal	10 sessions	Efficacy and safety of ECT in depressive patients	–
Izuhara et al. [30] 2020	ECT	Bitemporal	15 sessions	Effects on psychiatric symptoms and cognitive fluctuations	–
Loher et al. [39] 2002	DBS	Left internal segment of the globus pallidus stimulation	>1 year	Effects on disabling motor fluctuations and severe dyskinesia	–
Freund et al. [36] 2009	DBS	High frequency (130 Hz) of bilateral STN and low frequency (20 Hz) of bilateral NBM stimulation	23 weeks (STN) −18 weeks (NBM)	Effects on cognition	–

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Table 2 (continued)

Citation	Treatment	Characteristics of the treatment	Duration of treatment	Primary outcomes	Secondary outcomes
Ricciardi et al. [16] 2015	DBS	30 Hz frequency of unilateral PPN stimulation	4 years	Effects on cognition	–
Kim et al. [35] 2017	DBS	Bilateral STN stimulation	4–8 years	Effects on motor and non-motor symptoms	–
Gratwicke et al. [33] 2018	DBS	20 Hz frequency of bilateral NBM stimulation	6 weeks	Effects on cognition	Effects on psychiatric, motor symptoms and fMRI resting state
Gratwicke et al. [34] 2020	DBS	20 Hz frequency of bilateral NBM stimulation	6 weeks	Safety and tolerability of NBM DBS procedure	Effects on cognitive, psychiatric, motor scales and functional connectivity
Maltête et al. [32] 2021	DBS	20–100 Hz frequency of bilateral NBM stimulation	3 months	Effects on a memory test score (FCSRT)	Safety and effects on cognition, motor deficits, sleep, and PET

PT, physical therapy; QoL, quality of life; LSVT BIG, Lee Silverman Voice Treatment-Big; PD, Parkinson's disease; LBD, Lewy body disease; ADL, activity of daily living; CR, cognitive rehabilitation; LT, light therapy; tDCS, transcranial direct current stimulation; DLPFC, dorsolateral prefrontal cortex; TMS, transcranial magnetic stimulation; ECT, electroconvulsive therapy; DBS, deep brain stimulation; STN, subthalamic nucleus; NBM, nucleus basalis of Meynert; PPN, peduncolopontine nucleus; fMRI, functional magnetic resonance; FCSRT, Free and Cued Selective Reminding Test; PET, positron emission tomography. [a]Same study.

goal attainment and satisfaction. After 6 months at the follow-up, the CR group showed again higher values in goal attainment, higher rating in questionnaires assessing quality of life (The Parkinson's Disease Questionnaire; the Euroqol Questionnaire-short version), and better cognitive performance in a memory test (Table 4).

LT Studies

Only two studies investigated the efficacy of LT on both sleep quality and neuropsychiatric symptoms in LBD patients. Sekiguchi and colleagues [15] presented a case series of 5 DLB patients that underwent 2 weeks of daily light treatment with 2,500–5,000 lux; none of the patients improved in sleep score after treatment. Instead, in a case study, Akkaoui and colleagues [23] showed in a DLB patient clear improvements in both depression and sleep measures after 6 weeks of daily treatment with 10,000 lux, although the nature of the study (single case) does not allow statistically significant results (Table 5).

tDCS and TMS Studies

Interventions with tDCS were generally addressed to ameliorate cognition (especially attention) and neuropsychiatric symptoms (especially hallucinations). A randomized controlled trial by Wang and colleagues [24] tested the effect of 10 consecutive sessions of tDCS over the left dorsolateral prefrontal cortex (DLPFC) in 11 DLB patients. Neuropsychological evaluation, pre- and post-rehabilitation, did not show any difference between the active and sham groups. Another randomized controlled trial involving 36 LBD patients who underwent 4 consecutive sessions of tDCS with a focus on the right posterior parietal cortex did not report a reduction in the frequency and severity of visual hallucinations [25]. Elder and colleagues [26, 27] also tried to explore the effect of a single session of tDCS over the left DLPFC: one trial was effective in improving attentive measures like choice reaction time and digit vigilance [26], and the other did not report any beneficial effects on LBD participants [27]. In addition, there was a single trial in which 6 DLB participants underwent 10-day sessions of TMS. The case series by Takahashi and colleagues [28] showed that stimulating the left and right DLPFC with the TMS reduced significantly depressive symptoms (HAM-D score before treatment = 24; HAM-D after treatment = 11) (Table 6). In the same study, the authors treated another group of LBD patients with an electroconvulsive treatment (Table 7).

