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REVIEW

Systematic review of pharmacological interventions for people with Lewy body dementia

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ABSTRACT

Objective: Lewy body dementia (LBD) is the second most common neurodegenerative dementia, and it causes earlier mortality and more morbidity than Alzheimer's disease. Reviewing current evidence on its pharmacological management is essential for developing evidence-based clinical guidelines, and for improving the quality of its clinical care. Hence, we systematically reviewed all studies that investigated the efficacy of any medication for managing various symptoms of LBD.

Method: We identified eligible studies by searching 15 databases comprehensively. We completed quality assessment, extracted relevant data, and performed GRADE assessment of available evidence. We conducted meta-analyses when appropriate (PROSPERO:CRD42020182166).

Results: We screened 18,884 papers and included 135 studies. Our meta-analyses confirmed level-1 evidence for Donepezil's efficacy of managing cognitive symptoms of dementia with Lewy bodies (DLB) (SMD = 0.63; $p < 0.001$) and Parkinson's Disease Dementia (PDD) (SMD = 0.43; $p < 0.01$), and managing hallucinations in DLB (SMD=-0.52; $p = 0.02$). Rivastigmine and Memantine have level-2 evidence for managing cognitive and neuropsychiatric symptoms of DLB. Olanzapine and Yokukansan have similar evidence for managing DLB neuropsychiatric symptoms. Level-2 evidence support the efficacy of Rivastigmine and Galantamine for managing cognitive and neuropsychiatric symptoms of PDD.

Conclusion: We list evidence-based recommendations for the pharmacological management of DLB and PDD, and propose specific clinical guidelines for improving their clinical management.

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KEYWORDS
Systematic review; meta-analysis; dementia; dementia with Lewy bodies; Parkinson's disease dementia; drug therapy; behavioural symptoms

Introduction

Lewy body dementias (LBD) are the second most common neurodegenerative dementia after Alzheimer's disease (AD) (Walker et al., 2015). LBD include Dementia with Lewy bodies (DLB) and Parkinson's disease (PD) dementia (PDD). LBD warrant more attention because of their more severe effect on cognition, behaviour, sleep, and mobility (McKeith et al., 2017), and earlier institutionalisation, higher costs, earlier mortality and poorer quality-of-life (QoL) than AD (Black & Almeida, 2004; Bostrom et al., 2007; Etters et al., 2008; Murman et al., 2003; Williams et al., 2006). Despite the enormous public health importance of LBD (Wortmann, 2012), they remain relatively under-researched. Various medications are used for managing cognitive, neuropsychiatric, and motor symptoms of LBD without any specific clinical guidelines guiding their use.

Systematically reviewing all studies that have investigated various pharmacological interventions for managing LBD is essential for developing evidence-based clinical guidelines. Such a comprehensive systematic review, specific to LBD, is not available. A prior systematic review included studies that investigated PD without dementia and people with mild cognitive impairment, and it summarised evidence from only 44 studies (Stinton et al., 2015). It supported the efficacy of Donepezil for managing cognitive symptoms of DLB and neuropsychiatric symptoms of PDD, and of Rivastigmine for managing PDD cognitive and neuropsychiatric symptoms. Adequate evidence supporting the use of other medications for DLB and PDD were not available then. A meta-analysis including only 10 clinical trials that investigated acetylcholinesterase inhibitors (AChI) and Memantine for managing people with PD without dementia, DLB, and PDD was published in 2015 (Wang et al., 2015). Another meta-analysis including 17 studies that investigated AChI, and a meta-analysis including seven studies that investigated Memantine in Lewy body disorders (LBD and PD without dementia) were published in 2015 (Matsunaga et al., 2015a, 2015b). These four reviews were not specific to LBD. Similarly, a recent meta-analysis including only 15 studies that investigated AChI and Memantine in Lewy body disorders did not include people with LBD exclusively (Meng et al., 2019). More than 30 relevant studies, including those that presented high-quality research evidence specific to LBD, have been published since 2015 (Fernandez, 2019; Hershey & Coleman-Jackson, 2019; Murata et al., 2018; Svenningsson et al., 2020; Zhang et al., 2019). Moreover, the revised consensus diagnostic criteria for DLB, published in 2017, has changed its clinical definition (McKeith et al., 2017).

We have published a systematic review of studies investigating the efficacy of non-pharmacological interventions for LBD (Morrin et al., 2018). High quality evidence supporting routine clinical use of any non-pharmacological intervention for LBD is lacking (Connors et al., 2018; Morrin et al., 2018). Lack of evidence-based non-pharmacological interventions increases the reliance on pharmacological interventions in clinical settings. There is an urgent need for a comprehensive systematic review that will facilitate developing specific evidence-based clinical management guidelines and formulating future research directives for DLB and PDD. Hence, we aimed to systematically review all studies that have investigated the

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efficacy of various pharmacological interventions for managing people with LBD exclusively.

Methods

Study design: Our systematic review protocol has been registered in the international prospective register of systematic reviews (PROSPERO: CRD42020182166***;*** https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020182166).

Eligibility criteria: Primary research studies were included if i) Participants had clinical diagnoses of DLB or PDD; ii) Study investigated the efficacy of at least one pharmacological intervention; iii) At least one of the primary or secondary study outcomes was changes in cognition, motor symptoms, activities of daily living (ADL), neuropsychiatric symptoms, QoL, hospitalisation, institutionalisation, mortality, carers' burden or treatment-related adverse effects. Our exclusion criteria were, i) Study investigating only people with PD without dementia; ii) Study did not report LBD data separately; iii) Opinion papers or reviews; iv) not published in English. We did not exclude any study because of its control group or lack of it.

Search strategy: We identified eligible studies by searching the following 15 databases comprehensively, Allied and Complementary Medicine Database (since 1985), Applied Social Sciences Index and Abstracts (since 1987), ClinicalTrials.gov, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Dementia and Cognitive Improvement Group Specialised Register, Cumulative Index to Nursing and Allied Health Literature (since 1937), EMBASE (since 1974), Educational Resources Information Center (since 1966), Health Technology Assessment Database (until 2018), MEDLINE/PubMed (since 1946), Open Grey, PROSPERO (since 2011), PsycINFO (since 1806), and Scopus (since 1970).

The search strategy comprised of population and intervention terms. Population terms were (Parkinson* AND dementia) OR (Lewy AND dementia). Intervention search terms were (Cholinesterase AND inhibitor*) OR Donepezil OR Rivastigmine OR Galantamine OR Memantine OR Antipsychotic* OR Levodopa OR Antidepressant* OR Modafinil OR Piracetam OR Amantadine OR Rotigotine OR Selegiline OR Clozapine OR Olanzapine OR Quetiapine OR Risperidone OR Aripiprazole OR Citalopram OR Sertraline OR Trazadone OR Duloxetine OR Mirtazapine OR SSRI OR SNRI OR (reuptake AND inhibitor) OR Haloperidol OR Clonazepam OR Ramelteon OR Lorazepam OR Diazepam OR Gabapentin OR Pregabalin OR Zonisamide OR Herbal* OR Valproate OR (Dopamine AND antagonist). All articles published before 1st July 2020 were considered. Backward citation analyses enhanced comprehensiveness.

