

Evidence-Based Review of Therapeutic Approaches in Dementia with Lewy Bodies

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Abstract

Dementia with Lewy Bodies (DLB) is estimated to affect around 15-20% of dementia cases globally. This places it as the second most common type of dementia after Alzheimer's disease (AD). Paradoxically, clinical trials addressing the complex symptomatology of DLB are sparse compared to AD. While substantial progress has been made in overcoming the diagnostic challenges, evidence-based treatment is elusive.

In this review we summarize the available placebo-controlled clinical trials and identify areas of need to develop treatment strategies.

Keywords: Dementia; Alzheimer's disease; Lewy bodies

Introduction

Our understanding of Dementia with Lewy Bodies is progressively updated and shaped every few years. The most recent consensus report of DLB consortium proposes essential, core and supportive clinical features [1-3]. The following are the core clinical features of the disease: Cognitive Fluctuations, Visual Hallucinations, Parkinsonism and REM sleep behavior disorder [3]. While the latter was previously considered only suggestive of the disease, built on accumulating longitudinal evidence, it is now among the core features. The most recent consensus has also re-assigned all of the suggestive features to the supportive clinical feature and indicative biomarkers categories. The severe sensitivity to neuroleptic agents is now one of the supportive clinical features and the low dopamine transporter uptake Imaging is within the indicative biomarkers [3].

Tools for the diagnostic suspicion of DLB have been lacking and have been a limitation to the diagnosis of the disease outside expert centers. The Lewy Body Composite Risk score [4,5] was developed to help differentiate DLB patients from other types of dementia; ($p < 0.001$). It can also assist physicians to distinguish Mild Cognitive Impairment (MCI) due to Dementia with Lewy Bodies from the MCI due to Alzheimer's disease (AD). The composite score relies on the caregivers' input and was designed as an easy assessment tool to be used by clinicians that need only 3 min to be performed. It is composed of ten structured questions that are divided to ask about motor disturbances (questions 1-4), i.e., bradykinesia, rigidity, falls, tremors and non-motor features (questions 5-10), i.e., sleep disorders, staring spells, visual hallucinations, RBD, autonomic dysregulation. Positive answers to these questions are suggestive of dementia with lewy bodies. A score of equal to or more than 3 is suggestive of lewy body pathology with a sensitivity of 94.2% and specificity of 78.2% [4].

Once DLB is suspected, diagnostic certainty can be increased by the use of biomarkers. Biomarker development is an active field of research in all types of dementia as early diagnosis is recognized as a prerequisite for an optimum therapeutic impact. In the basal Ganglia, mesostriatal neuronal ends secrete dopamine to interact with the post-synaptic dopamine receptors. Both SPECT and PET imaging are able to assess dopamine activity in the pre- and post-synaptic ends with appropriate tracers [6,7]. Dopamine Transporter Uptake (DAT) on the pre-synaptic ends of dopaminergic neurons is a broadly utilized approach and part of the diagnostic criteria. Diminished DAT uptake as demonstrated

by the 123Iodine FP-CIT SPECT imaging is considered indicative of DLB and along with other clinical features ascertains the diagnosis [3]. Polysomnography diagnostic of REM sleep behavior disorder and 123Iodine-MIBG myocardial scintigraphy are also accepted indicative biomarkers [3]. 18F-FDG PET scan has a role in the differential diagnosis of DLB from other types of dementia. In DLB, marked hypometabolism is seen mainly in the parieto-occipital cortex. The involvement of the visual association cortex along with hypometabolism in the pons, thalamus and amygdala may explain the visual hallucinations in these patients [8]. Experimentally, new biomarker tracers with higher affinity are still under investigation [6].

