Review

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Insights into the management of Lewy body dementia: a scoping review

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Abstract

Lewy body dementia (LBD) is situated at the convergence of neurodegenerative disorders, posing an intricate and diverse clinical dilemma. The accumulation of abnormal protein in the brain, namely, the Lewy body causes disturbances in typical neural functioning, leading to a range of cognitive, motor, and mental symptoms that have a substantial influence on the overall well-being and quality of life of affected individuals. There is no definitive cure for the disease; however, several nonpharmacological and pharmacological modalities have been tried with questionable efficacies. The aim of this study is to figure out the role of different interventional strategies in the disease. Donepezil, rivastigmine, memantine, and galantamine were the commonly used drugs for LBD. Together with that, levodopa, antipsychotics, armodafinil, piracetam, and traditional medications like yokukansan were also used, when indicated. Talking about nonpharmacological measures, exercise, physical therapy, multicomponent therapy, occupational therapy, psychobehavioral modification, transcranial stimulation, and deep brain stimulation have been used with variable efficacies. Talking about recent advances in the treatment of LBD, various disease-modifying therapies like ambroxol, neflamapimod, irsenontrine, nilotinib, bosutinib, vodobatinib, clenbuterol, terazosin, elayta, fosgonimeton, and anle138b are emerging out. However, there drugs are still in the different phases of clinical trials and are not commonly used in clinical practice. With the different pharmacological and nonpharmacological modalities we have for treatment of LBD, all of them offer symptomatic relief only. Being a degenerative disease, definite cure of the disease can only be possible with regenerative measures.

Keywords: dementia with lewy body, interventional strategies, parkinson's disease dementia

Introduction

Lewy body dementia (LBD) is a multifaceted neurodegenerative condition that frequently poses difficulties in diagnosis due to the varied nature of its clinical manifestations, which might be similar to those observed in other cognitive and mobility problems. The clinical spectrum of LBD encompasses two primary categories, namely dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD)[1]. DLB is distinguished by notable cognitive impairments and variable cognitive performance, while PDD is predominantly characterized by motor manifestations linked to Parkinson's disease[2]. Both subtypes exhibit shared characteristics, including visual hallucinations, variations in alertness, and the presence of rapid eye movement sleep behavior disorder[3]. The presence of these common symptoms highlights the complex connection between LBD and other neurodegenerative conditions,

HIGHLIGHTS

- Donepezil, rivastigmine, memantine, and galantamine were the commonly used drugs for Lewy body dementia (LBD).
- Levodopa, antipsychotics, armodafinil, piracetam, and traditional medications like yokukansan were also used, when indicated.
- In nonpharmacological measures exercise, physical therapy, multicomponent therapy, occupational therapy, psychobehavioral modification, transcranial stimulation, and deep brain stimulation have been used with variable efficacies.
- Talking about recent advances in the treatment of LBD, various disease-modifying therapies like ambroxol, neflamapimod, irsenontrine, nilotinib, bosutinib, vodobatinib, clenbuterol, terazosin, elayta, fosgonimeton, and anle138b are emerging out.
- Even with the availability of these diverse pharmacological and nonpharmacologoical modalities, LBD is still incurable.

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emphasizing the importance of proper identification as a crucial measure for effective treatment.

The comprehensive management of LBD involves a multidimensional approach that typically requires the implementation of a combination of pharmaceutical, nonpharmacological, and supportive interventions[4]. Nevertheless, the limited availability of therapeutic alternatives tailored to individual diseases, combined with the diverse range of symptom manifestations, presents distinct obstacles. Cholinesterase inhibitors have been shown to be effective in the management of cognitive symptoms[5]. However, the administration of antipsychotic drugs in patients with LBD necessitates cautious evaluation due to the heightened susceptibility of these individuals to negative outcomes. Furthermore, the effective management of motor symptoms and the implementation of fall prevention strategies continue to be of utmost importance in the care of individuals with LBD. The main objective of this review is to provide an analysis of the various strategies utilized in the management of LBD. We also aim to shed light into some recent advances in the treatment of LBD, with a special focus on disease-modifying therapies. In order to accomplish this purpose, we have delineated the subsequent goals: a thorough investigation of the efficiency of different interventional techniques would enable a well-informed evaluation of their advantages and disadvantages in the therapy of LBD. Our objective is to provide guidance to physicians in making evidence-based decisions through the synthesis of existing research. This methodology will incorporate a diverse array of interventions, encompassing pharmacological, psychological, and developing therapeutic modalities, thus providing a comprehensive comprehension of the discipline. The objective of our analysis is to uncover deficiencies in the existing understanding and therapeutic approaches for managing LBD. Our objective is to stimulate progress in the comprehension and enhancement of care for people with LBD by identifying specific areas that require additional investigation.

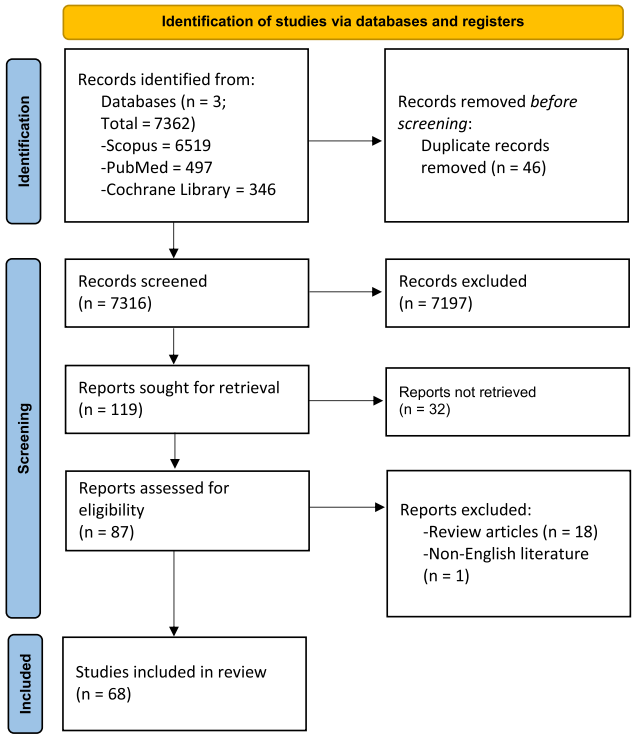

Figure 1. PRISMA flow diagram depicting the flow of information through the different phases of the review.

