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Treatment Efficacy and Acceptabilityof Pharmacotherapies for Dementia with Lewy Bodies: A Systematic Review and Network Meta-Analysis

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ABSTRACT

Introduction: We investigated the efficacy and acceptability of pharmacotherapy for dementia with Lewy bodies (DLB) while simultaneously considering the neuropsychiatric symptoms (NPS), cognitive function, motor symptoms, and acceptability.

Methods: Electronic databases were searched from inception through June 5, 2019, for randomized controlled trials (RCTs) and open-label trials (OLTs) in patients with DLB. We performed a pairwise conventional meta-analysis (PWMA) and network meta-analysis (NMA) within a frequentist framework. The main outcomes were mean change scores in NPS, general cognition, motor symptoms and acceptability. The effect sizes and odds ratios with 95% confidence intervals (CIs) were calculated. This study was registered with PROSPERO (CRD42018096996).

Results: In total, we included 29 studies (9 RCTs and 20 OLTs). In the NMA with 9 RCTs, both high- (mean difference [MD] 2.00, 95% CIs, 0.69 to 3.31) and low-dose (1.86, 0.58 to 3.15) donepezil were associated with a greater cognitive improvement than placebo. High-dose zonisamide was associated with greater motor symptom improvement (-4.10, -7.03 to -1.17]). No medications reached statistical significance regarding improving

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neuropsychiatric symptoms or developing intolerable adverse effects as compared to placebo. In the second NMA, with 29 studies as an exploratory analysis, aripiprazole and yokukansan may be effective for neuropsychiatric symptoms, while levodopa may be associated with cognitive impairment.
Conclusions: We report the most comprehensive evidence for the selection of pharmacotherapy for treating different clusters of DLB-related symptoms. Due to the limited availability of RCTs on DLB, more well-conducted RCTs are needed for MMA to warrant clinical efficacy in the future.

Introduction

The management of Dementia with Lewy bodies (DLB) is challenging and complex. Patient-centered intervention is often needed given the disease heterogeneity.[1] To date, there is no effective therapy to cure DLB and symptomatic treatments show only a temporary and modest clinical effect.[2] In addition, treatment for one of the core features of DLB may worsen another symptom. For example, the use of antipsychotic agents in patients with DLB with psychotic symptoms could not only cause irreversible parkinsonism but also cognitive impairment to some degree.[1,3] Therefore, it is challenging for clinicians to choose appropriate strategies to treat patients with DLB.

Lewy body disorders (LBD), which consist of Parkinson's disease dementia (PDD) and DLB, are neurodegenerative diseases characterized by the accumulation of Lewy bodies in brain cells.[4] Previous meta-analyses of DLB pharmacotherapy focused mainly on the whole group of LBD and only included a few medications such as acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate antagonists (i.e., memantine).[5-9] For example, a meta-analysis of 17 randomized controlled trials (RCTs) showed that AChEIs were superior to placebos in improving cognitive function, activities of daily living, and overall function in patients with LBD.[6] Another meta-analysis of 15 RCTs on LBD reported that both AChEIs and memantine improved global cognitive function and motor symptoms.[7] However these meta-analyses provided little information on how and which pharmacotherapy should be chosen to treat patients with DLB showing different clusters of core features. In addition, findings from studies drawn from a wide spectrum of LBD may pose challenges in interpreting responses to DLB alone, as neuropathological and genetic differences existed between the two groups studied.[4] Finally, there are several medications other than anti-dementia drugs that were not included in the previous meta-analyses,[6-8] such as antipsychotic,[10-16] antidepressant,[16] anti-parkinsonism,[17-20] and anticonvulsant medications.[21] Therefore, a meta-analysis of these drugs is required.

The majority of pharmacological studies related to the DLB treatment are uncontrolled clinical trials (single treatment arm) and high-quality RCTs on DLB are relatively lacking. Thus, there is a lack of direct comparisons among RCTs for DLB pharmacotherapies. Network meta-analysis (NMA), incorporating direct and indirect evidence simultaneously, can generate estimates with precision and accuracy. This study aimed to provide credible evidence on the safety and efficacy of DLB pharmacotherapies.

The main objectives of this study were as follows: 1) To compare treatment efficacy of RCTs for DLB pharmacotherapies with a NMA technique; 2) To obtain optimal efficacy when simultaneously considering neuropsychiatric, cognitive, and motor symptoms, and the acceptability of DLB pharmacotherapies; and 3) To explore the potential benefits of DLB pharmacotherapies in RCTs and uncontrolled single-arm trials.

Methods

Search strategy and selection criteria

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the PRISMA NMA extension statement.[22] All clinical trials for DLB pharmacotherapies were eligible and included for analyses. All enrolled trials were peer-reviewed and published in English. The DLB diagnosis was based on consensus guidelines for the clinical and pathological diagnosis of DLB.[1] This study was registered in PROSPERO (CRD42018096996).

We excluded non-clinical trials (e.g., case reports, case series, and observational studies) and studies investigating mixed groups of patients, such as all-cause dementia or LBD (PDD and DLB), unless the articles provided data for the DLB group.