Biomarkers looking at the alpha-synuclein deposition in other peripheral tissues in these patients are under investigation [9-12]. One study looked at the presence of alpha-synuclein in the nasal mucosa [12], which was pertinent in clinically diagnosed PD and DLB. The additional discovery of alpha-synuclein in the GIT within the lower esophagus [10,11] and the submandibular glands [9,10] is of major interest. These two locations were the most affected non-neural tissues and the easy accessibility of these two; make them of high value in future biomarker development.

The cognitive deficit in Dementia with Lewy bodies' is attributed to the cholinergic deficit. In DLB, degeneration of cholinergic neurons of the basal ganglia projecting to the cortex has been identified in disease pathology [13]. The Neuropsychiatric symptoms observed by the patients and their caregivers have also been attributed to this cholinergic deficit. Thus, cholinomimetics have been a focus of investigation in the past decade. Neuropsychiatric symptoms, however, are not only caused by the cholinergic deficit but are also caused by an imbalance of neurotransmitters, including but not limited to dopamine, glutamate and serotonin [14]. DLB is less studied than AD, as clinical trials

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traditionally face more challenges with the diagnostic uncertainties and the complex array of symptomatology experienced by these patients. The lower incidence and faster progression pose a challenge for subject enrollment to double-blind studies and the complexity of phenotype is a burden for assessment strategies and makes the identification of primary outcome measures difficult.

This paper will review the role of current therapeutic modalities for the treatment of DLB, from an evidence-based perspective.

Methods

We performed an online search of Pubmed, Google Scholar and Clinicaltrials.gov using the following keywords: “Dementia with Lewy bodies”-“Donepezil”-“Memantine”-“double-blind, placebo-controlled trials”-“Lewy body dementia”-“Screening”-“therapy”-“antipsychotics”-“REM sleep behavior disorder”. The search resulted in 2 consensus reports, 2 meta-analyses, 2 review papers, 5 placebo-controlled randomized trials, 6 uncontrolled study, 3 Open-label extensions, 2 case series, 3 post-hoc analyses. The results were stratified according to level of evidence under the US Preventive Services Task Force (USPSTF) recommendations [15] into: Level 1-the highest evidence-based on well-designed Randomized control trials, Level 2.1 being controlled trials without randomization, Level 2.2 evidence from well-designed cohort studies or case-control studies, Level 2.3 being evidence from multiple time series with/without intervention or uncontrolled trials and Level 3-lowest level of evidence being based solely on clinical expertise and descriptive studies.

Results

Cognition and cognitive fluctuations

Double-blind, randomized, placebo-controlled, trials (RCT) tested the efficacy of cholinesterase inhibitors in DLB. Donepezil was tested in 3 RCT, Rivastigmine in 1 RCT and one post-hoc analysis on donepezil are summarized in Table 1. Change in MMSE showed improvement of 1.5 points on average compared to the placebo group with Rivastigmine (p=0.072) [16] While one study reports significant improvements in MMSE with both the 5 and 10 mg dosing of donepezil [17] as a 3.8 point difference and 2.4 respectively, the confirmatory study only shows significance with the 10 mg Donepezil compared to the placebo group, with a 2.2 point mean improvement [18]. A post-hoc multivariate regression analysis studied whether using a higher dose of donepezil is beneficial in patients with Dementia with Lewy Bodies [19,20]. This analysis showed that patients on higher doses of donepezil had higher plasma levels compared to those on a low dose. This analysis showed change in MMSE correlation with higher plasma levels of the medicine; (p=0.040). A study looked at the difference in treatment response between patients who had mixed AD-DLB pathology and those with pure Dementia with Lewy Bodies. It showed an enhanced response with acetylcholine esterase inhibitors in those with pure DLB when compared to those with concomitant AD pathology [21-24].