Methods

Study selection

Two independent reviewers conducted a systematic search of the PubMed, Scopus, and Cochrane Library databases to identify potentially relevant studies. The search was conducted using the following keywords: 'Lewy Body Dementia', 'Lewy Body Disease', 'Lewy Body Disorder', 'Dementia with Lewy Bodies', 'Lewy-Body Variant of Alzheimer Disease', in combination with terms related to management and treatment (e.g. 'Management', 'Treatment', 'Intervention', 'Therapeutics', 'Care', 'Supportive Care', 'Therapy', 'Strategies').

The titles and abstracts of the retrieved articles were screened independently by the two reviewers to identify potentially relevant studies. Full-text articles of the selected studies were then obtained and assessed for eligibility based on predefined inclusion and exclusion criteria. Any discrepancies between the two reviewers were resolved through discussion, and a third reviewer was consulted if necessary.

Eligibility criteria

The applicability of each paper was assessed manually by all authors and articles meeting the inclusion criteria were selected for comprehensive evaluation (Fig. 1).

Inclusion criteria

Any study published in English language dealing with pharmacological and nonpharmacological interventional strategies along with the treatment outcome in diagnosed cases of LBD.

Exclusion criteria

Cases with diagnostic uncertainty and cases without proper documentation of the treatment outcomes were excluded. We also excluded review articles, hypotheses papers, and papers published in languages other than English.

Data extraction

Data was manually extracted from eligible studies by different authors independently.

Outcome measures

Our outcome measures were to uncover the positive and negative aspects of different interventional strategies used for the treatment of LBD.

Quality assessment

The quality of included studies was assessed using appropriate tools, such as the Newcastle–Ottawa Scale for nonrandomized studies and the Cochrane risk of bias tool for randomized controlled trials. Studies with a high risk of bias were carefully considered during the interpretation of the results.

Results

Study characteristics

We found a total of 7361 articles after searching PubMed, Scopus, and Cochrane library databases. After excluding duplicates, we were left with 7316 articles processed for abstract screening. With abstract screening, we excluded 7197 articles and ended-up with 119 articles. Among them, 87 articles were assessed for eligibility. Based on our inclusion and exclusion criteria, we excluded 19 articles, and finally, a total of 68 articles were included in this systematic review (Table 1).

Pharmacological measures

Donepezil

Donepezil is a widely used drug for dementia, which improves cognitive function by inhibiting acetylcholinesterase enzyme in the brain[59]. Mori E *et al.*[6], in a randomized clinical trial, 140 patients with DLB, were randomly assigned to receive placebo or 3, 5, or 10 mg of donepezil hydrochloride daily for 12 weeks ($n = 35$, 35, 33, and 37, respectively), on assessment after completion of the treatment donepezil at 5 and 10 mg/day was significantly superior to placebo on both the mini mental status examination (5 mg: mean difference, 3.8; 95% CI: 2.3–5.3; $P < 0.001$; 10 mg: mean difference, 2.4; 95% CI: 0.9–3.9; $P = 0.001$) and change-plus caregiver input ($P < 0.001$ for each); 3 mg/day was significantly superior to placebo on change-plus caregiver input ($P < 0.001$), but not on the mini mental status examination ($P = 0.017$). Another randomized clinical trial performed by Ikeda *et al.*[7] in 142 patients of DLB in which 5 mg or 10 mg of donepezil administered once daily for 12 weeks, mini mental state examination (MMSE) score improved significantly compared to placebo in the 10 mg group [10 mg: 2.2 ± 0.4, placebo: 0.6 ± 0.5 (mean ± standard error); $P = 0.016$] but change in MMSE score in 5 mg group was not significant [1.4 ± 0.5 (mean ± standard error); $P = 0.232$].

Talking about PDD, in a randomized clinical trial of 22 patients treated with donepezil 5–10 mg per day for 10 weeks, there was a 1.9 point trend toward better scores on treatment compared with placebo that was not statistically significant on the Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAScog)[8]. Similarly, in an another study on PDD, nine patients received placebo and seven patients received donepezil (2.5–10 mg per day), selective and significant ($P < 0.05$) improvement on the memory subscale of the Dementia Rating Scale was noted amongst patients treated with donepezil; however, adverse effect of the drug, which were dose-dependent, resulted premature withdrawal of four patients on donepezil[9]. Dubois B *et al.*[10] conducted a randomized clinical trial on 550 patients with PDD receiving placebo or donepezil (5–10 mg per day) for 24 weeks, MMSE score showed significant benefit for both donepezil doses ($P \leq 0.007$). Similarly, Aarsland D *et al.*[11] randomized 14 patients with PDD receiving placebo or donepezil (5–10 mg per day) for 10 weeks and MMSE score was increased by 2.1 (SD 2.7) points on donepezil and 0.3 (SD 3.2) points on placebo, and the change-plus caregiver input score was 3.3 (SD 0.9) on donepezil and 4.1 (SD 0.8) on placebo, but two patients on donepezil (14%) dropped out after one and 4 weeks of the first treatment period because of peripheral cholinergic side effects, otherwise the adverse effects were few and not severe.

So far visual hallucination is concerned, 13 DLB patients with visual hallucination were given oral donepezil 5 mg per day and on assessment after 3 months visual hallucination completely disappear in six patients (46.15%) with significantly decreased glucose metabolism in the medial occipital cortex, on PET studies[12].

Hence, from above clinical trials donepezil was superior to placebo in terms of enhancement of cognition when assessed with relevant scoring systems. Few patients did require withdrawal of drug due to cholinergic side effects but those adverse effects were dose-dependent and can be minimized by close monitoring of the patients and individualizing the dose.

Rivastigmine

Rivastigmine acts by inhibiting both acetylcholinesterase and butyrylcholinesterase by covalently binding to the active site of these enzymes[60]. A placebo-controlled, double-blind, multicentre study was done in 120 patients with Lewy-body dementia, individuals were given up to 12 mg rivastigmine daily or placebo for 20 weeks, followed by 3 weeks rest. Almost twice as many patients on rivastigmine (37, 63%), than on placebo (18, 30%), showed at least a 30% improvement from baseline; however, on drug withdrawal, cholinergic adverse effects were more common with rivastigmine than with placebo[13]. Emre *et al.*[14] performed a randomized clinical trial among 410 patients randomly assigned to receive placebo or 3–12 mg of rivastigmine per day for 24 weeks, rivastigmine-treated patients had a mean improvement of 2.1 points in the score for the 70-point ADAS-cog, from a baseline score of 23.8, as compared with a 0.7-point worsening in the placebo group, from a baseline score of 24.3 ($P < 0.001$).