ECT Studies

Electroconvulsive treatments were mainly focused on neuropsychiatric and depressive symptoms of LBD

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Table 3. Summary of the results of physical therapy (PT) studies

Citation		Target of the treatment	Measure	Baseline scores mean (SD)	Scores after treatment mean (SD)
Tabak et al. [20] 2013		Cognition	MOCA	17	24
		Motor	Usual gait speed, m/s	0.96	0.92
			Walking (2MWT)	100	129
			Balance (FGA)	13	23
Dawley et al. [19] 2015		Motor	Sit to stand (CST)	4	8
			Risk of falls (TUG)	15.45	9.05
			Usual gait speed m/s	0.8	1.43
			Walking (6MWT)	480	562
			Balance (MBT)	21	25
Telenius et al. [18] 2015	Case 1	Cognition	MMSE	16	NR
		Motor	Sit to stand (CST)	6	8
			Usual gait speed, m/s	0.35	0.3
			Balance (BBS)	23	27
	Case 2	Cognition	MMSE	16	NR
		Motor	Sit to stand (CST)	5	8
			Usual gait speed m/s	0.41	0.71
Longhurst et al. [17] 2020		Cognition	MOCA	16.9 (6.7)	17.8 (6.9)
		Motor	Sit to stand (5STS)	19.3 (13.5)	14.7 (5.6)[a]
			Risk of falls (TUG)	13.5 (10.2)	11.1 (6.7)[a]
			Usual gait speed, m/s	0.90 (0.27)	1 (0.27)[a]
			Walking (6MWT)	348 (105)	381 (120)[a]
			Balance (MBT)	18.2 (4.4)	20.4 (4.5)[a]
Kegelmeyer et al. [21] 2021		Cognition	MMSE	19.14 (10.83)	NR
		Motor	Risk of falls (TUG)	24.56 (14.99)	21.57 (12.12)
			Usual Gait speed, m/s	0.66 (0.25)	0.79 (0.23)

MOCA, Montreal Cognitive Assessment; 2MWT, 2 Minute Walk Test; FGA, Functional Gait Assessment; CST, Chair Stand Test; TUG, Time Up and Go test; 6MWT, 6 Minute Walk Test; MBT, Mini Balance Evaluation System Test; BBS, Berge Balance Scale; MMSE, Mini Mental State Examination; 5STS, Five Times Sit-to-Stand Test; NR, not reported. [a]Significant differences.

patients. Takahashi and colleagues [28] reported a successful therapy in a group of 8 DLB patients that underwent bifrontotemporal stimulation that significantly decreased depressive symptoms. A case series by Rasmussen and colleagues [29] described 7 DLB patients after different sessions (from 4 to 33) of bifrontotemporal ECT that improved neuropsychiatric symptoms (delusions, hallucinations) and depression except for two participants that did not improve. Izuhara and colleagues [30] reported a case study of a DLB patient that impressively improved after 15 sessions of bitemporal ECT. The patient improved cognitive performance as evaluated by the Mini Mental State Examination (MMSE) score from 15/30 (before treatment) to 29/30 (after treatment), depression and hallucinations as evaluated with the Neuropsychiatric Inventory (NPI) score from 12/44 (before treatment) to 0/44 (after treatment). Another case study reported a DLB patient that reduced neuropsychiatric and depressive symptoms after 2 weeks of unilateral ECT, although the benefit did not last long [31] (Table 7).

DBS Studies

As regards DBS, we identified 7 studies involving a total of 26 LBD patients (PDD and DLB) with implantations in different locations. The primary goal of DBS treatments was generally the improvement of motor and cognitive deficits of LBD patients. In 3 studies, DBS treated the bilateral nucleus basalis of Meynert (NBM) [32–34], one study treated the bilateral subthalamic

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Table 4. Summary of the results of cognitive rehabilitation (CR)