Memantine, an NMDA receptor antagonist, approved for AD was tested in 2 RCTs. Emre et al. [25], showed a mean change in CGIC of 3.9 in Memantine-treated groups compared to 3.3 in the placebo group. (p=0.023). This was the largest scale study performed for the use of

Authors	Study Design	Target Population	Agent tested	Duration	Enrollment	Primary Outcome Measures	Secondary Outcome Measures	Results
McKeith et al. [16]	Randomized, double blind, placebo-controlled trial	DLB	Rivastigmine 6-12 mg	20 weeks	120	NPI-4, cognitive drug research computerized cognitive assessment system	CGC-plus, NPI-10, MMSE,	Mean change from baseline on NPI-4 at week 20 favored rivastigmine over placebo. (p<0.05). No significant change was noted in the mean change in CGC-plus score. Mean improvement in MMSE scores for patients on rivastigmine. (p=0.072)
Mori et al. [17]	Randomized, double blind, placebo-controlled trial	DLB	Donepezil Hydrochloride 3, 5 or 10 mg	12 weeks	140	No primary endpoint was defined. MMSE, Cognitive testing for attention, executive function and visuospatial function; using the WMS-R, Verbal Fluency Test, WAIS-III and the visual perception test for agnosia, NPI-plus, Clinician's Interview Based Impression of Change plus Caregiver Input (9CIBC-plus), Zarit Caregiver Burden Interview (ZBI)		MMSE change >=3 points was significantly higher in patients treated with donepezil (3 mg, 42.9%, p=0.013; 5mg, 65.6%, p<0.001; 10 mg, 44.4%, p=0.007). Significant improvement in the attention domain but none detected on verbal fluency and visuospatial testing.
Ikeda et al. [18]	Open label, extension phase	DLB	Donepezil 5 mg	52 week	108	MMSE, NPI, CFI	ZBI	Mean change in MMSE showed marked improvement in the original placebo group. (p<0.05). Overall mean improvement in MMSE in all groups. (p<0.05)
Ikeda et al. [19]	Randomized, placebo-controlled, confirmatory phase III trial	DLB	Donepezil 5 or 10 mg	16 weeks	142	MMSE, NPI-2	NPI-10	Co-primary endpoints were not met. Improvement in MMSE in the 10 mg group compared to the placebo group was significant (p=0.016) but not in the 5 mg group. No significant difference in NPI-2 and NPI-10 scores was shown.

Table 1: Clinical trial characteristics for cholinesterase inhibitors.

memantine in PDD/DLB. The initial study by Aarsland et al. [21] looked at the change in CGIC of the memantine-treated groups compared to placebo. The change measured by this trial was a mean difference of 0.7, 95% CI 0.04-1.39; $p=0.03$ [21]. After the original study [21], a post-hoc analysis showed improvement in the attentional deficit in these patients as measured by the simple reaction time (SRT and choice reaction time (CRT) was statistically significant as shown by Wesnes et al. [22].

In a follow-up open-label extension phase, patients who were started on memantine in the original RCT were shown to have a better 3 year survival compared to those on placebo ($p=0.045$) [23,24].

Visual Hallucinations/Delusions

Treatment of the neuropsychiatric symptoms, probably the most challenging symptom of DLB causing anxiety and caregiver burden, remains elusive. Almost all of the RCTs performed contained a version of the Neuropsychiatric Inventory (NPI); NPI-2, NPI-4 and NPI-plus as secondary outcome measures. Cholinesterase inhibitors have been reported to show some efficacy. In the initial study designed by Mori et al. [17] and the confirmatory phase 3 trials, the NPI-2, which is the sum of hallucinations and cognitive fluctuations, was significantly improved in the 5 mg Donepezil group with a linear dose-dependent improvement. The NPI-4; assessing the delusions, hallucinations, apathy and depression, also showed significant improvement in the 5 mg Donepezil group. However, the confirmatory phase 3 trial failed to show a significant improvement compared to placebo [18]. In an uncontrolled study, there was improvement in the visual symptoms on administering Donepezil in 13 patients with LBD ($p=0.009$) [25,26]. In a Case series, the use of Donepezil in patients with Capgras Syndrome was effective [27-30]. Not only does Donepezil cause regression of neuropsychiatric symptoms, like visual hallucinations; but increasing the dose of Donepezil has also been shown to treat relapses [27,28].