The following electronic databases were searched from the date of their inception to June 5, 2019: PubMed, Medline, Embase, the Cochrane Library, and PsycINFO, without any restrictions on age, setting, sex, ethnicity, or publication year. The search terms included *dementia, Lewy bodies, treatment, anti-dementia medication, donepezil, rivastigmine, galantamine, memantine, intepirdine, nelotanserin, antidepressant, antipsychotic, and pharmacological*. Medical subject headings, free text terms, and variations were applied, and Boolean operators (OR, AND) were used to combine the searches. ClinicalTrials.gov was searched to identify unpublished and ongoing studies. Reference lists of the included articles and reviews were manually searched to identify potentially eligible studies. A search algorithm was developed and adapted for each database, without any restrictions on age, setting, sex, ethnicity or publication year. Online supplementary data presents the full search strategy (supplementary Table S1 and Table S2) and the PRISMA checklist (supplementary Table S3).

Outcomes

The outcomes were the treatment efficacy and acceptability. Treatment efficacy was defined as mean change scores in neuropsychiatric symptoms measured using the Neuropsychiatric Inventory (NPI-10), general cognition measured using the Mini-Mental State Examination (MMSE), and motor symptoms (extrapyramidal symptoms) measured using the Unified Parkinson's Disease Rating Scale part III (UPDRS-III). The obtained scores for measurements other than NPI-10, MMSE, and UPDRS-III were converted to the corresponding natural units.[23] Acceptability was defined as all-cause discontinuation, and premature discontinuation of treatment for any reason (e.g., lack of efficacy, adverse effects, or poor reliability).

Data extraction and quality assessment

Review authors worked in pairs to screen and review articles (Chu CS, Yang FC, Tsai CK, and Liang CS). When multiple publications from the same trial were encountered, studies with the most informative and complete datasets were included in the analyses. Risk of bias (ROB) was assessed using the Cochrane ROB tool.[24] In case of disagreement, another two authors (Chen TY and Tseng PT) were consulted to obtain consensus. Authors of RCTs and drug manufacturers were contacted when clarification was needed regarding raw data, study designs, or outcome measurements. Unavailable data were considered missing data.

Statistical analysis

The primary NMA included nine RCTs under a frequentist framework. A random-effects model with an intention-to-treat analysis was

conducted. The effect sizes (ESs) were calculated with 95% confidence intervals (CIs), and the efficacy for neuropsychiatric and motor symptoms was negative for ESs. Odds ratios were calculated dichotomous outcomes. Heterogeneity among the included studies was evaluated using the tau value, which is the estimated standard deviation of the effect across the included studies.

Generalized linear mixed models were used for direct and indirect comparisons. Indirect comparisons were conducted by transitivity, indicating that the differences between treatments A and B could be calculated from their comparisons with the treatment C. We calculated the relative ranking probabilities for all treatments. The surface under the cumulative ranking curve (SUCRA) indicates the percentage of the mean rank of each medication relative to an imaginary intervention that is the best without uncertainty. When the area under the curve was larger, the treatment had a higher rank of benefit for DLB treatment.

The rankings of all treatment outcomes were illustrated in a rank-heat plot, which was used to simultaneously recognize the best and worst interventions for the four outcomes (neuropsychiatric, cognitive, and motor symptoms and acceptability).[25]

We evaluated the potential inconsistency between direct and indirect evidence within the network using the node-splitting method. In addition, we used the design-by-treatment model to evaluate the global inconsistency among all NMAs. Publication bias was investigated using Egger's test and visual inspection of comparison-adjusted funnel plots.

The secondary NMA included both RCTs and uncontrolled single-arm trials under a Bayesian framework, and arm-based analysis was performed, which allows for the inclusion of single-arm studies and does not require a reference treatment for interpretation and contrast effects for which a reference group is selected for comparison.[26,27] The ESs of the secondary NMA were the median values with 95% credible intervals (Crls).

The NMA was performed using R-Project statistical software (version 3.5.3, R Foundation), and the *pcnetmeta* and *netmeta* statistical packages were used. The *netmeta* package calculates the P-score, which is a frequentist analogue to the SUCRA concept in Bayesian NMA methodology. Network plots were constructed using the statistical software package Stata (version 15, College Station, Texas, USA). The *p* values for all comparisons were two-tailed, and a cutoff point of 0.05 was considered statistically significant.

Results

The search strategy yielded 5006 records, and 29 studies met our inclusion criteria (supplementary Figure S1). Supplementary Table S2 provides details of the reasons for exclusion. Of the included trials, nine were RCTs[10,12,16,21,28-32], and 20 were uncontrolled single-arm trials.[11,13-15,17-20,33-44]

Characteristics of the Included Studies

Table 1 summarizes the characteristics of the included studies. A total of 29 studies were published between 2000 and 2019, of which 13 investigated pharmacological interventions, including aripiprazole, armodafinil, citalopram, donepezil, galantamine, levodopa, memantine, olanzapine, quetiapine, risperidone, rivastigmine, yokukansan, and zonisamide.