Study selection: All identified abstracts were assessed for their eligibility. Full texts were sought for all potentially eligible abstracts. When full texts were not available, we contacted the corresponding author(s) by email. When the corresponding author(s) did not respond within 14 days, those abstracts were excluded. Later, full texts were assessed for their eligibility by a three-member review team. Any discrepancies were resolved through discussion with the involvement of an additional reviewer.

Data extraction: We extracted the following data, i) Study characteristics: study design, methods, study groups and sample sizes in each study group; ii) Participant characteristics: clinical diagnoses and mean age; iii) Investigated intervention, dosage, and follow-up duration; iv) Outcome measures; v) Results: study findings, attrition, baseline and follow-up data of relevant outcome measures, adverse effects, statistical methods, mean differences and standard errors of relevant outcome measures, and effect sizes; vi) Reported conclusions.

Quality assessment: We completed quality assessment using the Quality Assessment Tool for Quantitative Studies (Thomas et al., 2004). Quality of eligible case reports and case series were assessed using the CARE checklist (Gagnier et al., 2013). Quality concerns were highlighted, and we did not exclude any eligible study because of its quality.

Data synthesis: Narrative synthesis was carried out using extracted data. We synthesised data by grouping them according to their LBD subtype (DLB or PDD), symptom clusters, and pharmacological interventions. We established hierarchies of evidence using the Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence version-2.1 (OCEBM-Levels-of-Evidence-Working-Group, 2011). Clinical practice recommendations were made on the basis of available evidence and the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework (Guyatt et al., 2008). When three or more studies have investigated the efficacy of an intervention towards a specific outcome variable, meta-analyses were conducted using the STATA 16.1 software and its "metan" command (StataCorp, 2019). We assessed the degree of heterogeneity using Higgin's I^2. We employed either random-effects or fixed-effects meta-analyses. Standardised mean differences (SMD) were used to synthesise continuous data.

Results

Figure 1 presents the study selection process. A supplementary online material lists all 135 included studies. Supplementary Table 1 summarises the characteristics of all Randomised Controlled Trials (RCTs) that investigated pharmacological intervention(s) for managing LBD. Supplementary Tables 2–5 present our quality assessment findings.

Dementia with Lewy bodies

Tables 1 and 2 present the OCEBM levels of Evidence and GRADE certainty ratings (Guyatt et al., 2008) of various pharmacological interventions for managing DLB and PDD, respectively.

Cognitive symptoms

Donepezil: Twenty studies including three RCTs (Beversdorf et al., 2004; Ikeda et al., 2015; Mori et al., 2012) have investigated Donepezil for managing DLB cognitive symptoms. 17 studies including two longitudinal studies with 12 months follow-up (Ikeda et al., 2013; Mori et al., 2015) reported Donepezil leading to significant improvements. Our fixed-effects meta-analysis (Figure 2A) confirmed the efficacy of Donepezil (SMD = 0.63;95%CI = 0.42-0.83; $p < 0.001$). Dose-specific meta-analyses confirmed that low-doses (3-5mg/day; Figure 2B) (SMD = 0.64;95%CI = 0.12-1.16; $p = 0.02$) and routine clinical dose of Donepezil (10 mg/day; Figure 2C) (SMD = 0.64;95%CI = 0.33-0.96; $p < 0.001$) improve cognitive symptoms of DLB significantly.

Rivastigmine: Six studies including a RCT (McKeith et al., 2000) have investigated Rivastigmine. Four studies have reported significant improvements. A case report documented that increasing oral Rivastigmine dose up to 22.5 mg/day led to sustained benefits over four years without any safety concerns (Nour et al., 2016).

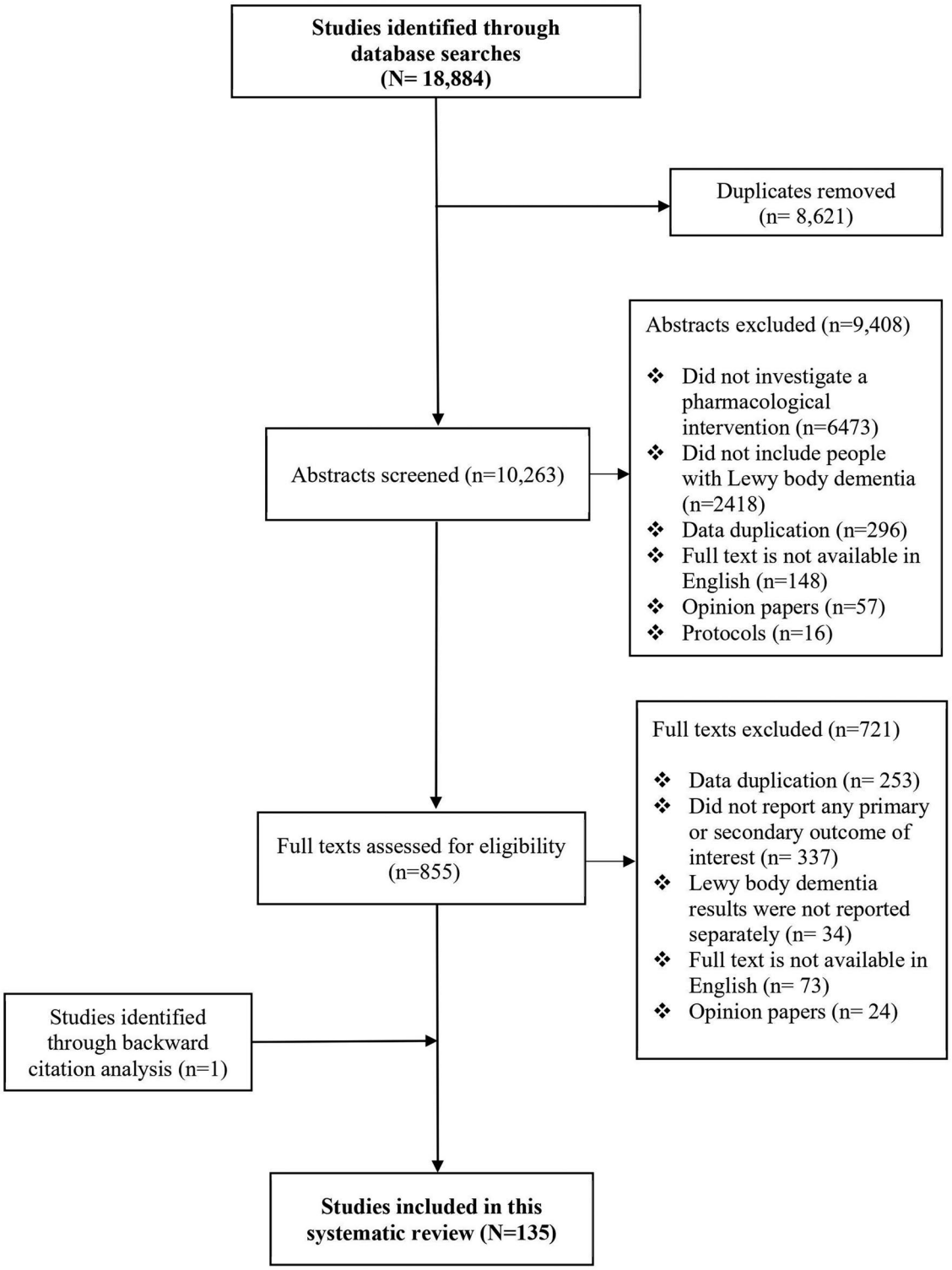

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.