Atypical antipsychotics offer an alternative approach. However, sensitivity to these drugs marks a challenge, including the risk of neuroleptic malignant syndrome. In a post-hoc analysis of a RCT investigating the role of Olanzapine in AD patients, a subgroup of patients who met criteria for DLB ($n=29$) showed reduction in hallucinations as recorded by the NPI-NH [31]. Another looked at Quetiapine and its effect on dementia-related psychosis in 10 male patients and a reduction in the NPI overall score and the NPI subscale scores was observed. The major limitation of these studies is the size of the patient group and the uncontrolled design, hence the inability to draw a definite conclusion based solely on them. The black box warning of the atypical antipsychotics is a major drawback.

Memantine's effect on the NPI scores was tested on patients with PDD and DLB. Emre et al. showed a significant improvement in the DLB memantine group but none in the PDD group [25].

Parkinsonism

Four un-controlled trails investigated the use of L-dopa in patients with lewy body pathology, i.e., DLB, PDD. An uncontrolled study measuring the difference using the Unified Parkinson's Disease Rating Scale. This study looked at the effect of dopaminergic agents in 19 patients who met criteria for probable LBD and it showed motor improvement without causing psychosis in 22% of patients [32]. Two trials studying the effect of Levodopa in patients with Parkinson's disease, PDD or DLB also showed improvement motor symptoms [33,34].

REM sleep behavior disorder (RBD)

The hallmark of the diagnosis of REM sleep behavior disorder is the

absence of atonia during REM sleep and "dream enactment" [35-40]. Reliable history has to be obtained from caregivers in order to give such diagnosis because not all patients are aware of themselves having this disorder. A cohort study found that REM sleep behavior disorder was, in fact, one of the earlier symptoms that developed before cognitive symptoms in patients who are to develop LBD [31]. Other researchers have backed this up by following up on patients with idiopathic REM sleep behavior disorder with a final conclusion that 25% of these patients converted to an overt synucleinopathy within 3 years [40] or in a similar study 17.7% over 5 years [41].

Interventional, large-scale trials targeting REM sleep behavior are still lacking. The highest level of evidence is provided in an uncontrolled trial in patients with DLB ($n=7$). RBD in general, not in the context of DLB, was studied in a placebo-controlled, randomized crossover study in patients with iRBD [36] and an observational study in patients with idiopathic RBD (Irbd) [37]. In the uncontrolled study, 7 patients with DLB-associated REM sleep behavior disorder among a group of 14 patients with other neurological diseases were started on melatonin 3-12 mg [35]. Among the 14 patients, the average period of use was 14 months. Most patients showed improvement over the course of a year and 6 were controlled. In the observational study, 39 patients with iRBD all underwent treatment with Clonazepam over a follow-up duration of 28.8 ± 13.3 months. Over that period of time, the injury caused to self or to partner as a consequence of RBD was diminished in 2/3 of the patients treated. The RCT had a crossover design with two groups of patients, each receiving placebo/Melatonin for 4 weeks then switching to the other. There were decreased episodes of REM sleep without atonia (RSWA) compared to baseline in patients receiving Melatonin ($p=0.012$) and also decreased sleep-onset latency ($p=0.05$) [36]. In a case series, Ramelteon, a synthetic melatonin agonist, showed efficacy in 4 patients after failure of improvement with other therapies, including AchIs [38]. These two reports warrant further trials to test melatonin or synthetic analogues for the treatment of RBD. Anti-dementia drugs may have a role as well. In a RCT the use of memantine in PDD and DLB patients was shown to have some effect on the physical activity seen with REM sleep behavior disorder. It decreased movement during sleep while symptoms in the placebo group were worse at the end of the 24 week study ($p=0.006$) [36].