For the nine RCTs, 467 participants were assigned to the intervention group, while 273 were assigned to the placebo group. Pharmacological interventions included citalopram, low-dose donepezil (3 or 5 mg), high-dose donepezil (10 mg), memantine, low-dose olanzapine (5 mg), high-dose olanzapine (10 or 15 mg), quetiapine, risperidone, rivastigmine, low-dose zonisamide (25 mg), and high-dose zonisamide (50 mg). We did not categorize rivastigmine into high and low doses, as there was only a single regimen in this RCT. The mean age was 77.2 years (SD = 5.2) for the treatment group and 75.9 years (SD = 5.4) for the placebo group. The mean study duration was 14 weeks (range, 6 - 24 weeks).

Figure 1 illustrates the network plots of primary and secondary outcomes. Each node represents a treatment, and each edge is a treatment comparison. The size of each node was proportional to the number of participants subjected to this treatment. The edge width represents the number of trials that compared the two treatments.

NMA of RCTs

Figure 2 shows the primary results of the NMA, and ESs for each treatment were calculated and compared to the placebo. For neuropsychiatric symptoms (k = 6, n = 653) (Fig. 2a), none of the treatments reached statistical significance because their CIs contained zero. No treatment was significantly associated with the exacerbation of neuropsychiatric symptoms.

For general cognition (k = 6, n = 655), Figure 2b shows that low-dose and high-dose donepezil were associated with greater improvement than placebo. High-dose donepezil had an increase of 2.00 points (95% CIs: 0.69 to 3.31), and low-dose donepezil had an increase of 1.86 points (95% CIs: 0.58 to 3.15) in the MMSE score, respectively. The cognitive effects of rivastigmine did not reach statistical significance because of the wide CI. Memantine and quetiapine decreased MMSE scores, although the difference was not statistically significant

For motor symptoms (k = 7, n = 693), Figure 2c demonstrates that high-dose zonisamide was associated greater improvement than placebo, with a decrease of 4.10 points (95% CIs: -7.03 to -1.17) in the UPDRS-III score. Other treatments showed favorable effects, without statistical significance. For all-cause discontinuation (k = 8, n = 720), no difference was observed in all treatments when compared to the placebo, as shown in Figure 2d.

Treatment ranking based on RCT evidence

Figure 3 shows the rank-heat plot based on the SUCRA of the RCT evidence. High-dose donepezil showed a statistically significant favorable effect in the domain of general cognition and ranked the best treatment option among all pharmacotherapies. In the other three domains, high-dose donepezil was superior to placebo with no statistical significance. Low-dose donepezil ranked second among all pharmacotherapies in the domain of general cognition and the effect was statistically significant. In the domain of neuropsychiatric and motor symptoms, low-dose donepezil was superior to placebo, although without statistical significance. In the domain of acceptability, low-dose donepezil was inferior to placebo with no statistical significance. High-dose zonisamide was ranked the best among all pharmacotherapies in the domain of motor symptoms, with statistical significance on point estimates. In the domain of neuropsychiatric and motor symptoms, high-dose zonisamide was superior to placebo with no statistical significance. In the domain of acceptability, high-dose zonisamide was inferior to placebo, with no statistical significance.

Inconsistency, publication bias, and ROB in the NMA of RCTs

The node-splitting and design-by-treatment interaction models of the four study outcomes did not show any evidence of inconsistency (supplementary Table S4). The comparison-adjusted funnel plots and Egger's tests did not show any potential publication bias (supplementary Figure S2). Supplementary figure S3 shows that none of the included studies had high ROB.

Visual inspection of the potential effect modifiers across treatments and studies

We assessed whether trials of different interventions were similar with respect to important clinical characteristics that could potentially influence any differences in treatment effects. Supplementary figure S4 illustrates the distribution across trials of potential effect modifiers.