Galantamine: Two non-randomised trials and three case reports have investigated Galantamine. An interim analysis reported significant improvement in cognitive symptoms (Edwards et al., 2004), and this effect was not sustained after 24 weeks (Edwards et al., 2007).

Memantine: Two RCTs have investigated Memantine, and both reported significant improvements after 24 weeks (Aarsland et al., 2009; Wesnes et al., 2015).

Neuropsychiatric symptoms

Donepezil: Twenty studies including two RCTs (Ikeda et al., 2015; Mori et al., 2012) have investigated Donepezil. Eleven studies reported significant improvements. One non-randomised trial (Minett et al., 2003) and a case report (Bhanji & Gauthier, 2005) have reported worsening of neuropsychiatric symptoms, while withdrawing Donepezil. Most studies measured the changes in neuropsychiatric symptoms using the Neuropsychiatric Inventory (NPI). Our random-effects meta-analysis confirmed the efficacy (SMD=-0.52;95%CI=-0.95–0.09; $p=0.02$) of Donepezil for reducing hallucinations and cognitive fluctuations (NPI-2) (Figure 3A). However, further meta-analyses (Figure 3B–D) showed that evidence supporting Donepezil for improving overall neuropsychiatric symptoms (NPI-10 scores) was not significant (SMD=-0.14;95%CI=-0.34–0.07; $p=0.19$). Moreover,

Table 1. Levels of evidence and GRADE certainty ratings of pharmacological interventions for people with dementia with Lewy bodies.

Outcome	Medication	Level of Evidence	GRADE certainty ratings
Cognitive symptoms	Donepezil	1	High
	Rivastigmine	2	High
	Memantine	2	High
	Galantamine	4	Low
Neuropsychiatric symptoms	Donepezil*	1	Moderate
	Rivastigmine	2	Moderate
	Yokukansan	2	Moderate
	Memantine	2	Low
	Olanzapine	2	Low
	Aripiprazole	4	Low
	Quetiapine	4	Very Low
	Clozapine	4	Very Low
	Paroxetine	4	Very Low
REM Sleep Behaviour Disorder	Memantine	2	Moderate
	Ramelteon	4	Low
	Clonazepam	4	Very Low
Motor symptoms	Zonisamide	2	High
	Levodopa	3	Moderate
Restless leg syndrome	Gabapentin	4	Low
Excessive daytime sedation	Armodafinil	4	Low
Mortality	Memantine	2	Low
	Donepezil	4	Low

*Hallucinations and cognitive fluctuations only; REM = Rapid Eye Movement; Levels of evidence: 1= Systematic review of randomised trials, 2= Randomised trial or observational study with dramatic effect, 3= Non-randomised controlled cohort/follow-up study, 4 = Case-series, case-control studies, or historically controlled studies, 5= Mechanism based reasoning; Grade of certainty: High = the true effect is similar to the estimated effect, Moderate = the true effect is probably close to the estimated effect; Low = the true effect may be markedly different from the estimated effect; Very Low = the true effect is probably markedly different from the estimated effect.

Table 2. Levels of evidence and GRADE certainty ratings of pharmacological interventions for people with Parkinson's disease dementia.

Outcome	Medication	Level of Evidence	GRADE certainty ratings
Cognitive symptoms	Donepezil	1	High
	Rivastigmine	2	High
	Galantamine	2	Moderate
	Donepezil & Di-Huang-Yi-Zhi	2	Moderate
	Memantine	3	Moderate
Neuropsychiatric symptoms	Rivastigmine	2	High
	Galantamine	2	Moderate
	Donepezil	3	Low
	Memantine	3	Low
	Clozapine	4	Low
	Risperidone	4	Low
	Quetiapine	4	Low
	Yokukansan	4	Low
	Olanzapine	4	Very Low
Depressive symptoms	Duloxetine	2	Moderate
	Sarcosine	2	Low
REM Sleep Behaviour Disorder	Memantine	2	Moderate
Motor symptoms	IRL752	2	Low
	Levodopa	3	Moderate
	Amantadine	4	Low
	Rotigotine	4	Low
	Zonisamide	4	Very Low

REM = Rapid Eye Movement; Levels of evidence: 1= Systematic review of randomised trials, 2= Randomised trial or observational study with dramatic effect, 3= Non-randomised controlled cohort/follow-up study, 4 = Case-series, case-control studies, or historically controlled studies, 5= Mechanism based reasoning; Grade of Certainty: High = the true effect is similar to the estimated effect, Moderate = the true effect is probably close to the estimated effect; Low = the true effect may be markedly different from the estimated effect; Very Low = the true effect is probably markedly different from the estimated effect.

three studies including 12 months follow-up did not support long-term efficacy of Donepezil (Ikeda et al., 2013; Mori et al., 2015; Tanaka & Kita, 2005).

Rivastigmine: Five studies including an RCT (McKeith et al., 2000) investigated Rivastigmine, and they reported significant improvements in NPI scores that were sustained up to 26 weeks. However, one longitudinal study with 96 weeks follow-up did not find significant improvement in NPI scores after 24 weeks (Grace et al., 2001).

Memantine: A RCT reported significant ($p = 0.04$) improvements in NPI scores after 24 weeks (Emre et al., 2010). Another RCT reported statistically not significant improvements (Aarsland et al., 2009). One case report has reported severe worsening of hallucinations following Memantine discontinuation, and substantial improvement after reinstating Memantine (Mathys et al., 2013). However, three case reports (Alisky, 2007; Menendez-Gonzalez et al., 2005; Ridha et al., 2005) have reported worsening of neuropsychiatric symptoms, especially visual hallucinations, with Memantine. Besides, another RCT has reported significant improvement in REM sleep behaviour disorder (RBD) with Memantine (Larsson et al., 2010).

Modafinil/Armodafinil: A non-randomised single-arm study reported significant improvements in sleepiness and neuropsychiatric symptoms in people with DLB and hypersomnia (Lapid et al., 2017). A case series reported improvements in global mental status, measured by the Clinical Global Impression scale (Varanese et al., 2013). However, worsening of psychosis and agitation in DLB ($N = 2$) with Modafinil has been reported (Prado et al., 2012).

Clozapine: Only four case reports provide evidence for Clozapine. Two case reports reported favourable outcomes (Chacko et al., 1993), and one of them reported virtual remission in agitation and marked reduction in hallucinations (Bhamra et al., 2018). However, worsening of confusion and other neuropsychiatric symptoms have been reported in DLB ($N = 2$) following Clozapine treatment (Burke et al., 1998). Severe neuroleptic sensitivity and coma following a single Clozapine dose have been reported (Sadek & Rockwood, 2003).

Quetiapine: A case series and two case reports ($N = 8$) have supported the efficacy of Quetiapine (Rice et al., 2013; Takahashi et al., 2003; Terao et al., 2003). However, severe neuroleptic malignant syndrome (NMS) have been reported in two people with DLB following Quetiapine treatment (Kobayashi et al., 2017; Shea & Chu, 2016).

Risperidone: A 12-week long RCT reported substantial worsening of NPI scores and significantly more frequent adverse events in DLB following Risperidone treatment (Culo et al., 2010). Five case reports added evidence for worsening of neuropsychiatric symptoms with Risperidone and they reported severe adverse events including torticollis, rigidity, and NMS (Boothby, 1996; McKeith et al., 1995; Sechi et al., 2000). There is level-2 evidence for the harmful effects of Risperidone in DLB.

