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Clinical drug development for dementia with Lewy bodies: past and present

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Abstract

Introduction—Dementia with Lewy bodies (DLB) is an under-researched area despite being the second most common type of degenerative dementia after Alzheimer's disease. It is an area of unmet need with no approved symptomatic or disease-modifying therapies. The pharmacological management of DLB is complex and challenging because early trials of drugs for DLB have resulted in no demonstrable efficacy. Randomized controlled trials (RCTs) in the DLB population have only recently been initiated. Understanding results from previous and current clinical trials in DLB can provide insights for future research and development.

Areas covered—We provide an overview of the DLB drug development landscape and the current treatment strategies. We reviewed ClinicalTrials.gov to identify all clinical trials for the treatment of DLB.

Expert opinion—DLB drug development has significantly improved in recent years with eight agents now in clinical trials. However, more rigorous RCTs are urgently needed. Diagnostic criteria must be optimized to accurately diagnose patients for clinical trials and care. New biomarker strategies are necessary to improve diagnostic capabilities and trial designs, and novel drug targets should be identified to develop DLB specific disease-modifying therapies. Evaluating the current drug development landscape can provide insight into how best to optimize development practices.

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1. INTRODUCTION

Dementia with Lewy bodies (DLB) is a devastating neurodegenerative dementia that remains an under-researched area. It is the second most common type of degenerative dementia after Alzheimer's disease (AD), accounting for about 5% of all dementia cases [1,2], and the third most common of all the neurodegenerative diseases after AD and Parkinson's disease (PD) [3]. DLB is associated with a poorer prognosis than AD with higher healthcare costs, greater caregiver burden, and a greater impact on quality of life [1]. Despite all this, DLB has received little attention and the majority of drug development for the dementias has been focused on AD in the past decades. There are currently no medications approved by the US Food and Drug Administration (FDA) for the treatment of DLB. Randomized controlled trials (RCTs) for DLB have only recently begun and the majority of studies in the past have been case studies or open-label observations with no controls [4,5]. Current pharmacological management strategies for DLB aim at providing symptomatic relief and involve medications approved for other indications. No disease-modifying therapies (DMTs) exist for DLB.

In this review of the DLB drug development pipeline, we provide a summary of the current pharmacological treatment strategies and the current state of progress in developing new therapies for DLB. We review trials of the past and trials that are currently active and ongoing, and provide insight into future clinical trials. We also review trials that have failed and their results, when available.

1.1 Clinical Features and Diagnosis

DLB is a complex clinical syndrome characterized by a variety of symptoms including cognitive, motor, and behavioral alterations. DLB is often misdiagnosed due to its similarity to other types of dementia and the lack of widely available biomarkers. It shares many clinical and pathological features with Parkinson's disease dementia (PDD) [6]. In 2007, a DLB/PDD Working Group agreed to use the term Lewy body disorders as an umbrella term to include PD, PDD, and DLB [7]. DLB is characterized by Lewy body pathology at autopsy, which is also seen in PD and PDD—however, there are no definite pathological criteria that separate DLB, PD, and PDD from each other [8]. In general, DLB and PDD are clinically distinguished by the sequence of their symptoms. If dementia occurs before, concurrently, or within 1 year of motor parkinsonism, DLB is diagnosed; if dementia occurs more than 1 year after an established PD diagnosis, then PDD is diagnosed [9]. Furthermore, some DLB patients present with clinical and pathological features of AD, adding more complexity to the differential diagnosis [10]. Clinical and neuropathological overlap of DLB and PDD, and the frequent presence of Lewy body pathology in sporadic and familial AD have contributed to controversies around where patients with a clinical DLB picture and confirmed Lewy body pathology should be categorized [11,12].

Substantial effort has been devoted to improving the sensitivity and specificity of the clinical diagnosis of DLB [7]. In 2017, the Dementia with Lewy Bodies Consortium revised their recommendations on the diagnostic criteria for DLB based on new information accrued since their prior recommendations in 2005 [13,14]. The criteria for diagnosing prodromal DLB are also in development [15]. Dementia—defined as progressive loss of cognition

sufficient to compromise function—is a required clinical feature for the diagnosis of DLB. Dementia in DLB often presents with more prominent deficits in attention, executive function, and visuoperceptual ability than other types of dementias [16]. The core clinical features of DLB, according to the revised diagnostic criteria, include fluctuations in cognition and attention, visual hallucinations, parkinsonism, and rapid eye movement (REM) sleep behavior disorder (RBD). Visual hallucinations are highly prevalent in DLB, occurring in up to 80% of patients, and typically feature false perceptions of people, children, or animals [13]. They happen most commonly in the night and are usually not frightening or threatening, although they may become so in more severe patients or when accompanied by other neuropsychiatric symptoms [17]. RBD is a REM-related parasomnia manifested by recurrent dream enactment behavior that includes movements and/or vocalizations mimicking dream content [18]. Most patients do not recognize this as a problem until the enactments become violent and pose a threat to themselves or their bed partners. RBD was added as a core clinical feature of DLB to the revised diagnostic criteria after research showed that RBD occurred more frequently in DLB than in other dementias [19,20]. Fluctuations, visual hallucinations, and RBD typically occur early in the disease and assist in differentiating DLB from AD and PDD. Parkinsonism, including bradykinesia, rest tremor, or rigidity, is highly prevalent in DLB, occurring in over 85% of patients [13]. Compared to PDD, rest tremor is less frequent and more symmetrical in DLB [21]. Supportive clinical features of DLB include hypersensitivity to neuroleptics, hypersomnia, neuropsychiatric symptoms (e.g., depression, anxiety, delusions), and autonomic dysfunction [13]. DLB patients are highly sensitive to neuroleptic agents and are vulnerable to developing neuroleptic malignant syndrome (NMS) in response to antipsychotics [22]. NMS is a potentially fatal idiopathic reaction to neuroleptic medications, characterized by fever, extrapyramidal syndrome, and altered mental state [23]. Hypersomnia usually manifests as excessive daytime sleepiness due to sleep/wake cycle disturbances. Autonomic dysfunction includes constipation, orthostatic hypotension, and urinary and sexual dysfunction; these symptoms can occur in any stage of the disease [24].