Table 1
Characteristics of included trials

Randomized controlled trials (k = 9)												
Author (year)	Inclusion	Scale	Location	Duration	Intervention	n	Age (Mean ± SD)	Female (%)	MMSE	NPI	UPDRS	ROB
Murata et al., (2018)	Probable DLB Outpatients, 56 to 84 years MMSE: 10 to 26; UPDRS-III: 10 to 19	MMSE NPI-10 UPDRS-III	Outpatient	12 wk	Zonisamide 50mg Zonisamide 25mg Placebo	49 51 58	74.6 ± 6.6 74.3 ± 5.5 76.3 ± 6.8	42.9 37.5 43.6	21.2 ± 3.8 21.4 ± 5.8 21.5 ± 4.7	7.7 ± 8.1 6.3 ± 8.6 7.3 ± 8.4	32.4 ± 10.5 33.2 ± 13.4 31.4 ± 10.3	Low
Ikeda et al., (2015)	*Probable DLB Outpatients≧50 years MMSE: 10 to 26; CDR≧0.5 NPI-plus≧8; NPI-2≧1	MMSE NPI-10 UPDRS-III	Outpatient	12 wk	Donepezil 10 mg Donepezil 5 mg Placebo	49 47 46	77.7 ± 6.8 78.8 ± 5.1 77.2 ± 6.1	57.1 55.6 61.4	20.3 ± 4.8 20.6 ± 4.1 20.3 ± 4.2	16.6 ± 11.7 18.9 ± 15.3 20.5 ± 15	NA -1.7 ± 6.0 -0.9 ± 6.0	Low
Mori et al., (2012)	Probable DLB Outpatients≧50 years MMSE: 10 to 26; CDR≧0.5 NPI-plus≧8	MMSE NPI-10 UPDRS-III	Outpatient	12 wk	Donepezil 10 mg Donepezil 5 mg Donepezil 3 mg Placebo	37 33 35 35	78.6 ± 6.1 77.9 ± 6.8 79.6 ± 4.5 78.6 ± 4.7	88.9 50.0 51.4 71.9	19.8 ± 4.4 19.8 ± 4.4 20.4 ± 4.1 18.3 ± 4.7	19.5 ± 12.8 14.0 ± 8.3 20.7 ± 12.8 18.3 ± 8.9	18.9 ± 11.6 19.1 ± 10.7 17.9 ± 9.0 20.8 ± 10.6	Low
Culo et al., (2010)	Probable DLB	MMSE NPI	Inpatient and outpatients	12 wk	Citalopram 23.6mg Risperidone 1.1mg	14 17	81.8 ± 7.8	64.5	9.4 ± 8.6	36.5 ± 20.7	NA	Low
Emre et al., (2010)	Probable DLB Outpatients≧50 years MMSE: 10 to 24 Hoehn and Yahr scale≦3	ADCS-ADL23 NPI-12 UPDRS-III	Outpatient	24 wk	Memantine 20 mg Placebo	34 41	77.2 ± 5.3 73.4 ± 7.5	41.0 41.0	48.3 ± 16.7 49.3 ± 18.6	18.0 ± 15.1 17.3 ± 12.3	25.3 ± 12.4 22.1 ± 12.6	Low
Kurlan et al., (2007)	Probable DLB Age 50 years or older MMSE≧8; UPDRS≧2 BPRS≧3 (DLB:23; PDD:9; AD:8)	MMSE NPI-10 UPDRS-III	Home / residential care setting	10 wk	Quetiapine Placebo	20 20	73.5 ± 5.8 74.1 ±6.1	45.0 30.0	19.2 ± 6.5 17.2 ± 5.9	25.1 ± 18.1 25.9 ± 15.6	17.2 ± 7.5 17.5 ± 7.1	Low
Beversodorf et al., (2004)	Probable DLB	MMSE UPDRS-III	Outpatient	8 wk	Donepezil 5mg Placebo	8 8	65 ± 3.5 65 ± 3.5	57.1 57.1	18.7 ± 10.7 18.7 ± 10.7	NA	31.6 ± 7.3 31.6 ± 7.3	Low
Cummings et al., (2002)	Probable DLB At least 40 years MMSE < 24; NPI-NH≧3 on agitation, delusion or hallucination subscales	MMSE NPI-NH-Delusion / Disurptiveness SAS	Nursing home	6 wk	Olanzapine 15mg Olanzapine 10mg Olanzapine 5mg Placebo	7 7 5 10	82.3 ± 7.6 84.6 ± 3.5 85.4 ± 3.7 83.3 ± 6.7	42.9 85.7 100 80	5.0 ± 4.0 6.7 ± 7.7 8.8 ± 6.2 6.1 ± 6.5	1.6 ± 1.7 3.0 ± 1.6 2.8 ± 1.6 2.3 ± 1.7	10.4 ± 8.4[a] 3.0 ± 1.0 4.8 ± 4.1 6.2 ± 5.2	Low
McKeith et al., (2000)	Probable DLB Outpatients MMSE>9 Hoehn and Yahr scale≦3	MMSE NPI-10 UPDRS-III	Outpatient	20 wk	Rivastigmine 12 mg Placebo	59 61	73.9 ± 6.5 73.9 ± 6.4	47.5 39.3	17.9 ± 4.7 17.8 ± 4.4	23.2 ± 15.0 20.2 ± 14.2	NA NA	Low
Uncontrolled single-arm trials (k = 20)												
Author (year)	Inclusion	Scale	Location	Duration	Intervention	n	Age (Mean ± SD)	Female (%)	MMSE	NPI	UPDRS	
Sugawara et al., (2019)	Probable DLB	MMSE NPI SAS	NA	10 wk	Aripiprazole 10.3mg	11	76	81.8	15	58	9	
Kazui et al., (2017)	Probable DLB Outpatients, 60 to 85 years MMSE: 10 to 26; CDR≧0.5	MMSE NPI-12	Outpatient	16 wk	Donepezil 5mg	24	77.1 ± 4.6	50.0	19.8 ± 4.4	22.1 ± 14.8	NA	
			Outpatient	12 wk		20	72.0	20.0	22.0	11.0	NA	

(continued on next page)

Table 1 (*continued*)