Galantamine

Galantamine is a reversible inhibitor of acetylcholinesterase and enhances the intrinsic action of acetylcholine on nicotinic receptors, leading to increased cholinergic neurotransmission in the brain[61]. Fifty patients with DBL received galantamine for 24-week and after completion of the treatment the scores on the Neuropsychiatric Inventory (NPI-12) improved by 8.24 points from baseline ($P = 0.01$) especially in visual hallucinations and nighttime behaviors ($P = 0.004$). The scores on the Clinician's Global Impression of Change improved by 0.5 points from baseline ($P = 0.01$)[15]. Litvinenko IV *et al.* performed a clinical trial on the use of galantamine at a maximum dose of 16 mg/day included 41 patients with Parkinson's disease (21 receiving galantamine and a control group of 20 patients). Patients treated with galantamine had better scores on the MMSE ($P < 0.05$), ADAS-cog ($P < 0.05$), the clock drawing test ($P < 0.05$), and the Frontal Assessment Battery ($P < 0.01$) at the end of the study period as compared with the control group; further, changes in total point scores on the NPI-12 at the ends of weeks 12 and 24, as compared with the beginning of the trial, were in favor of the group treated with galantamine, with significant changes in the hallucinations ($P = 0.0002$), anxiety ($P = 0.04$), sleep disturbance ($P = 0.04$), and apathy ($P = 0.006$) sections[16].

Memantine

Memantine acts by the blockade of current flow through channels of N-methyl-d-aspartate (NMDA) receptors[62]. Twenty-four patients with PDD were randomized to placebo or 20 mg per day of memantine, no participants need withdrawal because of adverse events of the drug; however, 6 weeks after drug withdrawal, a

Table 1

Details of the studies enrolled in this review.

References	Study title	Interventional modality	Number of participants
Mori E *et al.*[6]	Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial	Donepezil	140
Ikeda M *et al.*[7]	Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled, confirmatory phase III trial	Donepezil	142
Ravina B *et al.*[8]	Donepezil for dementia in Parkinson's disease: a randomised, double-blind, placebo-controlled, crossover study	Donepezil	22
Leroi I *et al.*[9]	Randomized placebo-controlled trial of donepezil in cognitive impairment in Parkinson's disease	Donepezil	9
Dubois B *et al.*[10]	Donepezil in Parkinson's disease dementia: a randomized, double-blind efficacy and safety study	Donepezil	550
Aarsland D *et al.*[11]	Donepezil for cognitive impairment in Parkinson's disease: a randomised controlled study	Donepezil	14
Satoh M *et al.*[12]	Improved visual hallucination by donepezil and occipital glucose metabolism in dementia with Lewy bodies: the Osaki-Tajiri project	Donepezil	13
McKeith I *et al.*[13]	Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study	Rivastigmine	120
Emre M *et al.*[14]	Rivastigmine for dementia associated with Parkinson's disease	Rivastigmine	410
Edwards K *et al.*[15]	Efficacy and safety of galantamine in patients with dementia with Lewy bodies: a 24-week open-label study	Galantamine	50
Litvinenko IV *et al.*[16]	Efficacy and safety of galantamine (reminyl) for dementia in patients with Parkinson's disease (an open controlled trial)	Galantamine	41
Leroi I *et al.*[17]	Randomized controlled trial of memantine in dementia associated with Parkinson's disease	Memantine	24
Aarsland D *et al.*[18]	Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial	Memantine	72
Lapid MI *et al.*[19]	Efficacy, safety, and tolerability of armodafinil therapy for hypersomnia associated with dementia with Lewy bodies: a pilot study	Armodafinil	17
Sano M *et al.*[20]	A controlled trial of piracetam in intellectually impaired patients with Parkinson's disease	Piracetam	20
Molloy S *et al.*[21]	The role of levodopa in the management of dementia with Lewy bodies	Levodopa	14
Goldman JG *et al.*[22]	Effects of dopaminergic medications on psychosis and motor function in dementia with Lewy bodies	Levodopa	19
Fanciulli *et al.*[23]	Rotigotine for anxiety during wearing-off in Parkinson's disease with dementia	Rotigotine	2
Portin R *et al.*[24]	The effect of deprenyl (selegiline) on cognition and emotion in parkinsonian patients undergoing long-term levodopa treatment	Selegiline	7
Lee HB *et al.*[25]	Clozapine for treatment-resistant agitation in dementia	Clozapine	16
Cummings JL *et al.*[26]	Efficacy of olanzapine in the treatment of psychosis in dementia with lewy bodies	Olanzapine	29
Walker Z *et al.*[27]	Olanzapine in dementia with Lewy bodies: a clinical study	Olanzapine	8
Marsh L *et al.*[28]	Olanzapine for the treatment of psychosis in patients with Parkinson's disease and dementia	Olanzapine	5
Prohorov T *et al.*[29]	The effect of quetiapine in psychotic Parkinsonian patients with and without dementia	Quetiapine	14
Takahashi H *et al.*[30]	Quetiapine treatment of psychotic symptoms and aggressive behavior in patients with dementia with Lewy bodies: a case-series	Quetiapine	9
Workman RH Jr *et al.*[31]	The use of risperidone for psychosis and agitation in demented patients with Parkinson's disease	Risperidone	9
Culo S *et al.*[32]	Treating neuropsychiatric symptoms in dementia with Lewy bodies: a randomized controlled trial	Risperidone	31
Kasaknuki K *et al.*[33]	Effectiveness of ramelteon for treatment of visual hallucinations in dementia with Lewy bodies: a report of four cases	Ramelteon	4
Fujishiro H *et al.*[34]	Effects of gabapentin enacarbil on restless legs syndrome and leg pain in dementia with Lewy bodies	Gabapentin	1
Odawara T *et al.*[35]	Administration of zonisamide in three cases of dementia with Lewy bodies	Zonisamide	3
Tombini M *et al.*[36]	Zonisamide for seizures in Parkinson's disease with dementia	Zonisamide	1
Kawanabe T *et al.*[37]	Successful treatment with Yokukansan for behavioral and psychological symptoms of Parkinsonian dementia	Yokukansan	7