Olanzapine: A post-hoc analysis of people with DLB ($n = 29$), included in a larger double-blind RCT of Olanzapine for treating psychosis in dementias, showed significant improvements in delusions and hallucinations of people with DLB, who received 5-10mg/day of Olanzapine. The study reported that Olanzapine could reduce psychosis in DLB without worsening Parkinsonian symptoms (Cummings et al., 2002). A longitudinal study followed four people with DLB, treated with Olanzapine for 24 months, and reported significant improvements in overall NPI scores, delusions, hallucinations, agitation and depression (Moretti et al., 2003). Both studies reported that Olanzapine was well-tolerated in DLB. However, a case series including eight people with DLB reported substantial improvements in only two people (Walker et al., 1999). Only five of them could tolerate Olanzapine (2.5-7.5 mg/day). Reported adverse effects included somnolence, disorientation, and postural instability.

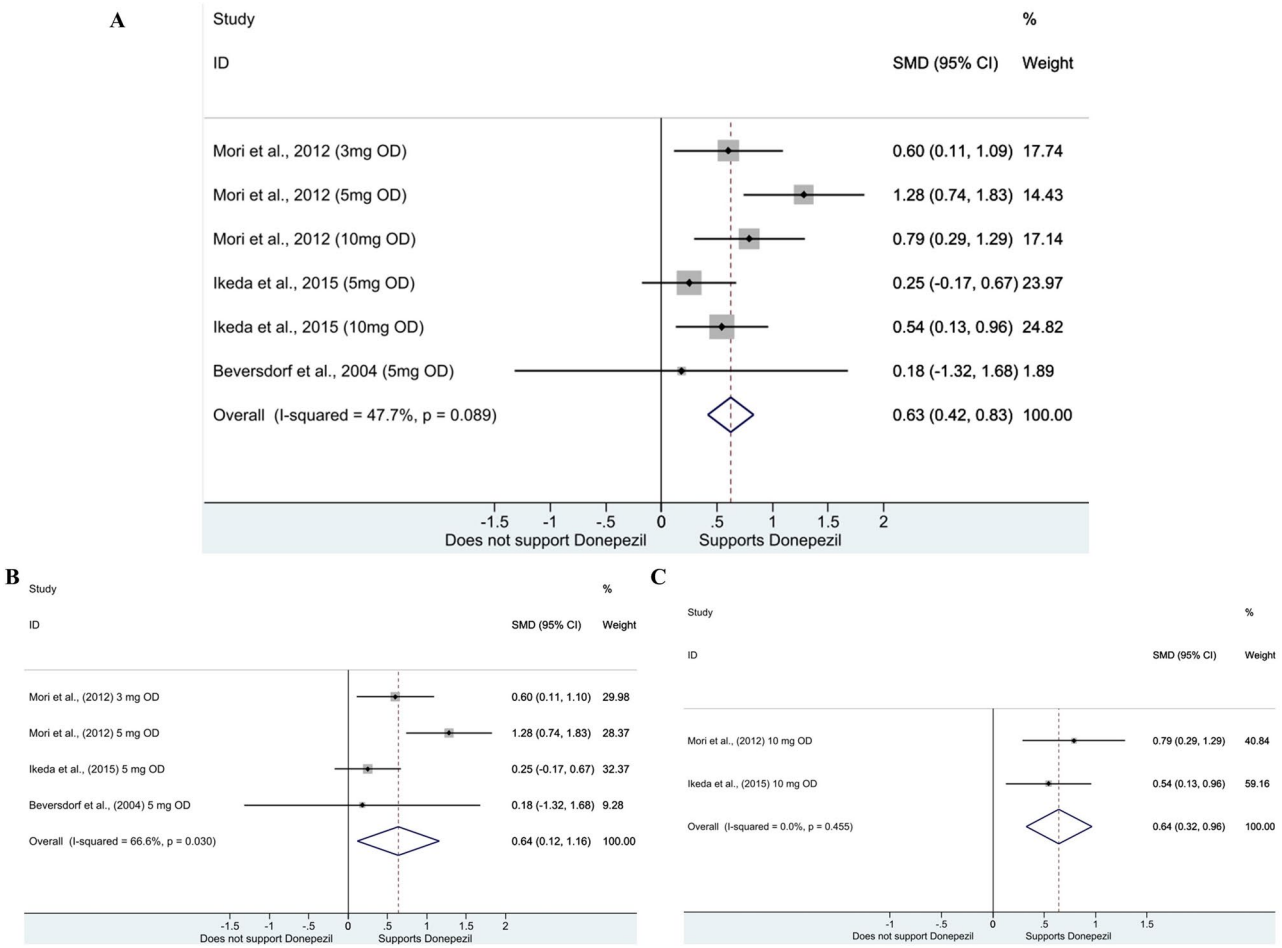

Figure 2. Meta-analyses of studies that have investigated the efficacy of Donepezil for managing cognitive symptoms in people with dementia with Lewy bodies. **2-A**: Fixed-effects meta-analysis of studies that have investigated the efficacy of Donepezil (3-10mg/day) for managing cognitive symptoms in people with dementia with Lewy bodies (DLB); **2-B**: Random-effects meta-analysis of studies that have investigated the efficacy of 3-5mg/day doses of Donepezil for managing cognitive symptoms in people with DLB; **2-C**: Fixed-effects meta-analysis of studies that have investigated the efficacy of 10mg/day dose of Donepezil for managing cognitive symptoms in people with DLB.

Aripiprazole: A 10-week long open-label trial ($N = 11$) and a case report reported significant improvements in NPI scores and indicated that Aripiprazole was well tolerated in DLB (Lee & Shen, 2017; Sugawara Kikuchi & Shimizu, 2019).

Dopamine antagonists: A case series presented the efficacy and safety of Thioridazine, Haloperidol, Trifluoperazine, Flupentixol decanoate, Sulpiride, and Promazine in DLB ($N = 20$). It did not find clinical benefits, and reported severe neuroleptic sensitivity including three fatal outcomes (McKeith et al., 1992).

Herbal medicines (Yokukansan/Feru-guard): A single-blind RCT reported that Asian traditional medicine Yokukansan (*Yi-Gan San*;TJ-54) led to significant improvements in NPI scores in people with dementia including DLB (Iwasaki et al., 2005). A multi-centre cross-over open-label RCT reported significant improvements in NPI scores in DLB, treated with Yokukansan (Mizukami et al., 2009). A multi-centre case series ($N = 63$) reported that Yokukansan led to significant improvements in neuropsychiatric symptoms without worsening Parkinsonian symptoms (Iwasaki et al., 2012) in DLB. Another case report added evidence for the efficacy and safety of Yokukansan for managing psychosis in DLB (Shinno et al., 2007). Besides, an open-label trial ($N = 10$) supported the efficacy and safety of another herbal medicine, Feru-guard, for managing DLB neuropsychiatric symptoms (Kimura et al., 2011).

Ramelteon: A case series ($N = 4$) reported substantial improvements in visual hallucinations and RBD in DLB (Kasanuki et al., 2013).

Clonazepam: Clinically significant improvements in RBD in two people with DLB have been reported (Massironi et al., 2003).