Randomized controlled trials (k = 9) Author (year)	Inclusion	Scale	Location	Duration	Intervention	n	Age (Mean ± SD)	Female (%)	MMSE	NPI	UPDRS	ROB
Lapid et al., (2017)	Probable DLB Outpatients, 50 to 90 years MMSE: 10 to 26	MMSE NPI-10			Armodafinil 250mg							
Yoshino et al., (2017)	Probable DLB	MMSE NPI-10	Outpatient	21 wk	Donepezil 5mg	21	78.7 ± 4.5	71.4	19.7 ± 6.4	19.3 ± 20.8	NA	
Manabe et al., (2016)	Probable DLB	MMSE	Outpatient	4 wk	Donepezil 10mg	24	80.5	62.5	18.0	NA	NA	
Onofrj et al., (2013)	Probable DLB	MMSE NPI-10 UPDRS-III	Outpatient	104 wk	Levodopa 300mg	67	72.2 ± 5.4	46.3	18.1 ± 3.3	20.7 ± 1.6	27.0 ± 5.1	
Iwakasi et al., (2011)	Probable DLB NPI-10≧4	MMSE NPI-10	NA	4 wk	Yokukansan 7.5g	63	78.2 ± 5.8	52.3	18.0 ± 7.0	30.5 ± 18.5	NA	
Lucetti et al., (2010)	Probable DLB	MMSE NPI-10 UPDRS-III	NA	52 wk	Levodopa 452mg	20	76.8 ± 4.8	40.0	20.6 ± 3.1	30.8 ± 12.5	24.4 ± 3.3	
Levin et al., (2009)	Probable DLB	MMSE BIS UPDRS-III	NA	16 wk	Memantine 20mg Placebo	14 9	69.2 ± 5.9 69.2 ± 5.9	39.1 39.1	19.4 ± 5.6 19.6 ± 5.3	49.5 ± 15.1[b] 45.9 ± 16.2	14.5 ± 4.5 13.9 ± 4.1	
Goldman et al., (2008)	Probable DLB	MMSE UPDRS-III	NA	12 wk	Levodopa 479mg	19	74.5 ± 4.1	42.1	20.5 ± 6.0	NA	37.6 ± 10.7	
Edwards et al., (2007)	Probable DLB At least 50 years MMSE≧7; NPI-12≧8	MMSE NPI-12 UPDRS-III	Home / residential care setting	24 wk	Galantamine 24mg	50	76.5	42.0	20.8	27.0	18.8	
Molloy et al., (2006)	Probable DLB	MMSE NPI-10 UPDRS-III	Hospital and community	12 wk	Levodopa 286mg	11	76.4 ± 6.8	36.4	19.5 ± 3.6	11.9 ± 12.1	34.3 ± 12.7	
Mori et al., (2006)	Probable DLB CDR=0.5, 1, or 2 MMSE≧10	MMSE NPI-11	Outpatient and inpatient	12 wk	Donepezil 5mg	14	78.7 ± 5.1	50.0	19.3 ± 4.9	14.8 ± 3.4	NA	
Rowan et al., (2007)	Probable DLB MMSE<24	MMSE	NA	20 wk	Donepezil 10mg	12	64 to 86	54.0	17.4 ± 5.5	NA	NA	
Iwakasi et al., (2005)	Probable DLB	MMSE NPI-10	NA	4 wk	Yokukansan with unknown mg	14	73.3	35.7	17.5 ± 6.8	34.7 ± 21.8	NA	
Thomas et al., (2005)	Probable DLB MMSE<24	MMSE NPI-10 UPDRS-III	NA	20 wk	Donepezil 10mg	30	75.4 ± 6.7	46.7	17.7 ± 5.3	23.7 ± 20.8	25.1 ± 14.3	
Takahashi et al., (2003)	Probable DLB MMSE<25 NPI≧3 on agitation, delusion or hallucination subscales	MMSE NPI-10 UPDRS-III	NA	8 wk	Quetiapine 44mg	9	74.3	NA	15.3	14.4	6.0[a]	
Fernandez et al., (2002)	Probable DLB	UPDRS-III	NA	56 wk	Quetiapine 69mg + Levodopa 372mg	11	77.0	NA	NA	NA	40.0	
Samuel et al., (2000)	Probable DLB MMSE<24	MMSE	Outpatient	24 wk	Donepezil 5mg	4	79.8 ± 5.6	0	20.5 ± 3.1	1.5 ± 1.6[c]	NA	
Walker et al., (1999)	Probable DLB	MMSE	NA	12 wk	Olanzapine 4.5mg	8	81.4	37.5	15.7	NA	NA	

Abbreviation: ADCS-ADL23 = Alzheimer's Disease Cooperative Study Activities of Daily Living, 23 Items; BEHAVE-AD = Behavioral Symptoms in Alzheimer's Disease; BIS = Behavioral Impairment Scale; BPRS = Brief Psychiatric Rating Scale; DLB = Dementia of Lewy bodies; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; NPI-NH = Neuropsychiatric Inventory- Nursing Home version; NPI-10 = 10-Item Neuropsychiatric Inventory Sub-score; UPDRS-III = Unified Parkinson's Disease Rating Scale Part 3, ROB = risk of bias; SAS = Simpson-Angus Scale.

* McKeith et al., Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 1996, 47:1113–1124.

[a] Scores are from Simpson-Angus scale.

[b] Scores are from Behavioral Impairment Scale.

[c] Scores are from Behavioral Symptoms in Alzheimer's Disease.

