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

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Abstract

Dementia with Lewy Bodies (DBL) 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 DBL 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 (questions1-4), 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, mesostrial 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 pareto-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.  | 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.     | 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 visuoperceptual 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 SCIBC-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 visuoperceptual testing. |
| Ikeda et al.    | Open label, extension phase   | DLB               | Donepezil 5 mg     | 52 week  | 108        | MMSE, NPI, CFI            | ZBI                       | Mean change in MMSE shied marked improvement in the original placebo group. (p=0.05). Overall mean improvement in MMSE in all groups. (p=0.05) |
| Ikeda et al.    | 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/LDB. 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 Morì 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 DLM. Emre et al. showed a significant improvement in the DLB memantine group but none in the PDD group [25].

**Parkinsonism**

Four un-controlled trials 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 DLM 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 [38]. 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 Achls [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...
diagnostic criteria are a foundation for research. RCTs are needed to score assists primary care in identifying patients while the improved diagnostic sensitivity and specificity of DLB. The composite risk in RCT for the treatment of DLB associated RBD [46].

Nelotanserin, an inverse agonist of the serotonin receptors is currently tested. Its safety and efficacy have been demonstrated in several clinical trials. It has shown promising results in reducing REM sleep behavior disorder and improving sleep quality [43].

Clonazepam. Melatonin decreases RSW A thus may be more relevant to self and to the bed partner. Treatment strategies include Melatonin and N-acetylcysteine. Low dose and slow titration are favorable. While the psychosis risk is higher than in PD [43]. While L-dopa improves the parkinsonian motor features, the increased dopaminergic activity may induce psychosis. A newer antipsychotic, Pimavanserin, was recently approved for visual hallucinations and delusions, with fewer side effects. Memantine is a potential treatment option for DLB, with a focus on cognition and behavior [43-45]. Larger scale RCTs would eagerly anticipate its role in DLB [43-45].

Methylphenidate is a stimulant that improves attention and cognitive function. However, it has not been extensively studied in DLB. Risperidone is another antipsychotic that has been tested in DLB, with mixed results [43].

Table 2: Clinical trial characteristics for memantine.

| Authors          | Study Design                  | Target Population | Agent tested | Duration | Enrollment | Primary Outcome Measures | Secondary Outcome Measures | Results                                                      |
|------------------|-------------------------------|-------------------|--------------|----------|------------|--------------------------|-----------------------------|-------------------------------------------------------------|
| Aarsland et al.  | 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 assessment (DAD). | Improvement in CGIC scores compared to placebo (p=0.03). No significant differences in secondary outcome measures. |
| Wesnes, et al.   | Washout, open-label, Extension Study | DLB/PDD | Memantine 20 mg | 30 weeks | 58         | 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) |
| Johansson et al. | 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) |
| Stubendorff et al. | 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. |

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.

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