Table 1

(*Continued*)

References	Study title	Interventional modality	Number of participants
Mizukami K *et al.*[38]	A randomized crossover study of a traditional Japanese medicine (kampo), yokukansan, in the treatment of the behavioral and psychological symptoms of dementia	Yokukansan	106
Telenius EW *et al.*[39]	Effect of a high-intensity exercise program on physical function and mental health in nursing home residents with dementia: an assessor blinded randomized controlled trial	High-intensity exercise	4
Tabak R *et al.*[40]	Aerobic exercise to improve executive function in Parkinson disease: a case-series	Aerobic exercise	2
Dawley C *et al.*[41]	The use of Parkinson's disease specific rehabilitative interventions to treat a patient with Lewy body dementia: a case report	Lee Silverman Voice	1
Hsu MH *et al.*[42]	Individual music therapy for managing neuropsychiatric symptoms for people with dementia and their carers: a cluster randomised controlled feasibility study	Music therapy	1
Cheston R *et al.*[43]	Simulated presence therapy, attachment and separation amongst people with dementia	Simulated presence therapy	1
Ciro CA *et al.*[44]	Enhanced task-oriented training in a person with dementia with Lewy bodies	Enhanced task-oriented training	1
Graff MJ *et al.*[45]	Community-based occupational therapy for patients with dementia and their care givers: randomised controlled trial	Occupational therapy	1
Logemann JA *et al.*[46]	A randomized study of three interventions for aspiration of thin liquids in patients with dementia or Parkinson's disease	Honey-thickened fluid, nectar-thickened fluid and chin-down posture	132
Rochster L *et al.*[47]	Does auditory rhythmical cueing improve gait in people with Parkinson's disease and cognitive impairment? A feasibility study	Auditory cueing	5
Huh TJ *et al.*[48]	The effectiveness of an environmental and behavioral approach to treat behavior problems in a patient with dementia with Lewy bodies: a case study	Environmental and Behavioral approach	1
Ota *et al.*[49]	Effect of psychological intervention for visual hallucinations in patients with dementia with Lewy bodies	Psychological intervention	2
Gil-Ruiz-N *et al.*[50]	An effective environmental intervention for management of the 'mirror sign' in a case of probable Lewy body dementia	Environmental intervention	1
Kung *et al.*[51]	ECT in Lewy body dementia: a case report	Electroconvulsive therapy	1
Rasmussen KG *et al.*[52]	Electroconvulsive therapy for patients with major depression and probable Lewy body dementia	Electroconvulsive therapy	7
Yamaguchi *et al.*[53]	The effect of electroconvulsive therapy on psychiatric symptoms of dementia with Lewy bodies	Electroconvulsive therapy	6
Takahashi S *et al.*[54]	Depression associated with dementia with Lewy bodies (DLB) and the effect of somatotherapy	Electroconvulsive therapy	8
Elder GJ *et al.*[55]	Effects of transcranial direct current stimulation upon attention and visuoperceptual function in Lewy body dementia: a preliminary study	Transcranial direct current stimulation	13
Takahashi S *et al.*[54]	Depression associated with dementia with Lewy bodies (DLB) and the effect of somatotherapy	Bilateral transcranial magnetic stimulation	6
Freund HJ *et al.*[56]	Cognitive functions in a patient with Parkinson-dementia syndrome undergoing deep brain stimulation	Deep brain stimulation	1
Loher TJ *et al.*[57]	Pallidal deep brain stimulation in a parkinsonian patient with late-life dementia: sustained benefit in motor symptoms but not in functional disability	Deep brain stimulation	1
Ricciardi L *et al.*[58]	Pedunculopontine nucleus stimulation in Parkinson's disease dementia	Deep brain stimulation	1

significantly greater proportion ($P = 0.04$) of memantine-treated participants deteriorated globally compared with those treated with placebo[17]. Aarsland *et al.*[18] randomly assigned 72 patients with LBD or PDD: 34 with memantine and 38 with placebo, 16 (22.22%) participants withdraw due to adverse events of the drugs, which was same in both groups, after 24-weeks of therapy the patients in the memantine group had better clinical global impression of change (CGIC) scores than those taking placebo (mean difference 0.7, 95% CI: 0.04–1.39; $P = 0.03$).

Thus, memantamine is usually safe and well-tolerated but continued treatment over time is needed.

Armodafinil

A 12-week pilot trial of armodafinil therapy (125–250 mg orally daily) in DLB outpatients with hypersomnia was conducted, 17 completed the protocol, Epworth Sleepiness Scale ($P < 0.001$), Maintenance of Wakefulness Test ($P = 0.003$), and CGIC ($P < 0.001$) scores improved at week 12, NPI total score ($P = 0.003$), visual hallucinations ($P = 0.003$), agitation ($P = 0.02$) improved at week 4 and caregiver overall quality of life improved at week 12 ($P = 0.004$) with no documented adverse events[19]. Hence, armodafinil seems to have promising response to manage hypersomnolence in these patients.

Piracetam

Twenty patients were randomized to 3.2 g of piracetam or an identical amount of placebo for 12-weeks, the dose was increased to 4.8 g for additional 12-weeks, there was a significant improvement on one subtest of the functional scale but no significant effects were demonstrated in cognitive or neurological

measures and five patients did not complete the trial for reasons unrelated to the medication[20].

Levodopa

Acute levodopa challenge test was carried out in 14 DLB patients, which yielded a mean 13.8% ($P = 0.02$) improvement in Unified Parkinson's Disease Rating Scale (UPDRS) III score, compared with 20.5% in PD ($n = 28$, $P < 0.0001$) and 23% in PDD ($n = 30$, $P < 0.0001$) respectively, Finger tapping scores increased (12.3% vs 20% and 23%), while walking test scores decreased (32% vs 41% and 67%) and a total of 19 DLB patients were treated for 6 months with L-dopa (mean daily dose 323 mg) but two withdrew prematurely with gastrointestinal symptoms and two with worsening confusion, in a trial conducted by Molloy *et al.*[21]. Similarly, Goldman *et al.*[22] found more than 10% over baseline motor improvement in UPDRS III scoring system in only one-third of a total of 19 patients with DLB.