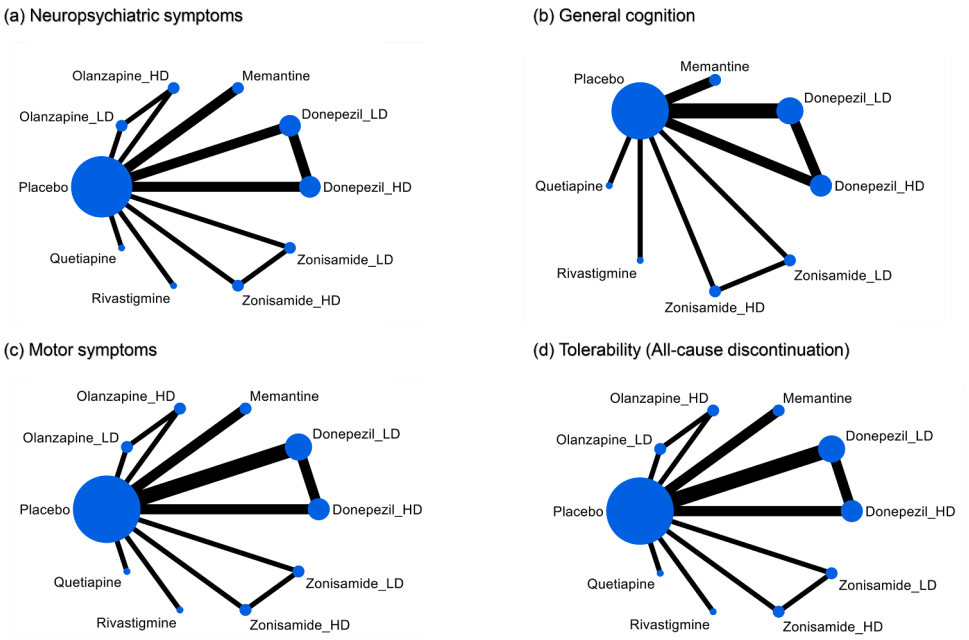

Figure 1. Network meta-analysis of eligible comparisons for the neuropsychiatric symptoms.
HD = high-dose; LD = low-dose.

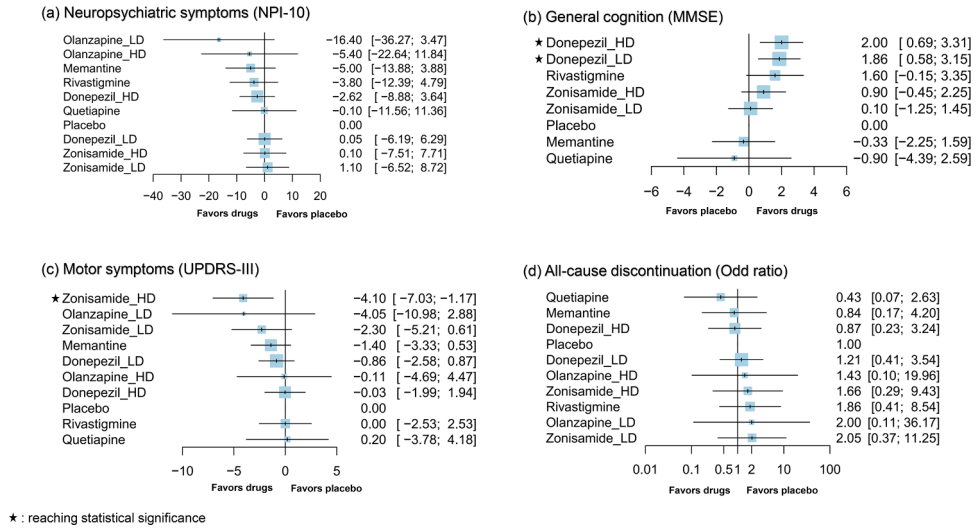

Figure 2. The forest plots of network meta-analysis of RCTs for (a) neuropsychiatric symptoms, (b) general cognition, (c) motor symptoms, and (d) all-cause discontinuation. The estimated effects were compared with placebo.

Notably, the study by Cummings et al.[12] was the only study that used olanzapine to manage patients with DLB. However, this study recruited patients with DLB with severely impaired cognition; these patients were older and there was a higher proportion of female patients in the study. Another RCT by Culo et al.[16] investigated the efficacy of risperidone vs. citalopram and had distinct study characteristics; however, this study did not contribute to study outcomes because it did not have a common comparator placebo. As only nine RCTs were recruited, we did not conduct meta-regression analysis to examine the influence of potential effect modifiers, as this generally requires large study numbers for reliable estimation.

NMA of RCTs and uncontrolled single-arm trials

The results of the secondary NMA with RCTs and uncontrolled single-arm trials are shown in Figure 4 and were used to reveal the potential benefits of each treatment. For neuropsychiatric symptoms (k = 27, n = 1073) (Fig. 4a), aripiprazole, low-dose olanzapine, yokukansan, and high-dose donepezil were significantly associated with improvement in NPI-10 scores compared with the placebo.