Citation	Target of the treatment	Measure	Baseline scores mean (SD)	After treatment scores (2 months) mean (SD)	Follow-up scores (6 months) mean (SD)
Hindle et al. [22] 2018	Goal Attainment	BGSI	3.08 (1.43)	6.29 (1.44)[a] (CR vs. TAU and RT)	6.6 (1.93)[a] (CR vs. TAU and RT)
	Satisfaction	BGSI	3.3 (1.36)	6.54 (1.48)[a] (CR vs. TAU and RT)	5.98 (1.7)
	Neuropsychiatric symptoms	Depression (HADS)	9.13 (1)	5.5 (3.5)[a] (CR vs. TAU)	6.14 (4.14)
	Quality of life	Physical (WHOQOL-BREF)	13.2 (2.57)	12.5 (3.12)	13.15 (2.1)
		Psychological (WHOQOL-BREF)	14.5 (2.22)	13.25 (2.82)	14.49 (2.65)
		Social (WHOQOL-BREF)	14.4 (3.92)	15.85 (2.31)[a] (CR vs. TAU and RT)	15.47 (2.02)
		Environmental (WHOQOL-BREF)	15.7 (2.54)	16.13 (2.23)	15.98 (1.49)
		PDQ8	21.56 (15.27)	29.3 (10.95)	26.18 (16.1)[a] (CR vs. TAU)
		ED5D3L	0.65 (0.27)	Not measured	0.59 (0.31)[a] (CR vs. TAU)
		GSES	31 (4.15)	31.5 (4.24)[a] (CR vs. RT)	31.83 (5.07)
	Cognition	Memory recall (RBMT)	1.7 (2.46)	2.17 (1.36)	3.06 (1.57)[a] (CR vs. TAU)
		Attention (TMT)	4.33 (3.21)	4 (3.46)	4.5 (2.1)
		Verbal fluency	27.4 (11.83)	30.13 (14.4)	23.14 (7.58)
	Functional activity	FAQ	9.5 (7.04)	Not measured	13.57 (7.87)

BGSI, Bangor Goal Setting Interview; HADS, Hospital Anxiety and Depression Scale; WHOQOL-BREF, World Health Organization Quality of Life Scale – Brief version; PDQ8, Parkinson's Disease Questionnaire—8; ED5D3L, Euroqol Questionnaire-short version; GSES, Generalized Self-Efficacy Scale; RMBT, Rivermead Behavioural Memory Test; TMT, Trial Making Test; FAQ, Functional Activity Questionnaires; CR, cognitive rehabilitation; TAU, treatment as usual; RT, relaxation therapy. [a]Significant differences.

Table 5. Summary of the results of light therapy (LT) studies

Citation		Target of the treatment	Measure	Baseline scores	After treatment scores
Sekiguchi et al. [15] 2017	Case 1	Neuropsychiatric symptoms	NPI (sleep score)	8	3
	Case 2	Neuropsychiatric symptoms	NPI (sleep score)	12	12
	Case 3	Neuropsychiatric symptoms	NPI (sleep score)	9	9
	Case 4	Neuropsychiatric symptoms	NPI (sleep score)	8	6
	Case 5	Neuropsychiatric symptoms	NPI (sleep score)	8	8
Akkaoui et al. [23] 2019		Neuropsychiatric symptoms	NPI (sleep score)	10	7
			Depression (MADRS)	22	11
		Sleep	PSQI	22	13
			ESS	17	12

NPI, Neuropsychiatric Inventory; MADRS, Montgomery-Åsberg Depression Rating Scale; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale.

nucleus (STN) [35], one the pedunculopontine nucleus [16], one the internal segment of the globus pallidus, and one combined NBM and STN stimulation [36]. As regards NBM treatments, two trials obtained significant results: in the first study, six LBD improved motor functions tested with the Unified Parkinson's Disease Rating Scale (UPDRS) after 3 months of DBS treatments [32]; in the second study, six PDD experienced a

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Table 6. Summary of the results of transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) studies

Citation	Target of the treatment	Measure	Baseline scores mean (SD)	After treatment scores mean (SD)
Elder et al. [26] 2016 (tDCS)	Cognition (attentional tasks)	SRT (mean RT ms) active stimulation	454.65 (130.63)	453.65 (139.41)[a]
		CRT (mean RT ms) active stimulation	620.44 (202.9)	608.78 (157.18)[a]
Elder et al. [27] 2017 (tDCS)	Cognition (attentional tasks)	SRT (mean RT ms) active stimulation	NR	589.29 (461.97)
		SRT (mean RT ms) placebo stimulation	NR	561.25 (396.43)
		CRT (mean RT ms) active stimulation	NR	785.20 (241.92)
		CRT (mean RT ms placebo stimulation	NR	859.65 (419.01)
Elder et al. [25] 2019 (tDCS)	Cognition (visuoperceptual tasks)	Angle (degrees) active stimulation	41.34 (31.79)	39.89 (30.47)
		Motion (speed) active stimulation	3.57 (0.89)	3.49 (0.97)
	Neuropsychiatric symptoms	NPI (hallucinations) active stimulation	2.80 (1.61)	3.07 (2.52)
Wang et al. [24] 2021 (tDCS)	Cognition	MMSE active stimulation	NR	No improvement
Takahashi et al. [28] 2009 (TMS)	Neuropsychiatric symptoms	Depression (HAM-D)	24 (8)	11 (5.9)[a]