Rotigotine

Fanciuli *et al.*[23] reported two cases of PDD on levodopa therapy experiencing anxiety as a nonmotor symptom, transdermal rotigotine (4 mg per day) was added to the original dopaminergic therapy and was proved to be beneficial in relieving symptoms of anxiety in both patients, without worsening cognitive and behavioral symptoms.

Selegiline

A study conducted in seven patients of Parkinson's disease (four with progressive dementia based on follow-up study of 8–10 years) on long-term levodopa therapy were treated with a 4-week course of selegiline, patients with slow progressive dementia failed to respond to treatment, whereas patients without progressive impairment tended to show improvement in memory and motor speed; the former group also showed more emotional changes than the latter[24].

Clozapine

Sixteen dementia patients were treated with clozapine for treatment-resistant agitation, and their charts were blindly rated by three clinicians on the Clinical Global Impression (CGI) Scale, Brief Agitation Rating Scale (BARS), and the Cohen-Mansfield Agitation Inventory-Short Form (CMAI-SF), with significant benefit documented on post-treatment assessment[25].

Olanzapine

A clinical trial conducted in 29-patients of DLB:10 were randomized to placebo, five received 5 mg of olanzapine, seven received 10 mg of olanzapine and seven received 15 mg of olanzapine, among them patients with 5 mg of olanzapine showed significant reductions in delusions and hallucinations, those treated with 10 mg showed a significant reduction in the Neuropsychiatric Inventory/Nursing Home (NPI-NH) delusion subscale score but no significant differences were found between the 15 mg group and the placebo group[26]. Walker Z *et al.*[27] reported eight-cases of DLB with associated psychotic and behavioral difficulties and all of them received olanzapine 2.5–7.5 mg, three out of them could not tolerate olanzapine even at the lowest available dose, two patients had clear improvement in psychotic and behavioral symptoms and three patients were able to tolerate olanzapine but gained only minimal benefit. Poor outcome and tolerability to the drug was documented an open-label 6-week trial of olanzapine in five PDD patients[28].

Quetiapine

Fourteen patients of PDD with drug-induced psychosis with quetiapine 25–600 mg daily, no change in Brief Psychiatric Rating Scale (BPRS) was noted but a good improvement was observed in 50% of the patients (7/14) in Clinical Global Improvement Scale (CGIS)[29]. Similarly, a case-series of nine patients of DLB with psychosis were treated quetiapine 25–75 mg per day: five patients had a positive response with a decline of more than 50% in the sum of scores for three items of the NPI, three patients withdrew from quetiapine treatment due to somnolence or orthostatic hypotension and the remaining patient exhibited no clinically significant change in the NPI score[30].

Risperidone

A pilot study investigated effectiveness and tolerability of risperidone for the treatment of psychosis and agitation in nine inpatients with Parkinson's disease and dementia and risperidone was found to be effective and safe, without worsening extrapyramidal symptoms or further impairing cognition[31]. However, in a randomized clinical trial of 31-patients of DLB, 65% of patients on risperidone need to discontinue the drug because of adverse events and scores on the NPI and the CGIC get worsened[32].

Ramelteon

There are four-cases reported on use of ramelteon in DLB patients for visual hallucinations, excessive daytime sleepiness and rapid eye movement sleep behavioral disorder, and apparent reduction in symptoms was noted when assessed with appropriate scoring system[33].

Gabapentin

There is a reported case of use of gabapentin enacarbil for restless leg syndrome in a DLB patient and marked improvement was noted without worsening of psychiatric symptoms[34].

Zonisamide

Zonisamide 25 mg for 4-week add-on administration was used to treat Parkinsonian symptoms in three cases DLB with mild-moderate improvement of Parkinsonian symptoms in two cases, but it did not affect the cognitive functions and behavioral or psychological symptoms[35]. Tombini *et al.*[36] reported a case of 78 year-old male patient with longstanding PD and dementia, who came-up for nocturnal seizures; zonisamide treatment significantly improved both his epilepsy and PD, without affecting cognitive functions.

Traditional medications

Seven patients of PDD were treated with Yokukansan, a traditional Chinese herbal medicine, for 4 weeks. Significant improvements in behavioral and psychological symptoms, particularly in the incidence and duration of hallucinations, were observed in most PDD patients after 4 weeks of Yokukansan

treatment[37]. Similarly, there has been documented benefit with yokukansan (TJ-54), a traditional Japanese medicine, treatment in 106 patients with DLB[38].

Disease-modifying therapies

Different trials are being conducted comparing the efficacy of different disease-modifying therapies to be used in LBD and DBL (Table 2).

Ambroxol

Ambroxol is ideally a drug to be used in treatment of productive cough and related respiratory disorders, which stimulation of surfactant synthesis, a complex mechanism that is not yet fully understood[77]. In a study involving 23 patients of LBD a mean decrease of glucocerebrosidase activity by 19%, increase of glucocerebrosidase protein levels by 35%, and increase of alpha-synuclein levels by 13% in the CSF were noted along with improvement in motor function on unified Parkinson's disease rating scale (UPDRS); however, five withdrew due to lumbar punctures and one was excluded due to difficulty obtaining cerebrospinal fluid (CSF)[63]. Similarly, in a study involving 41 patients, seven had either Gaucher's disease with PD or PD with glucocebrosidase gene mutations, three of them had to discontinue the drug due to personal reasons, reimbursement, and elevated platelets, one improved on the UPDRS, one did not demonstrate any deterioration, and one did not show any improvement[64]. In a conference presentation, the investigators in the PDD trial reported preliminary results from 25 of 75 planned participants. Ambroxol was well-tolerated; there was increased glucocebrosidase activity in peripheral leukocytes[65].