For general cognitive function (k = 30, n = 1117) (Fig. 4b), the results were similar to those of the primary NMA in that high-dose and low-dose donepezil were positively associated with the MMSE score compared to the placebo. Notably, levodopa was associated with cognitive impairment, with a decrease of 3.4 points (95% Crls: -5.1 to -1.4) in the MMSE score. For motor symptoms (k = 20, n = 960) (Fig. 4c), low-dose and high-dose zonisamide were significantly associated with decreases in the UPDRS-III score compared to the placebo. Other treatments showed favorable effects, but the differences were not statistically significant. For all-cause discontinuation (k = 35, n = 1231) (Fig. 4d), citalopram and risperidone were significantly associated with increased odds when compared to the placebo.

SUCRA	NPI-10	MMSE	UPDRS-III	Tolerability
Donepezil_HD	54.8	85.4	29.7	62.6
Donepezil_LD	33.4	81.7	48.8	48.3
Memantine	67.5	23.1	58.8	62.2
Olanzapine_HD	59.9		35.4	45.7
Olanzapine_LD	91.3		78.6	37.1
Placebo	32.9	27.2	27.1	58.2
Quetiapine	37.6	20.2	30.6	81.2
Rivastigmine	59.6	74.2	30.9	34.1
Zonisamide_HD	35	57.2	90.4	39.2
Zonisamide_LD	27.9	31	69.8	31.6

★ : reaching statistical significance on point estimate

SUCRA, surface under the cumulative ranking curve; HD, high-dose; LD, low-dose

Figure 3. The rank-heat plot based on SURCA.

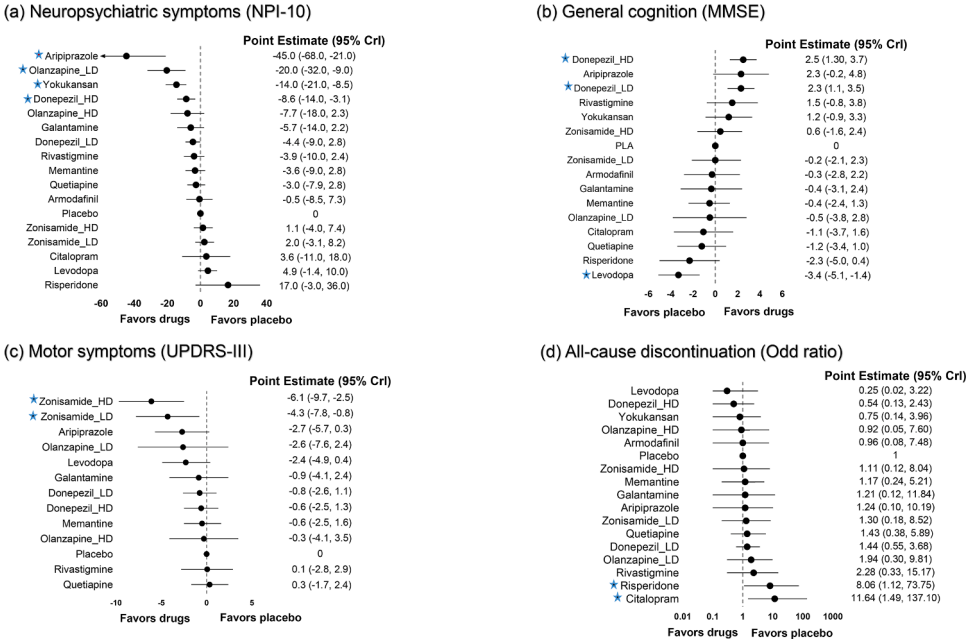

Figure 4. The forest plots of network meta-analysis of RCTs plus uncontrolled single-arm trials for (a) neuropsychiatric symptoms, (b) general cognition, (c) motor symptoms, and (d) all-cause discontinuation.

Discussion

Our NMA presents the most comprehensive overview of the available data on the safety and efficacy of DLB pharmacotherapies. Based on RCT data, the primary NMA provided credible evidence for DLB management, with precision and accuracy. Secondary NMA with RCTs and uncontrolled single-arm trials explored potential options for DLB treatments that require further investigation with large-scale RCTs.

Our study revealed that high-dose and low-dose donepezil were associated with cognitive improvement when compared with the placebo. For motor symptoms, only high-dose zonisamide significantly improved motor symptoms. For all-cause discontinuation, none of the included interventions showed higher odds of all-cause discontinuation than the placebo.

Previous studies reported inconsistent findings on the efficacy of memantine in neuropsychiatric symptoms of LBD.[9,45] Pairwise meta-analytic studies also showed no difference with memantine treatment for alleviating neuropsychiatric symptoms in both DLB and PDD.[7,8] A recent meta-analytic study found that memantine improved neuropsychiatric symptoms in DLB but not PDD in a sub-group analysis.[9] Another RCT also reported that the improvement in neuropsychiatric symptoms with memantine was only observed in DLB but not PDD.[28] In the present study, memantine showed favorable effects on neuropsychiatric symptoms, with no statistical significance. However, since only one RCT[28] and one uncontrolled clinical trial[44] were included for analyses, more well-conducted RCTs are required to confirm the robustness and accuracy of these results.