Antidepressants: A RCT found that Citalopram led to substantial worsening of NPI scores in DLB, and that 71.4% of people who received Citalopram discontinued the study (Culo et al., 2010). Clinically significant reductions in visual hallucinations in two people with DLB, treated with Paroxetine, have been reported (Tanaka & Kita, 2005). Other antidepressant medications have not been investigated in DLB.

Motor symptoms

Anticonvulsants: Zonisamide significantly ($p = 0.003$) improved motor symptoms, measured by the Unified Parkinson's Disease Rating Scale (UPDRS-III), without worsening cognitive and neuropsychiatric symptoms in DLB (Murata et al., 2018). A case series ($N = 3$) and a case report have corroborated these findings (Odawara et al., 2010; Sato et al., 2010). Furthermore, successful management of restless leg syndrome by Gabapentin in a person with DLB has been reported (Fujishiro, 2014). No evidence supports the use of other anticonvulsant medications including Valproate in DLB.

Antiparkinsonian medications: Seven non-randomised trials and a case report reported beneficial effects of Levodopa on motor symptoms of at least one third of people with DLB and the risk of Levodopa worsening DLB neuropsychiatric symptoms (Bonelli et al., 2004; Fujishiro et al., 2013; Goldman

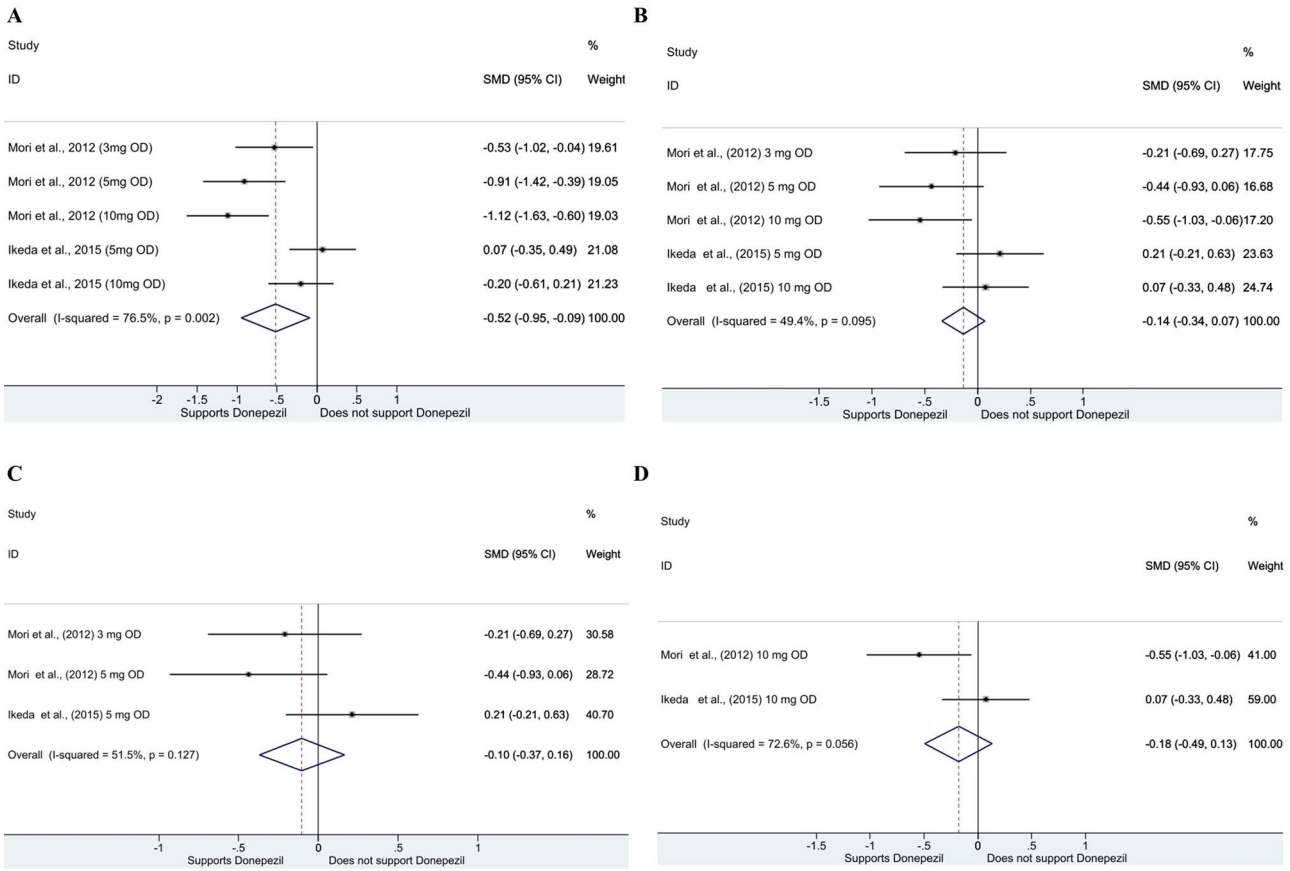

Figure 3. Meta-analyses of studies that have investigated the efficacy of Donepezil for managing neuropsychiatric symptoms in people with dementia with Lewy bodies. **3-A**: Random-effects meta-analysis of studies that have investigated the efficacy of Donepezil (3-10mg/day) for reducing hallucinations and cognitive fluctuations, measured by the Neuropsychiatric inventory (NPI) two-item subscore (NPI-2), in people with dementia with Lewy bodies (DLB); **3-B**: Fixed-effects meta-analysis of studies that have investigated the efficacy of Donepezil (3-10mg/day) for reducing overall neuropsychiatric symptoms, measured by NPI-10 score, in people with DLB; **3-C**: Fixed-effects meta-analysis of studies that have investigated the efficacy of 3-5mg/day doses of Donepezil for reducing neuropsychiatric symptoms, measured by NPI-10 score, in people with DLB; **3-D**: Fixed-effects meta-analysis of studies that have investigated the efficacy of 10mg/day dose of Donepezil for reducing neuropsychiatric symptoms, measured by NPI-10 score, in people with DLB.

et al., 2008; Molloy et al., 2005, 2006; Onofrj et al., 2013). Two longitudinal Levodopa studies reported less improvements in motor symptoms in DLB, compared to PD (Lucetti et al., 2010; Molloy et al., 2009).

Mortality

A retrospective chart review reported that Donepezil significantly improved life expectancy of people with DLB by 2.8 years (Meguro et al., 2018). A 36-months long open-label study following an RCT (Aarsland et al., 2009) found that early treatment with Memantine led to significantly longer survival in DLB (Stubendorff et al., 2014).

Parkinson's disease dementia

Cognitive symptoms

Donepezil: Nine studies including three RCTs (Dubois et al., 2012; Leroi et al., 2004; Ravina et al., 2005) have investigated Donepezil for managing cognitive symptoms of PDD. Eight studies including a longitudinal study with 52 weeks follow-up (Dubois, 2004) reported significant improvements. Our fixed-effects meta-analysis (Figure 4A) confirmed the efficacy of Donepezil (5-10mg/day) (SMD = 0.43;95%CI = 0.28-0.57; $p < 0.01$).

Rivastigmine: Nine studies including a RCT (Emre et al., 2004) and its extension study (Poewe et al., 2006) have investigated rivastigmine. Six studies have reported significant improvements. Long-term Rivastigmine treatment was well tolerated, and its benefits on cognitive symptoms were sustained up to 48 weeks (Poewe et al., 2006).