Neflamapimod

Neflamapimod (previously code named VX-745) is a clinical phase 2b-ready highly specific inhibitor of the intracellular enzyme p38 mitogen activated protein kinase alpha ('p38α') that is being developed as a disease-modifying drug for dementia primarily meant for Alzheimer's dementia[78], and a similar difference may be relevant in LBD. In a clinical trial, neflamapimod treatment group had improved performance on a test of gait dysfunction, but did not have a difference compared to the placebo group on a verbal learning test (International Shopping List Test), the mini mental state examination (MMSE), or four symptom domains of the 10-item neuropsychiatric inventory (depression, anxiety, hallucinations, and agitation/aggression). Interestingly, in a subgroup analysis in participants who received dosing three times daily (and excluded those that received twice daily dosing), there was a trend toward improvement in the study drug group in the primary endpoint (0.17 drug-placebo difference on the neuropsychological test battery Z-score) and a slightly higher drug-placebo difference on the CDR-SOB (0.56) and a notable that 87% of participants in the placebo arm and 85% of those in the treatment arm were male; in the general population, women represent ~40–60% of patients with DLB although studies have been variable, and this sample did not appear truly representative[66,79,80].

Table 2

Details of studies reporting the use of disease-modifying therapies in lewy body dementia.

References	Year	Agent used
Mullin *et al.*[63]	2020	Ambroxol
Istaiti *et al.*[64]	2021	Ambroxol
Pasternak *et al.*[65]	2018	Ambroxol
Jiang *et al.*[66]	2022	Neflamapimod
Landry *et al.*[67]	2022	Irsenontrine
Not applicable (conference abstract)	2022	Irsenontrine
Pagan *et al.*[68]	2016	Nilotinib
Pagan *et al.*[69]	2020	Nilotinib
Simuni *et al.*[70]	2021	Nilotinib
Pagan *et al.*[71]	2022	Bosutinib
Walsh *et al.*[72]	2023	Vodobatinib
MacDonald *et al.*[73]	2022	Clenbuterol
Simmering *et al.*[74]	2021	Terazosin
Grundman *et al.*[75]	2019	Elayta
MacDonald *et al.*[73]	2022	Fosgonimenton
Levin *et al.*[76]	2022	Anle138b

Irsenontrine

Irsenontrine, a phosphodiesterase-9 (PDE9) inhibitor, in a trial of 112 healthy adults was determined to be safe, and single doses led to increases in CSF cyclic guanosine monophosphate (cGMP)[81]. Oral administration of the drug was well-tolerated in a second randomized, double-blind phase I study of 74 elderly patients with the most common adverse events were postlumbar puncture (LP) syndrome and back pain following the use of LPs to monitor cGMP levels and there was a dose-dependent increase in CSF cGMP[67]. In an open-label study presented at some conference, participants with DLB or PDD demonstrated increased CSF cGMP regardless of amyloid status[82].

Nilotinib

Nilotinib is a tyrosine kinase inhibitors approved for the treatment of chronic myelogenous leukemia in imatinib resistance cases, which targets BCR-ABL chimeric gene[83]. In an open-label phase 1 study of 12 participants with PDD and DLB, the drug was generally well-tolerated; however, most participants experienced worsening psychiatric symptoms (hallucinations, paranoid ideation, and agitation), and some experienced worsened dyskinesia, at both doses studied (150 mg and 300 mg), there was evidence of target engagement via inhibition of phosphorylation of Abl kinase, improved motor and nonmotor symptoms in the UPDRS, a PD questionnaire of nonmotor symptoms, the MMSE, and a PD cognitive scale, moreover, participants on the low dose exhibited an increase in CSF levels of a dopamine metabolite at 2 months but not 6 months from baseline and those on the high dose demonstrated increased levels at 6 months but not at 2 month[68]. In the first 12-month phase 2 double-blinded RCT study of 75 participants with moderate PD given low dose nilotinib, high dose nilotinib, or placebo, there was a dose-related increase in the incidence of serious adverse events, and there was a trend toward increased incidence of falls in the treatment groups and both the treatment groups had an increase in CSF levels of dopamine metabolites and a decrease in CSF hyperphosphorylated tau[69]. Similarly, in a 6-month phase 2a double-blind RCT (NILO-PD) of 76 participants with moderate PD, nilotinib was found to be safe and tolerable, which were the primary outcome measures with the most common reasons for drug discontinuation were dose-dependent, asymptomatic elevations in amylase and lipase;

however, in secondary analyses, nilotinib did not result in symptomatic benefit and there was rather decline in motor function[70].

Bosutinib

Bosutinib, an Abl tyrosine kinase inhibitor, was found to be safe and well-tolerated with reported side effects limited to upset stomach, fatigue, and diarrhea, In an open-label phase 1 study of 31 participants with AD or PDD, four participants left the study for personal reasons, in exploratory analyses, there was less decline on the Quick Dementia Rating System (QDRS) and the Repeatable Battery Assessment of Neuropsychological Status at 12 months in those on treatment compared with population-based estimates of decline[84]. In a subsequent 12-week phase two study of 25 men and only one woman with DLB, there were no serious adverse events or dropouts and investigators noted a dose-dependent increase of bosutinib in plasma and CSF (100–400 mg per dose)[71].

Vodobatinib

Vodobatinib is also a tyrosine-kinase inhibitor and in a study of 19 healthy males and 60 participants with PD in a phase 1 trial, the drug was safe and well-tolerated with adequate penetrance in the CSF[72].

Clenbuterol

Clenbuterol is a β-adrenoreceptor agonist related to that is being repurposed to target the locus ceruleus to improve noradrenergic tone, which is often lost as part of the progression of LBD[85]. In a patient with PD, clenbuterol administration resulted in increased cerebral blood flow in the hippocampi, thalami, and amygdalae, as measured by pseudo-continuous arterial spin labeling MRI[73].

Terazosin

Terazosin, an α-1 blocker, in an in-vivo study, terazosin stimulated CNS ATP production, either prevented or slowed neuronal loss, increased dopamine levels, and partially restored motor function and in the same study, two patient databases demonstrated an association between terazosin use and slower disease progression of Parkinson's disease, decreased complications related to PD, and reduced frequency of diagnosis of PD[86]. Similarly, in a cohort study where 147 248 pairs of terazosin/doxazosin/alfuzosin users and tamsulosin users from Danish registries were compared and the result showed that those in the former group had a 12–37% decrease in PD risk compared with the tamsulosin group[74].

Elayta

Elayta, a sigma2 receptor antagonist, was found to be well-tolerated with good penetrance across the blood brain barrier in a phase 1 trial of healthy volunteers[75].