MMSE, Mini Mental State Examination; SRT, simple reaction time; CRT, choice reaction time; NPI, Neuropsychiatric Inventory; NR, not reported; HAM-D, Hamilton Depression Rating Scale. [a]Significant differences.

significant improvement in neuropsychiatric symptoms (NPI score) after 6 weeks of treatment, but no effects were found on cognition [33]. The same author in another trial [34] reported improvements, not statistically significant, in neuropsychiatric symptoms (NPI score) after 6 weeks of treatment of NBM in 6 DLB patients. Kim and colleagues [35] proposed a prolonged DBS treatment (4–8 years) of STN to 5 PDD patients; improvements were seen predominantly in motor symptoms (UPDRS score) in all patients after 1 year of treatment, although long-lasting benefits persisted only for one patient. A case study of a PDD patient reported a double-blinded sham stimulation trial that combined stimulation in bilateral STN (lasting 23 weeks) and bilateral NBM (lasting 18 weeks); the patient showed greater cognitive improvements concurrently with NBM stimulation, whereas STN improved motor symptoms [36]. Another case report [16] described a PDD patient who received a unilateral stimulation in pedunculopontine nucleus, an area implicated in cognition and alertness [37, 38]. When the DBS stimulation was switched off, the patient worsened cognitive performance, whereas with DBS stimulation switched on, cognitive performance improved. Finally, Loher and colleagues [39] reported a DBS treatment of the left internal segment of the globus pallidus on a PDD patient; the participant showed an initial improvement in motor functions postoperatively but worsened after 1 year of the implantation (Table 8).

Discussion

The present systematic review aimed to provide an updated and comprehensive overview of the efficacy of non-pharmacological treatments in patients with LBD. Although LBD is the second most common neurodegenerative dementia after Alzheimer's disease and causes a substantial social impact [6, 40], definitive clinical guidelines are still lacking. Previous systematic reviews on non-pharmacological interventions in people with LBD reported PT interventions [8] or other various evidence-based or non-evidence-based interventions, such as occupational therapy, psychoeducational therapy, music therapy [9, 10]. All three reviews found some evidence of the efficacy of these treatments in LBD, although no definitive recommendations were provided due to the small sample sizes and the low quality of the studies included. In this review, we provide an up-to-date

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Table 7. Summary of the results of electroconvulsive therapy (ECT) studies

Citation		Target of the treatment	Measure	Baseline scores	After treatment scores
Kung et al. [31] 2002		Neuropsychiatric symptoms	Neuropsychiatric symptoms	Present	Reduced
			Depression	Present	Reduced
Rasmussen et al. [29] 2003	Case 1 (31 sessions)	Cognition	MMSE	24	23–28
		Neuropsychiatric symptoms	Hallucinations	Intense	Reduced
			Depression (HAM-D)	Severe	6–8
	Case 2 (4 sessions)	Cognition	MMSE	19	23
		Neuropsychiatric symptoms	Depression (HAM-D)	33	8
	Case 3 (7 sessions)	Cognition	MMSE	4	4
		Neuropsychiatric symptoms	Hallucinations	Present	Initially reduced
	Case 4 (27 sessions)	Cognition	MMSE	NR	18–27
		Neuropsychiatric symptoms	Depression (HAM-D)	Severe	6–19
	Case 5 (33 sessions)	Cognition	MMSE	28	21
		Neuropsychiatric symptoms	Depression (HAM-D)	17	17
	Case 6 (36 sessions)	Neuropsychiatric symptoms	Delusion	Prominent	Reduced
			Depression	Present	Reduced
	Case 7 (9 sessions)	Neuropsychiatric symptoms	Depression	Present	Reduced
Takahashi et al. [28] 2009		Neuropsychiatric symptoms	Depression (HAM-D)	38 (5.8)	15 (9.6)[a]
Izuhara et al. [30] 2020		Cognition	MMSE	15	29
		Neuropsychiatric symptoms	NPI	12	0

MMSE, Mini Mental State Examination; HAM-D, Hamilton Depression Rating Scale; NPI, Neuropsychiatric Inventory; NR, not reported. [a]Significant differences.

overview, focussing only on the following evidence-based non-pharmacological treatments: PT, CR, LT, tDCS, TMS, ECT, and DBS.