Along with bedroom safety rules, pharmacologic supplementation is necessary for better control of the symptoms of this disorder. 3-12 mg Melatonin dosing is effective in enhancing the physiologic REM sleep phase. It decreases periods without atonia during REM sleep [36,42]. Clonazepam is also a first-line therapy for RBD [42]. It seems to alter dream content and consequently ameliorate the vigorous verbal and physical activity [37,42].

Discussion

Dementia with Lewy bodies is a tremendous burden to all caregivers and patients. The symptoms experienced over the course of disease are disheartening and are a source of anxiety and caregiver burnout. The motor and neuropsychiatric symptoms are also a cause of disability, resulting in the high cost of care needed for these patients. Dementia with Lewy bodies was constantly underdiagnosed or most commonly misdiagnosed as AD even in the recent past. FDA approved therapeutics are not available for DLB and the field mainly relies on consensus opinions and off-label use of medications.

Most experts agree that using Cholinesterase inhibitors as a first line treatment to ameliorate cognitive decline in these patients is reasonable [2,3] Despite the evidence presented above, Donepezil use remains

Authors	Study Design	Target Population	Agent tested	Duration	Enrollment	Primary Outcome Measures	Secondary Outcome Measures	Results
Aarsland et al. [21]	Randomized, double blind, placebo-controlled trial	DLB/PDD	Memantine 20 mg	24 weeks	72	ADCS-CGIC	MMSE, A quick test of cognitive speed (AQT), The disability assesment (DAD).	Improvement in CGIC scores compared to placebo (p=0.03). No significant differences in secondary outcome measures.
Wesnes, et al. [22]		DLB/PDD	Memantine 20 mg	24 weeks	51	Simple and choice reaction times and word recognition from the CDR system		Improvement in outcome measures. Statistical significance on the CRT (p=0.0086) and the word recognition tests (IWR, p=0.0176; DWR, p=0.0161) was noted in the memantine-treated groups.
Johansson et al. [23]	Washout, open-label, Extension Study	DLB/PDD	Memantine 20 mg	30 week	56	Recurrence of symptoms	CGIC and modified motor UPDRS scores	Recurrence of symptoms was more common in patients who were originally in the memantine group. (p=0.04)
Stubendorff et al. [24]	Open-label treatment	DLB/PDD	Memantine 20 mg	36 months	32	Survival	none	Memantine treated patients had a significantly improved 3 year survival. (p=0.045)
Emre et al. [25]	Randomized, double blind, placebo-controlled trial	DLB/PDD	Memantine 20 mg	24 weeks	199	No primary endpoint was defined. ADCS-CGIC, NPI, Zarit Caregiver Burden Score, ADCS-ADLs, Cognitive testing		Improvement in the CGIC (p=0.023). Improvement in the NPI in DLB patients (p=0.041) but not PDD patients. There was no significant improvement in other test scores.

Table 2: Clinical trial characteristics for memantine.

off-label in the US. Rivastigmine is the only approved medication for Parkinson's disease Dementia but remains off-label for DLB in the US. Japan was the first to approve Donepezil for treatment of DLB [14].

Cholinesterase inhibitors may also improve visual hallucinations and delusions at a better risk/benefit ratio than the atypical antipsychotics. Sometimes atypical antipsychotics are warranted, but discussion of the black box warning is necessary at the time of initiation. Seroquel may be the safest option and close monitoring is required to identify potential life-threatening side effects, such as Neuroleptic Malignant Syndrome. A newer antipsychotic, Pimavanserin, was recently approved for visual hallucinations and psychosis in Parkinson's disease Dementia. We are eagerly anticipating its role in DLB [43-45]. Larger scale RCTs would need to be conducted to favor a drug over the other for this symptom. Memantine has less supportive evidence for its off-label use, however, due to its relative safety, it is reasonable to use it with close monitoring for side effects.