Fosgonimeton

Fosgonimeton acts by activates hepatocyte growth factor/MET receptor signaling, which in turn promotes neuronal survival and hippocampal plasticity[87]. The drug was well-tolerated in a phase 1 study involving a single-dose arm in 48 healthy men and a multiple dose arm of 29 healthy elderly participants and 11 participants with Alzheimer's dementia (AD)[73].

Anle138b

Anle138b acts by inhibition of alpha-synuclein aggregation and phase 1a study in 68 healthy participants have shown a reasonable safety profile based on a single ascending dose or multiple ascending doses over 7 days compared with placebo[76].

Nonpharmacological measures

Exercise

A randomized clinical trial in four LBD patients underwent high-intensity functional exercise 2 sessions per week for 12 weeks, patients doing exercise improved the score on Bergs Balance Scale by 2.9 points, which was significantly more than the control group who improved by 1.2 points ($P = 0.02$)[39]. Two patients completed an 8-week program of aerobic exercise training on a stationary bicycle and marked improvement was noted in the executive function, disease severity, quality of life, and walking function[40].

Physical therapy

A 57-year-old man underwent Lee Silverman Voice Treatment-Big intervention for eight sessions over 3 weeks and was assessed using the timed up and go, 30 s sit-to-stand, mini-balance evaluation system (Mini-BES) test, 6 min walk test, and gait speed, in which he made improvements in all outcome[41].

Music therapy

Reduction in anxiety and agitation was noted in a patient with DLB when subjected to music therapy program[42].

Simulated presence therapy

Cheston *et al.*[43] reported a case of DLB patient in distress underwent simulated presence therapy for two sessions and decrease in distress behavior was noted.

Enhanced task-oriented training

A patient of DLB was subjected to five sessions of skill building through task-oriented motor practice for 2 weeks and marked improvement was noted in terms of ability to stand from a recliner, brush teeth, and put-on eye glasses[44].

Community-based occupational therapy

One PDD patient underwent community-based occupational therapy and the patient showed some improvement in function and greater improvement in autonomy and quality of life and care-taker reported improved communication with the patient and better understanding of the condition[45].

Intervention for aspiration

Logemann *et al.*[46] conducted a randomized clinical trials among 132 PDD patients with dysphagia regarding measures to prevent aspiration: 59% of people aspirated when given honey-thickened fluid, 64% aspirated with nectar-thickened fluid, and 69% aspirated when put in a chin-down posture with statistically

significant comparative analysis ($P < 0.001$). Hence, honey-thickened fluid is superior to both nectar-thickened fluid and chin-down posture in terms of aspiration secondary to dysphagia in LBD patients.

Intervention for gait improvement

Rochester *et al.*[47] reported five cases of PDD patients in whom improvement in gait speed and stride amplitude was noted when auditory cueing of gait was done with cues that focused on stepping to the metromone's beat (temporal aspects) and taking large steps (spatial aspects).

Environmental and behavioral approach

Huh *et al.*[48] reported a case of DLB in which one hourly 32 sessions were given to carer along with tailored environmental modification, decreased agitation in the patient, and reduction in carer burden was noted.

Psychoeducation and environmental modification

Two DLB patients underwent psychoeducation and environmental modification and experienced decreased anxiety with a drop in frequency of visual hallucination[49].

Environmental modification

An 85-year-old woman with LBD exhibited a delusional mirror sign for 9 months, which disappeared on reducing the mirror size and personalizing it with artwork[50].

Electroconvulsive therapy

Kung S *et al.*[51] reported a case of a 60-year-old female with DLB experiencing depression and neuropsychiatric symptoms refractory to sertraline and citalopram, she then received a course of seven unilateral electroconvulsive therapy (ECT) sessions and improvement in mood and neuropsychiatric symptoms were noted for 2 weeks following ECT, but the benefits were not sustained. A case-series of seven DLB patients experiencing less depression following ECT has been reported[52]. Similarly, Yamaguchi *et al.*[53] presented six cases of DLB along with depression and psychotic symptoms and all of them improved following ECT. Six sessions of bifrontotemporal ECT was given to eight patients of DLB with depression, and lower depression score was reported on Hamilton depression rating scale (mean of 38 and SD of 5.8 before treatment and mean of 15 with SD 9.6 after treatment; $P < 0.001$)[54].

Transcranial stimulation

Six DLB patients with depression received 10 sessions of bilateral transcranial magnetic stimulation of dorsolateral prefrontal cortex and a lower score of depression was noted in Hamilton depression scoring system (before treatment, mean = 24, SD = 8, after treatment, mean = 11 SD = 5.9 ; $P < 0.001$)[54]. Elder *et al.*[55] presented a case-series of five DLB and eight PDD patients treated with single 20 min session of transcranial direct current stimulation with improvement in some measures of attention (improved performance in choice reaction time task and digit vigilance task) but other measures of attention and visuo-perceptual performance remains unchanged.

Deep brain stimulation

A 71-year-old man with slowly progressive PDD was inserted two electrodes into the nucleus basalis of Meynert and sub-thalamic nucleus, turning on the subthalamic nucleus electrodes improved motor symptoms but left cognitive performance almost unchanged while turning on electrical stimulation of the nucleus basalis of Meynert resulted in markedly improved cognitive functions[56]. Loher *et al.*[57] reported a case of PDD treated by inserting single electrode in the left internal segment of globus pallidus, improvement in motor symptoms of the contralateral side was noted but cognitive and functional abilities keep on declining. Similarly, an interesting case of PDD underwent deep brain stimulation (unilateral stimulation of pedunculopontine nucleus) experienced gradual decline in cognitive function, upon withdrawal of deep brain stimulation patient's cognitive status deteriorated significantly and was put back to deep brain stimulation and cognition returned back to what it was immediately before withdrawal of deep brain stimulation[58].