Galantamine: An open-label RCT (Litvinenko et al., 2008) and an uncontrolled trial (Aarsland et al., 2003) found significant improvements in MMSE scores, and the benefits were sustained up to 24 weeks follow-up.

Memantine: Four studies among the eight studies that have investigated Memantine reported significant improvements after 16-24 weeks. Two studies that included 52 weeks (Litvinenko et al., 2010) and 18 months (Jeong et al., 2016) follow-up did not show significant differences. We combined the results of two non-RCTs (Levin et al., 2009; Litvinenko et al., 2010) and the only RCT (Leroi et al., 2009), which used MMSE, by random-effects meta-analysis (Figure 4B). Overall effects of Memantine on PDD cognitive symptoms was not significant (SMD = 0.68;95%CI=-0.63-1.98; $p = 0.31$).

Piracetam: One RCT did not find significant difference in cognitive symptoms after 24 weeks (Sano et al., 1990).

Selegiline: A non-randomised trial ($N = 4$) did not report significant difference in PDD cognitive symptoms (Portin & Rinne, 1983).

Neuropsychiatric symptoms

Donepezil: A RCT measuring neuropsychiatric symptoms by the Brief Psychiatric Rating Scale (BPRS) did not find significant difference (Ravina et al., 2005). We combined the results of both

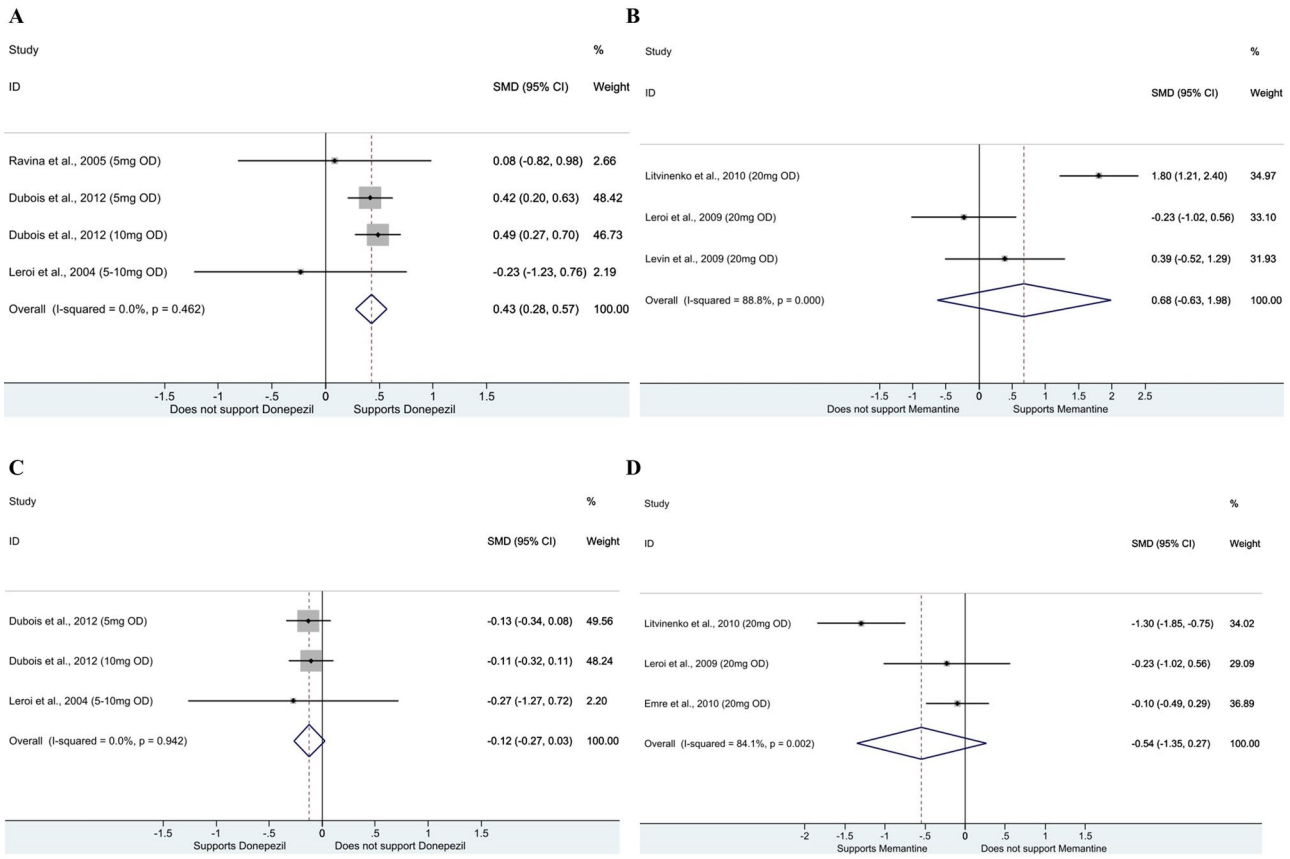

Figure 4. Meta-analyses of studies that have investigated the efficacy of Donepezil or Memantine for managing cognitive or neuropsychiatric symptoms in people with Parkinson's Disease Dementia. **4-A**: Fixed-effects meta-analysis of studies that have investigated the efficacy of Donepezil for managing cognitive symptoms in people with Parkinson's Disease Dementia (PDD); **4-B**: Fixed-effects meta-analysis of studies that have investigated the efficacy of Memantine for managing cognitive symptoms in people with PDD; **4-C**: Random-effects meta-analysis of studies that have investigated the efficacy of Donepezil for reducing neuropsychiatric symptoms in people with PDD; **4-D**: Random-effects meta-analysis studies that have investigated the efficacy of Memantine for reducing neuropsychiatric symptoms in people with PDD.

RCTs (Dubois et al., 2012; Leroi et al., 2004), which used the NPI, by fixed-effects meta-analyses (Figure 4C), and confirmed that Donepezil did not improve neuropsychiatric symptoms significantly (SMD=-0.12;95%CI=-0.27-0.03; $p=0.11$). However, a non-RCT (Thomas et al., 2005) and a single-arm open-label trial (Ishikawa et al., 2014) reported clinically significant improvements in NPI scores.

Rivastigmine: Six out of eight studies that have investigated Rivastigmine including the only RCT (Emre et al., 2004) and its extension study (Poewe et al., 2006) have reported significant improvements in NPI scores.

Galantamine: A RCT reported significant improvements in NPI hallucinations, anxiety, sleep disturbance, and apathy scores (Litvinenko et al., 2008). An uncontrolled trial (Aarsland et al., 2003) reported clinically significant improvements in seven people with PDD.

Memantine: Three RCTs did not find significant improvements (Aarsland et al., 2009; Emre et al., 2010; Leroi et al., 2009). One non-RCT reported significant improvements (Litvinenko et al., 2010). Two non-RCTs (Jeong et al., 2016; Levin et al., 2009) did not find significant improvements. We combined the results of two non-RCTs and an RCT, which used NPI, by random-effects meta-analysis (Figure 4D). We did not include the RCT (Aarsland et al., 2009) that recruited mixed group of PDD and DLB in this meta-analysis. Our meta-analysis confirmed that Memantine did not improve neuropsychiatric symptoms significantly (SMD=-0.54;95%CI=-1.35-0.27; $p=0.19$). Moreover, another RCT reported significant improvement in RBD of PDD with Memantine (Larsson et al., 2010).