Motor Symptoms are treated with levodopa, with fewer efficacies than in PD [43]. While L-dopa improves the parkinsonian motor features, the increased dopaminergic activity may induce psychosis. Low dose and slow titration are favorable. While the psychosis risk is there, DLB trials thus far have not reported an increase in psychosis.

REM sleep behavior disorder is frequent and may confer a risk to self and to the bed partner. Treatment strategies include Melatonin and Clonazepam. Melatonin decreases RSWA thus may be more relevant from the pathomechanistic point of view and affords a safer approach. Nelotanserin, an inverse agonist of the serotonin receptors is currently in RCT for the treatment of DLB associated RBD [46].

The field has made major strides in developing tools to increase the diagnostic sensitivity and specificity of DLB. The composite risk score assists primary care in identifying patients while the improved diagnostic criteria are a foundation for research. RCTs are needed to

improve outcomes. The complex symptomatology and the involvement of multiple neurotransmitter systems make measuring the efficacy challenging. Validated assessment tools are needed to capture phenotype complexity and optimize the selection of outcome measures. Moving forward, well-designed RCTs are needed to optimize therapy and put an end to disease progression.

References

1. Wang HF, Yu JT, Tang SW, Jiang T, Tan CC, et al. (2015) Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: Systematic review with meta-analysis and trial sequential analysis. *J Neurol Neurosurg Psychiatry* 86: 135-143.
2. O'Brien JT, Holmes C, Jones M, Jones R, Livingston G, et al. (2017) Clinical practice with anti-dementia drugs: A revised (third) consensus statement from the British Association for Psychopharmacology. *J Psychopharmacol* 31: 147-168.
3. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, et al. (2017) Diagnosis and management of dementia with lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology* 89: 88-100.
4. Galvin JE (2015) Improving the clinical detection of lewy body dementia with the lewy body composite risk score. *Alzheimers Dement (Amst)* 1: 316-324.
5. Ryu HJ, Kim M, Moon Y, Choi Y, Han JY, et al. (2017) Validation of the Korean version of the lewy body composite risk score (K-LBCRS). *J Alzheimers Dis* 55: 1395-1401.
6. Watanabe H, Ariyoshi T, Ozaki A, Ihara M, Ono M, et al. (2017) Synthesis and biological evaluation of novel radioliodinated benzimidazole derivatives for imaging alpha-synuclein aggregates. *Bioorg Med Chem* 25: 6398-6403.
7. Tatsch K, Poepperl G (2013) Nigrostriatal dopamine terminal imaging with dopamine transporter SPECT: An update. *J Nucl Med* 54: 1331-1338.
8. Iaccarino L, Cerami C, Iannaccone S, Magnani G, Cappa S, et al. (2015) Brain 18F-FDG PET Hypo- and Hypermetabolic patterns in dementia with lewy-bodies (P2.182). *Neurology* 84.
9. Del Tredici K, Hawkes CH, Ghebremedhin E, Braak H (2010) Lewy pathology in the submandibular gland of individuals with incidental Lewy body disease and sporadic Parkinson's disease. *Acta Neuropathol* 119: 703-713.