Discussion

DLB is the second most common cause of neurodegenerative dementia in older people, accounting for 10– 15% of all cases[88]. It is characterized by the accumulation of α-synuclein within vulnerable neurons[89]. Synucleinopathies are usually age-associated and, therefore, their prevalence rises with the increase in age of an individual[90]. Clinical features of LBD consists of progressive cognitive decline sufficient enough to impair daily routine activities, persistent memory impairment, which is usually evident with the progression of the disease and deficits on test of attention and of frontal sub-cortical skills and visuospatial ability may be seen[91]. The diagnosis of LBD is mainly clinical as there are no any electrophysiological, genotypic, or CSF markers specific to LBD[92]. However, dopamine transporter loss in the caudate and putamen on neuroimaging has shown specificity and sensitivity of 85% or higher in diagnosis of the disease[93].

Talking about treatment of the disease, as such there is no cure for the disease, when dealing with these patients, it is helpful first, to draw up a problem list of cognitive, psychiatric, and motor disabilities, and to then ask the patient and carer to identify the symptoms that, they find most disabling or distressing and which carry highest priority for treatment[94]. Compared to uncomplicated PD, response to levodopa in LBD and PDD is less which may be due to striatal degeneration[95]. However, increasing dose of levodopa in these group of patients will not be a very good decision and it can precipitate confusion and hallucination. Similarly, acetylcholinesterase inhibitors can also be used but their major limitation is cholinergic side effects like increased salivation, lacrimation, and rhinorrhea[96]. Apart from pharmacological measures, explanation, education, reassurance, orientation and memory prompts, attentional cues, and targeted behavioral interventions, are an integral part of the management of DLB, and pharmacological treatment is most successful when prescribed as part of a comprehensive management approach[88].

The management of LBD has been a subject of ongoing development and complexity within the field of neurology. Although several intervention techniques have been suggested, none of them provide a conclusive remedy for the ailment. This study provides a comprehensive analysis of the effectiveness of

various therapeutic options that are now available for the management of LBD.

A critical element addressed in the paper pertains to the utilization of pharmaceutical therapies, specifically acetylcholinesterase inhibitors such as donepezil, rivastigmine, galantamine, and memantine. The efficacy of these pharmaceuticals in enhancing cognitive abilities and alleviating behavioral manifestations in individuals with LBD has been substantiated by multiple clinical investigations. Nevertheless, it is imperative to recognize the constraints posed by the relatively limited sample sizes in certain research and the possible impact of publication bias, both of which might undermine the applicability of findings.

Moreover, the present research examines a range of alternative pharmacological interventions, encompassing armodafinil, piracetam, levodopa, as well as antipsychotic agents such as olanzapine, quetiapine, and risperidone. The efficacy of these medicines has been examined in relation to the management of certain symptoms, including hypersomnia, psychosis, and motor abnormalities. While some studies indicate potential advantages, it is crucial to acknowledge the accompanying dangers, such as side effects and the potential deterioration of cognitive function. Furthermore, it is imperative to do further research to investigate the enduring consequences and ideal dosages of these treatments, particularly considering the restricted sample size in certain clinical trials.

Nonpharmacological therapies are also discussed, with a focus on the significance of exercise, physical therapy, music therapy, and environmental adjustments. These therapies aim to address several aspects of the condition, encompassing both motor symptoms and behavioral abnormalities. Nevertheless, it is worth mentioning that the existing body of research in this particular field sometimes exhibits a scarcity of robust randomised controlled trials, instead depending heavily on case reports or studies with limited sample sizes. As a result, the degree of supporting evidence for these interventions may not be as substantial as that for pharmaceutical treatments.

The study examines the possible benefits of ECT and transcranial stimulation in controlling neuropsychiatric symptoms and depression in patients with LBD, based on a collection of case reports and short case-series investigations. Although the results of this study are interesting, it is important to approach them with caution because of the small number of participants included and the necessity for further comprehensive and controlled research to determine the effectiveness and safety of these interventions in this particular group.

So far disease-modifying therapies are concerned, till date very little evidence exist in the literature regarding their use and outcome, as their widespread clinical use is currently limited by lack of adequate trials to compare and contrast efficacy of various disease-modifying therapies. Based on findings from the trials included in our studies, promising and rewarding response is anticipated with the use of ambroxol, neflamapimod, irsenontrine, nilotinib, and bosutinib. However, efficacy of vodobatinib, clenbuterol, terazosin, elayta, fosgonimeton, and anle138b is uncertain due to inadequacy of the information.

A notable constraint of the review is the omission of a discourse regarding the possible interactions and adverse effects linked to the concurrent use of numerous drugs in the management of LBD. The issue of polypharmacy is frequently encountered in the context of dementia care, and it would have been advantageous to explore the complexities and factors involved in effectively managing many drugs in parallel.

In summary, the review presents a thorough and inclusive examination of the existing body of evidence pertaining to therapies for LBD. The results indicate possible advantages in both pharmaceutical and nonpharmacological interventions. However, it is important to recognize the constraints of current research, such as limited sample sizes, publication bias, and the requirement for more thorough investigations. Clinicians must to adopt a comprehensive approach when addressing the management of LBD, taking into account the unique requirements of each patient and thoroughly evaluating the potential advantages and disadvantages associated with each therapeutic option. In order to provide evidence-based guidelines for the management of this complicated and problematic condition, it is recommended that future research endeavors prioritize the implementation of bigger, well-designed studies. This study serves as an excellent source for clinicians who are seeking guidance in managing the complexities of LBD in order to deliver optimal treatment for persons impacted by this condition.

Conclusion

Early onset cognitive impairment in a patient with symptoms of Parkinson's disease raises the suspicion of LBD. Till date, there is no definitive cure for the disease and patients experience rapid deterioration in signs and symptoms of the disease ultimately leading to death due to complications like aspiration pneumonia. With this review, we have enlightened a holistic approach in management of LBD with different pharmacological and nonpharmacological modalities; however, these measures do not cure the disease but they improve the symptoms thereby decreasing the morbidity and disability due to the disease process.

Ethical approval

Being a scoping review, data were extracted from secondary sources and there was no need of ethical approval.

Consent

Informed consent was not required for this review.

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None.

Author contribution

S.A.K.: conceptualization; S.A.K., D.D., A.L., S.K.: methodology; M.A.B.K., S.B.P., V.K.R., and S.G.: supervision; S.A.K.: writing – original draft; M.A.B.K., S.B.P., V.K.R.: writing – review and editing.

Conflicts of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this study.

Research registration unique identifying number (UIN)

Not applicable. Being a scoping review, there was no need for registration.

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