Risperidone: A case series ($N=9$) reported significant improvements in the BPRS and the Cohen-Mansfield Agitation Inventory scores with Risperidone (Workman et al., 1997). People with PDD reportedly tolerated Risperidone well.

Quetiapine: An open-label study (Prohorov et al., 2006) did not find significant improvements in BPRS scores. A retrospective chart review (Reddy et al., 2002) reported that 90% (18/20) of people with PDD experienced clinically significant improvements in psychotic symptoms with Quetiapine, and only 25% experienced worsening of their motor symptoms. A small RCT that investigated Quetiapine in a group of people with DLB, PDD and AD with Parkinsonian symptoms did not report the data on LBD separately (Kurlan et al., 2007), so it was not included in this review. That RCT did not find significant differences in NPI scores.

Olanzapine: A longitudinal study that included three people with PDD reported significant improvements after 24 months (Moretti et al., 2003). An open-label trial ($N=6$) (Marsh et al., 2001) did not find improvement in psychotic symptoms, and it reported that four participants discontinued the trial early because of adverse effects.

Clozapine: A retrospective chart review ($N=8$) (Lee et al., 2007) is the only available evidence supporting the use of Clozapine in PDD. It has reported clinically significant improvements in agitation.

Herbal medicines: A double-blind RCT that investigated the efficacy of combined treatment with Donepezil and Di-Huang-Yi-Zhi ($n=60$) (Gu et al., 2015) reported that the combined treatment led to significant improvements in cognition and ADL.

Another RCT that evaluated a "cocktail therapy" (Donepezil, Dl-3n-butylphthalide, Oxiracetam, and Ginkgo biloba) ($N=60$) reported significant improvements in cognition and behaviours (Zhang et al., 2019). A single-arm trial (Kawanabe et al., 2010) ($N=7$) investigating Yokukansan reported significant improvements in NPI scores.

Modafinil/Armodafinil: A case series (Varanese et al., 2013) reported variable improvements in global mental status in four people with PDD.

Sarcosine: A RCT found that Sarcosine led to significant but transient improvements in depressive symptoms, measured by the Hamilton Depression Rating Scale (HDRS), at week two, and in NPI scores at week four without worsening motor and cognitive symptoms. These improvements were not sustained at eight weeks (Tsai et al., 2014).

Antidepressants: A single-blind three-arm RCT ($N=23$) investigated Duloxetine, Escitalopram and Trazodone in PDD (Vasile et al., 2010). All three antidepressants significantly improved depressive symptoms, compared to baseline scores. Duloxetine was significantly ($p<0.01$) more effective than Escitalopram and Trazodone in reducing depressive symptoms after eight weeks.

Motor symptoms

Memantine: Six studies including three RCTs (Aarsland et al., 2009; Emre et al., 2010; Leroi et al., 2009) did not find significant improvements. Our fixed-effects meta-analysis (Supplementary Figure 3) confirmed that Memantine did not improve motor symptoms significantly (SMD=-0.09;95%CI =-0.36-0.18; $p=0.52$).

Levodopa: A double-blind RCT ($N=11$) and four non-randomised trials have investigated Levodopa for managing motor symptoms. The experimental group undergoing Levodopa withdrawal and the control group continuing Levodopa in the RCT (Tse et al., 2008) did not differ significantly on their motor symptoms. Their findings supported withdrawing Levodopa in people with advanced PDD for reducing medication-related adverse effects and for improving health-related QoL. Three non-randomised trials have reported significant improvements in motor symptoms (Bonelli et al., 2004; Molloy et al., 2005, 2006).

Rotigotine: A case series ($N=9$) reported clinically significant improvements in motor symptoms with Rotigotine transdermal patch (Strothjohann & Fuchs, 2011). Slight improvement in motor symptoms without worsening cognitive and neuropsychiatric symptoms of two people with PDD have been reported. Rotigotine transdermal patches could reduce anxiety associated with Levodopa wearing off in PDD (Fanciulli et al., 2013).

Amantadine: A non-randomised trial ($N=10$) reported significant improvements in cognitive and motor symptoms of PDD after six months (Yablonskaya et al., 2011).

SYN120: A RCT ($N=82$) that investigated SYN120, an antagonist of 5-HT_6 and 5-HT_{2A} receptors, did not find significant improvements in cognition, and it found significant worsening of motor symptoms and visual hallucinations in PDD (Fernandez, 2019).

IRL752: IRL752 is a selective enhancer of cortical dopamine, acetylcholine and norepinephrine. A phase-2a double-blind RCT reported significant improvements in UPDRS scores with IRL752 (Svenningsson et al., 2020).

Anticonvulsants: A case report with one-year follow-up presented clinically significant improvements in motor symptoms, behaviours, mood and ADL of a man with PDD (Tombini et al., 2013).

QoL and caregiver burden

A 22-week-long double-blind RCT ($N=25$) found that Memantine significantly improved goal attainment and significantly reduced caregivers' burden. QoL did not differ significantly (Leroi et al., 2014). A secondary analysis (Larsson et al., 2011) of another RCT (Aarsland et al., 2009) reported that Memantine significantly ($p=0.01$) improved caregiver-rated QoL of people with DLB and PDD.

Discussion

This is the first comprehensive systematic review that summarised the efficacy of pharmacological interventions for managing all clinical symptoms of DLB and PDD exclusively. We have summarised evidence from 135 studies, and have presented the up-to-date evidence for the pharmacological management of DLB and PDD separately. Strengths include comprehensive searches of 15 databases including grey literature, rigorous quality assessment, and GRADE assessment of current evidence. Limitations include excluding non-English studies, and studies that included people with LBD but did not report their data separately. Current evidence for the pharmacological management of LBD is relatively weaker than those of AD and PD. Small sample sizes, and lack of appropriate controls, blinding, and attention to confounding variables were common limitations of included studies. Only seven DLB studies and five PDD studies had follow-up longer than a year, so evidence for the long-term efficacy and safety of pharmacological interventions for LBD is limited. There were few studies employing clinically important outcome measures such as QoL, ADL and time to nursing home admissions. Moreover, DLB clinical diagnostic criteria is still evolving (McKeith et al., 2017), and this should be considered while interpreting evidence from older studies.

Our meta-analyses confirmed the efficacy of Donepezil for managing cognition in DLB, and added new evidence for the efficacy of low-dose (3-5mg/day) Donepezil regime. People with DLB, who cannot tolerate 10 mg/day of Donepezil, are likely to benefit by staying on low doses. Moreover, prior meta-analysis (Stinton et al., 2015) reported that Donepezil did not improve DLB neuropsychiatric symptoms significantly. We confirmed this finding for total NPI scores, but found level-1 evidence for Donepezil improving hallucinations and cognitive fluctuations in DLB. There are level-2 evidence supporting the efficacy of Rivastigmine for managing cognitive and neuropsychiatric symptoms, Memantine for managing cognitive, neuropsychiatric, RBD and mortality, Olanzapine and Yokukansan for managing neuropsychiatric symptoms, and Zonisamide for managing motor symptoms of DLB. Yokukansan has stronger evidence supporting its efficacy than any antipsychotic or antidepressant medication for managing DLB neuropsychiatric symptoms, and it is used in only a few Asian countries. Severe neuroleptic sensitivity including NMS have been reported in people with DLB, treated with first-generation antipsychotics, Risperidone, Quetiapine and Clozapine, and safety data available for other antipsychotics are sparse.