The International DLB Consortium has endorsed the use of AChEIs (donepezil and rivastigmine) in treating neuropsychiatric symptoms in patients with DLB.[1] The Delphi consensus group also supports the beneficial effects of donepezil and rivastigmine on neuropsychiatric symptoms in patients with LBD.[45] However, previous meta-analytic studies reported a distinct effect of AChEIs between DLB and PDD, showing that donepezil and rivastigmine improved neuropsychiatric

symptoms in PDD but not in DLB. [8,9] The primary NMA in the present study showed that both donepezil and rivastigmine were not associated with greater improvement in neuropsychiatric symptoms than placebo, while high-dose donepezil showed favorable effect on neuropsychiatric symptoms, observed in the secondary NMA.

The Delphi consensus group[45] and the British Association for Psychopharmacology[46] have recommended the use of rivastigmine and donepezil in both PDD and DLB for the improvement of cognitive function. Furthermore, the DLB Consortium supports the use of AChEIs in DLB.[1] However, our primary NMA revealed that high-dose and low-dose donepezil were significantly associated with cognitive improvement, but not rivastigmine, which is supported by a recent meta-analytic study showing greater improvement of cognitive function found with donepezil in DLB, and with rivastigmine in PDD.[9] Donepezil is a reversible inhibitor, whereas rivastigmine is an irreversible inhibitor, which can explain why duration of action for donepezil is short lasting in comparison with that for rivastigmine.[47] Thus, DLB and PDD may respond to individual AChEI treatment differently, and hence, AChEIs treatment regimens should be carefully considered with the precise differentiation of LBD diagnoses.

In general, patients with PDD are subjected to long-term and high-dose antiparkinsonian medications, while patients with DLB may be naïve to antiparkinsonian medication. Therefore, the management of motor symptoms in patients with DLB and PDD may be markedly different. In our NMA, we found that only high-dose zonisamide was associated with a greater improvement in motor symptoms. Both high-dose and low-dose zonisamide showed improvements in motor symptoms in secondary NMA. Importantly, levodopa was not significantly associated with motor symptom improvement, while it may impair general cognition, showing a decrease of 3.4 points (-5.1 to -1.4) in the MMSE score. A previous study reported that one-third of patients with DLB receiving levodopa showed motor benefits, while worsened psychosis was observed in one-third of patients.[19] To date, and the risk of worsened cognitive function of levodopa has not been specifically addressed in DLB management. The trade-off between cognitive function, psychotic symptoms, and parkinsonism should be considered when prescribing levodopa to patients with DLB.

In the secondary group, yokukansan associated with a greater improvement in neuropsychiatric symptoms. Moreover, it did not worsen cognitive function and was well tolerated. Yokukansan, a Japanese formula, consists of seven herbs and is derived from Yi-Gan San of traditional Chinese medicine.[48] Another noteworthy finding is that aripiprazole provided the best effectiveness in improving neuropsychiatric symptoms, and it did not exert negative effects on cognitive function and motor symptoms in patients with DLB; however, the evidence was derived from one small uncontrolled single-arm trial.[15] Further RCTs are needed to validate the overall efficacy of yokukansan and aripiprazole in DLB.

Limitations

There were some limitations to this study. First, only nine RCTs were recruited; therefore, the current NMA may be underpowered. Although the point estimates appear beneficial, several treatments did not reach statistical significance. Moreover, the inconsistency test may also be subject to low statistical power. Second, the study by Cummings et al.[12] had distinct study characteristics. Therefore, the estimated treatment effect of olanzapine may be influenced by these potential effect modifiers. Third, the evidence of zonisamide was solely derived from one RCT[21] where zonisamide was used as an adjunct to levodopa. Therefore, the effect of zonisamide on motor symptoms needs to be interpreted with caution. Third, most of the comparisons of our NMA came from indirect evidence, and the network structure was not extensively connected. Therefore, the generalizability of our findings may be limited. Fourth, because most of the DLB studies were uncontrolled single-arm trials, we used a contrast-based approach for the NMA of RCTs and an arm-based approach for the NMA of RCTs plus uncontrolled single-arm trials. The aim of the arm-based NMA was to explore the potential benefits of the treatments. Therefore, the findings of our arm-based NMA should be viewed as provisional and hypothesis-generating. Given that the findings of the present study were based on a primary NMA with only nine RCTs and a secondary NMA with most uncontrolled single-arm trials, the findings should be interpreted cautiously.

In conclusion, the management of DLB remains challenging. Treatment of a single symptom may have a trade-off with others. The NMA included evidence from available RCTs and provided the most comprehensive evidence for the selection of pharmacotherapy for treating different clusters of DLB-related symptoms. The rank-heat plot may assist clinicians in quickly recognizing the most effective treatment in each domain for overall consideration when making decisions for treatment. More well-conducted RCTs for DLB pharmacotherapies are needed to warrant treatment recommendations with precision and accuracy with NMA findings, including donepezil, zonisamide, aripiprazole, and yokukansan.

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CRediT authorship contribution statement

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Declaration of Interest

None

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.archger.2021.104474.

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