Physical Therapy

Up to 85% of patients with DLB experience motor difficulties and in patients with PDD Parkinsonism can be moderate-to-severe [3]; thus, the management of motor symptoms should be a priority in the LBD population. This systematic search identified five studies with LBD patients that underwent exercise training. The rehabilitation programme was generally an intensive aerobic exercise training of the duration of several weeks (from 4 to 12 weeks) with the specific aim of improving gait and balance [17–19] or executive functions [20]. Four of these studies reported positive effects of exercises as regards balance, gait measures [17–19], and executive functions measured through the Montreal Cognitive Assessment test [20]. Instead, Kegelmeyer and colleagues [21] administered a single session of treadmill walking in LBD patients without showing specific gait improvements, probably due to the short duration of the treatment.

Current evidence highlights the importance of exercise training in the dementia population; however, only one of the reported studies was a randomized controlled trial [18]. The lack of a robust study design with a large sample of LBD highlights the need of developing further studies.

Cognitive Rehabilitation

The main purpose of CR is to maintain efficient cognitive performance of everyday tasks and to compensate for impairments, thus supporting independent living [41]. Evidence from literature showed beneficial effects of CR in healthy older adults [42, 43], patients with mild cognitive impairment [44], and patients with Alzheimer's disease [45]. Significant improvements after cognitive training were also reported in patients with Parkinson's disease [46].

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Table 8. Summary of the results of deep brain stimulation (DBS) studies

Citation		Target of the treatment	Measure	Baseline scores mean (SD)	After treatment scores mean (SD)
Loher et al. [39] 2002		Cognition	MMSE	22	17
		Motor	UPDRS (part III)	31	21
Freund et al. [36] 2009		Cognition	Memory (immediate RAVLT)	12	15
			Verbal fluency	23	30
			Attention (TMT A)	5:24	3:02
			Constructional praxia (clock drawing task)	4	7
		Neuropsychiatric symptoms	Depression (BDI)	26	20
Ricciardi et al. [16] 2015		Cognition	MMSE	29	28
			Working memory (WAIS-III digit backward)	4	2
			Memory (immediate RAVLT)	27	20
			Attention (Stroop interference time)	70	72
			Verbal fluency (letter fluency/ category fluency)	33/18	41/19
		Motor	UPDRS (part III)	23	25
Kim et al. [35] 2017	Case 1	Cognition	MMSE	24	22
		Motor	UPDRS	20.5	13.5
	Case 2	Cognition	MMSE	24	22
		Motor	UPDRS	16	21
	Case 3	Cognition	MMSE	23	NA
		Motor	UPDRS	39	23
	Case 4	Cognition	MMSE	15	NR
		Motor	UPDRS	56	20
	Case 5	Cognition	MMSE	22	27
		Motor	UPDRS	50.5	NA
Gratwicke et al. [33] 2018		Cognition	MMSE	24.5 (4)	23 (9)
			Working memory (WAIS-III Digit Backward)	4 (5)	4 (5)
			Memory (CVLT-II)	38 (24)	29 (24)
			Attention (Posner covert attention test accuracy)	64.5 (51)	41.5 (45)
			Verbal fluency (letter fluency/ category fluency)	4 (5)/2 (5)	3.5 (5)/1 (7)
		Neuropsychiatric symptoms	NPI	13 (20)	8.5 (22)[a]
		Motor	UPDRS (part IV)	7 (11)	4.5 (3)
Gratwicke et al. [34] 2020		Cognition	MMSE	23 (2)	24 (1)
			Working memory (WAIS-III Digit Backward)	7 (1.75)	6 (2)
			Memory (HVLT-R total recall)	31 (15)	26 (13)
			Attention (Posner covert attention test accuracy)	91 (24)	88 (37)
			Verbal fluency (letter fluency/ category fluency)	9 (2)/4 (3)	7 (4)/4 (6)
		Neuropsychiatric symptoms	NPI	15 (11)	9 (14.75)
		Motor	UPDRS (part III)	33.50 (17.8)	–