Our findings supported the efficacy of Donepezil for managing PDD cognitive symptoms. There are level-2 evidence supporting Rivastigmine and Galantamine for managing cognitive and neuropsychiatric symptoms, Memantine for managing RBD, Duloxetine for managing depressive symptoms, and IRL752 for managing motor symptoms of PDD. Although Clozapine is widely used in clinical settings for managing psychosis in PD without dementia (Seppi et al., 2019; Taylor et al.,

2021), there is very limited evidence supporting its use in PDD. Considering the weak evidence supporting other interventions, further research is warranted for investigating the efficacy and safety of Clozapine in PDD.

The clinical need for developing specific guidelines for the pharmacological management of LBD cannot be overemphasised. Current National Institute for Health and Care Excellence (NICE), UK, guidelines for assessment and management of dementia (NICE, 2018) includes only a few sentences regarding DLB pharmacological management. It guides to offer Donepezil or Rivastigmine to all people with DLB. Despite having only level-4 evidence, it recommends offering Galantamine to people with DLB, who cannot tolerate Donepezil and Rivastigmine. It recommends considering Memantine when AChI are poorly tolerated. It does not include any recommendation for managing neuropsychiatric or other symptoms of DLB. Similarly, the current NICE guidelines for PD (NICE, 2017) includes only four sentences about PDD pharmacological management. It recommends offering an AChI for all with PDD, and considering Memantine when AChI are not tolerated. People with LBD experience more frequent and more severe neuropsychiatric symptoms than AD (Rajkumar & Aarsland, 2020a). Lack of specific clinical guidelines leads clinical psychiatrists managing these symptoms to prescribe various medications that lack evidence for their efficacy and safety. Such prescription practices are often influenced by anecdotal evidence, popular beliefs, and evidence from AD or PD studies. Hence, we propose specific evidence-based clinical guidelines for the pharmacological management of DLB and PDD in Table 3. Considering ongoing research, we recommend reviewing evidence and updating these clinical guidelines every third year.

Pharmacological management of LBD should be a part of well-coordinated multidisciplinary management providing holistic person-centred care. Distressing neuropsychiatric symptoms associated with risks to self and others, and disabling motor symptoms associated with risk of falls often coexist in LBD. Most pharmacological interventions for managing neuropsychiatric symptoms worsen motor symptoms of LBD and vice versa, so clinical psychiatrists, service users and their carers often need to make a difficult choice between mobility and psychosis. This systematic review can aid such tough therapeutic decision making processes by informing the up-to-date evidence.

This review highlights the need for future research on, i) Long-term trials investigating the efficacy of Rivastigmine, Galantamine and Memantine for managing cognitive symptoms of LBD; ii) Clinical trials including clinically relevant effectiveness measures; iii) Clinical trials investigating the efficacy and safety of combined treatment with AChI and Memantine in LBD; iv) Trials investigating antidepressant medications for managing depressive symptoms in LBD; v) International multi-centre RCTs investigating the efficacy and safety of Asian herbal medicines, especially Yokukansan, for managing LBD neuropsychiatric symptoms; vi) Adequately powered clinical trials investigating the efficacy of Memantine and Ramelteon for managing RBD in LBD; vii) National level clinical audits and observational studies for gathering more evidence regarding the use of antipsychotics in LBD; viii) Pharmacogenetic studies for predicting clinical responses, and risks of severe adverse events, especially NMS, in LBD; ix) Multi-omics studies for identifying novel therapeutic targets (Rajkumar et al., 2020); x) Studies investigating potential immunotherapies for LBD (Wang et al., 2019).

Table 3. Proposed clinical guidelines for the pharmacological management of Lewy body dementias.

1 Pharmacological management of people with Dementia with Lewy bodies (DLB)

1.1 Cognitive symptoms:

1.1.1. Offer Donepezil for all people with DLB.

1.1.2. If Donepezil 10 mg/day dose is not tolerated, consider low dose (3-5mg/day) regime.

1.1.3. Consider Rivastigmine or Memantine if Donepezil is contraindicated or low dose Donepezil treatment is not tolerated.

1.1.4. There is no evidence supporting the prescription of Memantine and an acetylcholinesterase inhibitor (AChI) together.**1.2 Neuropsychiatric symptoms:**

1.2.1. Offer Donepezil for managing hallucinations and cognitive fluctuations associated with DLB.

1.2.2. Consider Rivastigmine or Memantine monotherapy if other neuropsychiatric symptoms associated with DLB lead to more clinical risks.

1.2.3. Typical antipsychotics and Risperidone must not be prescribed for people with DLB.

1.2.4. Use of any antipsychotic medication should be avoided.

1.2.4.1. When there is extremely high risk of harm to self or others despite the best possible treatment with non-pharmacological interventions and AChI or Memantine, options of Olanzapine, Aripiprazole, Quetiapine, Clozapine and Paroxetine can be considered after extensive risk benefit analyses involving the service user, family members and carers.

1.2.4.2. Olanzapine has better evidence than other antipsychotic medications. However, its safety in people with DLB remains uncertain.

1.2.5. Citalopram should not be prescribed. There is no evidence supporting the use of any antidepressant medication for managing depressive symptoms associated with DLB.

1.3 Other symptoms:

1.3.1. Consider Memantine monotherapy for managing REM sleep behaviour disorder (RBD).

1.3.1.1. Ramelteon and Clonazepam are second line options for managing RBD.

1.3.2. Consider Zonisamide for managing motor symptoms of DLB.

2 Pharmacological management of people with Parkinson's Disease Dementia (PDD)

2.1 **Cognitive symptoms**:

2.1.1. Offer Donepezil or Rivastigmine monotherapy for all people with PDD.

2.1.2. Consider Memantine or Galantamine if Donepezil and Rivastigmine are contraindicated or poorly tolerated.

2.1.3. There is no evidence supporting the prescription of Memantine and an AChI together.

2.2 Neuropsychiatric symptoms:

2.2.1. Offer Rivastigmine if there are neuropsychiatric symptoms leading to clinical risks.

2.2.2. Consider Donepezil or Galantamine or Memantine if Rivastigmine is contraindicated or not tolerated.

2.2.3. Use of any antipsychotic medication should be avoided.

2.2.3.1. When there is extremely high risk of harm to self or others despite the best possible treatment with non-pharmacological interventions and AChI or Memantine, options of Quetiapine, Clozapine, Risperidone and Olanzapine can be considered after extensive risk benefit analyses involving the service user, family members and carers.

2.2.4. Offer Duloxetine for managing depressive symptoms associated with PDD.

2.3 Other symptoms:

2.3.1. Consider Memantine monotherapy if RBD leads to more clinical risks.

2.3.2. Consider reducing or withdrawing dopaminergic medication(s) including Levodopa after detailed risk benefit analyses involving neurologists, service users, and carers.

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Data availability statement

Data availability is not applicable to this article because no new data were created by this study.

Author contribution

KEW and APR wrote the initial study protocol. KEW conducted the search, reviewed papers for inclusion, conducted quality assessments, extracted data, and wrote the initial manuscript. NJS and PGB reviewed papers for inclusion and contributed to quality assessment. APR provided necessary supervision, contributed to article selection, and completed all meta-analyses. All authors were involved in critical revisions of the manuscript and all authors have approved the final submitted version.

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