10. Beach TG, Adler CH, Sue LI, Vedders L, Lue L, et al. (2010) Multi-organ distribution of phosphorylated α -synuclein histopathology in subjects with lewy body disorders. *Acta Neuropathologica* 119: 689-702.
11. Gelpi E, Navarro-Otano J, Tolosa E, Gaig C, Compta Y, et al. (2013) Multiple organ involvement by alpha-synuclein pathology in lewy body disorders. *Mov Disord* 29: 1010-1018.
12. Funabe S, Takao M, Saito Y, Hatsuta H, Sugiyama M, et al. (2013) Neuropathologic analysis of Lewy-related β -synucleinopathy in olfactory mucosa. *Neuropathology* 33: 47-58.
13. Grothe MJ, Schuster C, Bauer F, Heinsen H, Prudlo J, et al. (2014) Atrophy of the cholinergic basal forebrain in dementia with lewy bodies and Alzheimer's disease dementia. *J Neurol* 261: 1939-1948.
14. Cummings J, Lai TJ, Hemrungronj S, Mohandas E, Yun Kim S, et al. (2016) Role of donepezil in the management of neuropsychiatric symptoms in Alzheimer's disease and dementia with lewy bodies. *CNS Neurosci Ther* 22: 159-166.
15. US Preventive Services Task Force (1989) Guide to clinical preventive services: Report of the US Preventive Services Task Force. DIANE Publishing.
16. McKeith I, Del Ser T, Spano P, Emre M, Wesnes K, et al. (2000) Efficacy of rivastigmine in dementia with Lewy bodies: A randomised, double-blind, placebo-controlled international study. *Lancet* 356: 2031-2036.
17. Mori E, Ikeda M, Kosaka K, Donepezil-DLB Study Investigators (2012) Donepezil for dementia with lewy bodies: A randomized, placebo-controlled trial. *Ann Neurol* 72: 41-52.
18. Ikeda M, Ikeda M, Kosaka K (2015) Donepezil for dementia with lewy bodies: A randomized, placebo-controlled, confirmatory phase III trial. *Alzheimers Res Ther* 7: 4.
19. Ikeda M, Mori E, Kosaka K, Iseki E, Hashimoto M, et al. (2013) Long-term safety and efficacy of donepezil in patients with dementia with lewy bodies: Results from a 52-week, open label, multicentre extension study. *Dement Geriatr Cogn Disord* 36: 229-241.
20. Mori E, Ikeda M, Nakai K, Miyagishi H, Nakagawa M, et al. (2016) Increased plasma donepezil concentration improves cognitive function in patients with dementia with lewy bodies: An exploratory pharmacokinetic/pharmacodynamic analysis in a phase 3 randomized controlled trial. *J Neurol Sci* 366: 184-190.
21. Aarsland D, Ballard C, Walker Z, Bostrom F, Alves G, et al. (2009) Memantine in patients with parkinson's disease dementia or dementia with lewy bodies: A double-blind, placebo-controlled, multicentre trial. *Lancet neurology* 8: 613-618.
22. Wesnes KA, Aarsland D, Ballard C, Londos E (2015) Memantine improves attention and episodic memory in parkinson's disease dementia and dementia with lewy bodies. *Int J Geriatr Psychiatry* 30: 46-54.
23. Johansson C, Ballard C, Hansson O, Palmqvist S, Minthon L, et al. (2011) Efficacy of memantine in PDD and DLB: An extension study including washout and open-label treatment. *Int J Geriatr Psychiatry* 26: 206-13.
24. Stubendorff K, Larsson V, Ballard C, Minthon L, Aarsland D, et al. (2014) Treatment effect of memantine on survival in dementia with Lewy bodies and parkinson's disease with dementia: A prospective study. *BMJ Open* 4: e005158.
25. Emre M, Tsolaki M, Bonuccelli U, Destée A, Tolosa E, et al. (2010) Memantine for patients with parkinson's disease dementia or dementia with lewy bodies: A randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 9: 969-977.
26. Satoh M, Ishikawa H, Meguro K, Kasuya M, Ishii H, et al. (2010) Improved visual hallucination by donepezil and occipital glucose metabolism in dementia with lewy bodies: The Osaka-Tajiri project. *Eur Neurol* 64: 337-344.