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Table 8 (continued)

Citation	Target of the treatment	Measure	Baseline scores mean (SD)	After treatment scores mean (SD)
Maltête et al. [32] 2021	Cognition	MMSE	23.8 (2.71)	20.8 (6.2)
		FAB	12.3 (1.6)	11 (2.7)
		Memory (FCSRT)	25.5 (8.4)	15 (8.7)
		Attention (Stroop interference time)	403 (267)	574 (515)
		Verbal fluency (letter fluency/ category fluency)	14.3 (4.5)/15.2 (2.6)	9 (3.5)/12.5 (3.9)
		Constructional praxia (Rey figure)	24.5 (12.1)	17 (14.9)
	Neuropsychiatric symptoms	NPI	10.8 (5.6)	12 (7.6)
	Motor	UPDRS (part III)	27.8 (10.3)	19.7 (9.4)[a]
	Sleep	EES	7 (2.6)	7.3 (3.9)

MMSE, Mini Mental State Examination; UPDRS, Unified Parkinson's Disease Rating Scale; RAVLT, Auditory Verbal Learning and Memory Test; TMT A, Trial Making Test part A; BDI, Beck Depression Inventory; WAIS-III, Wechsler Adult Intelligence Scale-III; CVLT-II, California Verbal Learning test-II; NPI, Neuropsychiatric Inventory; HVLT-R, Hopkins Verbal Learning Test Revised; FAB, Frontal Behavioural Battery; FCSRT, Free and Cued Selective Reminding Test; ESS, Epworth Sleepiness Scale; NR, not reported; NA, not applicable. [a]Significant differences.

To our knowledge, only one study has reported a trial in a population of LBD patients. Hindle and colleagues [22] proposed to LBD participants a CR programme of 8 weeks in which they underwent orientation, planning, and memory exercises. Significant improvements in quality of life, satisfaction, and mood were found, and patients also showed higher memory performance compared to healthy controls at follow-up. However, further evidence with larger samples of LBD population is needed to generalize the current results. In addition, CR specifically targeted to improve the cognitive domains commonly impaired in LBD patients (i.e., visuospatial abilities, executive functions, attention) should be designed.

Light Therapy

LT represents a non-pharmacological treatment used to modulate circadian biorhythms and psychiatric symptoms in patients with dementia. It has been suggested to be a promising intervention on sleep, cognition, and behaviour without significant adverse effects in Alzheimer's disease patients [47]. A recent randomized controlled trial assessing the effect of 4-week LT on delirium in older patients with Alzheimer's disease reported positive effects [48]. The LBD population should represent a target of particular interest for LT interventions since these patients are characterized often by REM sleep behaviour disorder [4]. Despite this, until now only two studies that experimented LT on LBD patients have been reported in the literature. Sekiguchi and colleagues [15] did not find any evidence of improved sleep measures on a group of DLB patients after 2 weeks of treatment; instead, Akkaoui and colleagues [23] treated a DLB patient for 6 weeks and obtained positive effects on depression and sleep measures. The discrepancy between the two studies may be related to the severity of dementia in the first study compared to the second and/or the duration of the treatment. Future randomized controlled trials with large samples of LBD could clarify the effectiveness of such treatments.

Transcranial Direct Current Stimulation and Transcranial Magnetic Stimulation

tDCS is a non-invasive technique able to manipulate brain neuroplasticity and modulate cortical function by delivering weak direct currents [49]. It represents an economic and painless therapeutic option for a wide range of neurological and neuropsychiatric disorders, and its effectiveness has been showed also in neurodegenerative diseases [50]. We identified four studies that used a tDCS treatment in LBD patients with a focus on cognition (i.e., attention) and visual hallucinations. To improve attentional functions, the anodal electrode was placed over the left DLPFC [24, 26, 27]. Instead, a recent randomized control trial assessed the effects of sessions of tDCS on visual hallucinations by applying the anodal electrode over the right posterior parietal cortex with the aim of reducing the frequency and severity of visual hallucinations. Only one tDCS study reported a beneficial

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effect on attention [26], whereas the others failed to achieve significant effects of the treatment and possible reasons could be the shortness of the treatment [27], the concurrent use of medications that could have masked the potential effect [27], the stimulation parameters like low current density and electrode type [25], the small sample size [24]. Many randomized controlled trials using tDCS have been conducted on Parkinson's disease patients with promising results. A recent extensive metanalysis [51] collecting results from 23 studies on various neurological/psychiatric diseases yielded definitive recommendations, specifically that anodal motor/premotor/supplementary motor area tDCS produces beneficial effects on motor symptoms and anodal DLPFC tDCS produces beneficial effects on cognition. Further randomized controlled trials involving LBD patients with representative sample sizes and adequate treatment duration would be necessary to clarify the possible beneficial effects of tDCS treatments to improve motor and cognitive deficits also in this population.

Another non-invasive type of brain stimulation is TMS that activates or modulates cortical targets in the central nervous system [52]. Our search identified only one study in which a repeated TMS (rTMS) trial on bilateral DLPFC was performed in a sample of 6 DLB patients with depression showing significant improvements [28]. DLPFC has been reported in the literature as the canonical target for the treatment of depressive symptoms in Parkinson's disease, with conflicting results [53, 54]. Unlike the little literature involving LBD patients in treatments with rTMS, a large number of studies have suggested the potential beneficial effects of rTMS on motor symptoms in Parkinson's disease patients [55]. Stimulating motor regions in PD with rTMS may present a slightly favourable effect on cognition too [56]. Future randomized controlled trials involving LBD patients in rTMS rehabilitative protocols will be useful to treat motor and non-motor symptoms.

Electroconvulsive Therapy

ECT represents an effective treatment for drug-resistant neuropsychiatric symptoms and mood disorders [57]. It involves the delivery of a small electrical current to the brain sufficient to induce a seizure for therapeutic purposes while the patient is under anaesthetic [58]. LBD patients often present depressive and psychiatric manifestations (mainly hallucinations and delusions), and pharmacological treatment may worsen Parkinsonism. Considering this conflicting scenario, ECT has been experimented in LBD populations as an ad hoc non-pharmacological treatment. Our search identified 4 studies describing ECT treatments in LBD patients that showed depression and neuropsychiatric symptoms. Of these studies, one reported significant positive effects of 10 bifrontal sessions of ECT for depression [28] whereas the other 3 studies [29–31] reported improvements only at a qualitative level. However, the design and the sample sizes of such studies (case reports and case series) do not allow a generalization of the results.

Deep Brain Stimulation

DBS is a neurosurgical procedure that involves the implantation of electrodes into specific targets within the brain and the delivery of constant or intermittent electricity from an implanted battery source [59]. In this review, we identified 7 studies involving LBD patients (both PDD and DLB) with DBS implantation in different locations. Studies that obtained improvements in motor functions were focused on stimulating the left internal segment of the globus pallidus [39] or the STN [36], whereas cognitive improvements were seen when stimulating the NBM [36] and the pedunculopontine nucleus [16]. Some studies, however, failed to find significant and long-lasting beneficial effects of DBS. Kim and colleagues [35] reported a case series in which despite some initial beneficial effects on motor symptoms after a stimulation treatment of STN in 5 PDD patients, benefits did not last longer. In three recent randomized control trials, none of the LBD patients reported significant cognitive improvements after a DBS treatment of the NBM, but they showed fewer neuropsychiatric symptoms [33, 34] and motor deficits [32]. The surgical procedure was well tolerated in all 3 studies, although a general cognitive worsening after electrode implantation was observed in one study, probably due to microlesion effects [32]. A possible reason for the lack of improvements in cognition would be the relatively short period of stimulation in some studies [32–34]; in addition, not all studies included a sham group of patients. Therefore, further larger randomized controlled trials with longer stimulation and a control group are needed to definitively clarify any potential benefits.

In conclusion, this review highlights that evidence-based rehabilitation studies in LBD populations are relatively few with small sample size and low quality of the study design. In addition, the heterogeneity of treatment duration, the different level of disease severity, and the absence of follow-up data in the majority of these studies do not allow the drawing of clear clinical guidelines. LBD is a very demanding disease for both patients and caregivers, with complex and invalidating clinical manifestations; therefore, it would be strongly necessary to develop further well-designed controlled trials with the aim of providing definitive recommendations of non-pharmacological treatments in the LBD population.

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Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

Conception and design of study and data acquisition, analysis, and interpretation: Lucia Guidi and Micaela Mitolo. Drafting and revising for critical intellectual content and final approval of the manuscript: Lucia Guidi, Stefania Evangelisti, Andrea Siniscalco, Raffaele Lodi, Caterina Tonon, and Micaela Mitolo.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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