27. Ukai K, Fujishiro H, Iritani S, Ozaki N (2014) Long-term efficacy of donepezil for relapse of visual hallucinations in patients with dementia with lewy bodies. *Psychogeriatrics* 15: 133-137.
28. Cummings J, Lai TJ, Hemrungronj S, Mohandas E, Yun Kim S, et al. (2016) Role of donepezil in the management of neuropsychiatric symptoms in Alzheimer's disease and dementia with lewy bodies. *CNS Neurosci Ther* 22: 159-166.
29. Graff-Radford J, Boeve BF, Pedraza O, Ferman TJ, Przybelski S, et al. (2012) Imaging and acetylcholinesterase inhibitor response in dementia with Lewy bodies. *Brain* 135: 2470-2477.
30. Reimers K, Emmert N, Shah H, Benedict RH, Szigeti K (2014) Capgras-like visual decomposition in lewy body dementia with therapeutic response to donepezil. *Neurol Clin Pract* 4: 467-469.
31. Cummings JL, Street J, Masterman D, Clark WS (2002) Efficacy of olanzapine in the treatment of psychosis in dementia with lewy bodies. *Dement Geriatr Cogn Disord* 13: 67-73.
32. Goldman JG, Goetz CG, Brandabur M, Sanfilippo M, Stebbins GT (2008) Effects of dopaminergic medications on psychosis and motor function in dementia with lewy bodies. *Mov Disord* 23: 2248-2250.
33. Molloy SA, Rowan EN, O'Brien JT, McKeith IG, Wesnes K, et al. (2006) Effect of levodopa on cognitive function in Parkinson's disease with and without dementia and dementia with lewy bodies. *J Neurol Neurosurg Psychiatry* 77: 1323-1328.
34. Bonelli SB, Ransmayr G, Steffelbauer M, Lukas T, Lampl C, et al. (2004) L-dopa responsiveness in dementia with lewy bodies, parkinson disease with and without dementia. *Neurology* 63: 376-378.
35. Boeve BF, Silber MH, Ferman TJ (2003) Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: Results in 14 patients. *Sleep Med* 4: 281-284.
36. Kunz D, Mahlberg R (2010) A two-part, double-blind, placebo-controlled trial of exogenous melatonin in REM sleep behaviour disorder. *J Sleep Res* 19: 591-596.
37. Li SX, Lam SP, Zhang J, Yu MW, Chan JW, et al. (2016) A prospective, naturalistic follow-up study of treatment outcomes with clonazepam in rapid eye movement sleep behavior disorder. *Sleep Med* 21: 114-120.
38. Kasanuki K, Iseki E, Nishida Y, Fujishiro H, Chiba Y, et al. (2013) Effectiveness of ramelteon for treatment of visual hallucinations in dementia with lewy bodies: A report of 4 cases. *J Clin Psychopharmacol* 33: 581-583.
39. St Louis EK, Boeve AR, Boeve BF (2017) REM sleep behavior disorder in Parkinson's disease and other synucleinopathies. *Mov Disord* 32: 645-658.
40. Postuma RB, Iranzo A, Hogl B, Amulic I, Ferini-Strambi L, et al. (2015) Risk factors for neurodegeneration in idiopathic rapid eye movement sleep behavior disorder: A multicentre study. *Ann Neurol* 77: 830-839.
41. Postuma RB, Gagnon JF, Vendette M, Fantini ML, Massicotte-Marquez J, et al. (2009) Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. *Neurology* 72: 1296-1300.
42. St Louis EK, Boeve AR, Boeve BF (2017) REM sleep behavior disorder in Parkinson's disease and other synucleinopathies. *Mov Disord* 32: 645-658.
43. Xie CL, Zhang YY, Wang XD, Chen J, Chen YH, et al. (2015) Levodopa alone compared with levodopa-sparing therapy as initial treatment for Parkinson's disease: A meta-analysis. *Neurol Sci* 36: 1319-1329.
44. Baskys A, Davis P (2003) Atypical antipsychotic quetiapine in the treatment of psychosis associated with Lewy body dementia. *Schizophrenia Res* 60: 272-273.
45. ClinicalTrials.gov (2017) Relapse prevention study of pimavanserin in dementia-related psychosis.
46. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 – Identifier NCT02708186, "Study Evaluating Nelotanserin for Treatment of REM Sleep Behavior Disorder in Subjects With Dementia (DLB or PDD)"