Direct biomarkers specific to DLB pathology are not yet available for clinical diagnosis. The revised version of the DLB criteria incorporated the use of indicative and supportive imaging and electrophysiological biomarkers in the diagnosis of DLB [13]. Probable DLB is diagnosed if two or more of the core clinical features are present, with or without the presence of indicative biomarkers; or if only one core clinical feature is present, but with one or more indicative biomarkers [13]. Reduced dopamine transporter (DAT) uptake demonstrated by single-photon emission computed tomography (SPECT)(DaT scan) or positron emission tomography (PET) is an indicative biomarker and remains the best neuroimaging technique to differentiate DLB from AD [25]. Other indicative biomarkers include polysomnographic confirmation of REM sleep without atonia and reduced uptake on ^{123}iodine-metaiodobenzylguanidine (MIBG) myocardial scintigraphy [13], with the latter being used extensively in Japan. Supportive biomarkers, which can help the diagnostic evaluation but without clear diagnostic specificity, include low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity +/− the cingulate island sign on fluorodeoxyglucose (FDG)-PET; less severe hippocampal atrophy than observed in AD with magnetic resonance imaging (MRI); and prominent posterior slow-wave activity on

electroencephalogram (EEG) with periodic fluctuations in the pre-alpha/theta range [13]. The cingulate island sign on FDG-PET shows higher glucose metabolism in the posterior cingulate surrounded by an area of reduced cortical metabolism [26]. Although not included in the diagnostic criteria, relative preservation of amygdala metabolism on FDG-PET could be used in earlier stages of DLB [27]. While these biomarkers are not specific to DLB, combining them with clinical features can increase the accuracy of DLB diagnosis.

1.2 Pathology

The pathologic hallmark of DLB is the presence of Lewy bodies, which are abnormal aggregates of proteins that accumulate in the brain neurons [25]. The progression of Lewy bodies to the limbic and neocortical structures is associated with the severity of dementia in DLB, and is an indicator for a neuropathological diagnosis of DLB [13]. However, DLB pathology is considered to be heterogeneous, including neuronal loss, cholinergic degeneration, AD and vascular pathology in addition to Lewy body pathology [7]. The underlying pathophysiology of DLB is not fully understood, which makes accurate diagnosis and developing targeted therapeutics challenging. Further complicating matters, Lewy bodies are not specific to DLB and the protein aggregates are also seen in other neurological disorders such as PD and PDD [6,28]. α-synuclein is the major component of Lewy bodies. In the normal brain, α-synuclein is abundant at the synaptic terminal and may protect presynaptic nerve terminals from injury and regulate dopamine release [7]. In its pathological state, α-synuclein aggregates into oligomers and fibrils predominantly in neuronal cells [28]. The accumulation of α-synuclein proteins has been linked to synaptic dysfunction and impairment in neuronal excitability leading to neuronal death [29]. The exact underlying mechanism by which α-synuclein leads to neuronal death is not fully understood. Several studies suggest that small, prefibrillar oligomers of α-synuclein are the toxic species leading to neuronal degeneration and dysfunction [7].

There are currently no validated biomarkers for α-synuclein aggregation and autopsy is the only way to confirm. Several studies have shown the presence of AD pathology in DLB, including amyloid-β and tau neurofibrillary tangles [30,31]. CSF amyloid-β and tau are useful in predicting cognitive decline in DLB where these constituents are present [32]. Amyloid-β was shown to be more prevalent in DLB than in PDD, and tau tangles appeared to have a synergistic relationship with α-synuclein, leading to worse prognosis [33,34].

Synaptic damage caused by the neurotoxic proteins can attribute to the clinical symptoms of DLB [35]. Changes in neurotransmitters and neurochemicals also play a role. Degeneration of dopamine is associated with motor deficits; cholinergic deficit has been linked to cognitive impairment; and delusions and hallucinations have been linked to alternations in the serotonin 5-HT system [36,37]. Genetic studies implicate the apolipoprotein epsilon-4 (APOE-4) locus, α-synuclein gene (SNCA), and glucocerebrosidase (GBA) gene in DLB where the heritability has been estimated to be 36% [38].

2. METHODS

ClinicalTrials.gov was used to identify past and present clinical trials in DLB as of August 1, 2019. Discussion and tables provided in this review apply to the information available at that

time. We used the methodology previously applied to assessing the drug development in AD [39–42]. Majority of the studies on DLB in the past have been case series or open-label observatory studies, and were not registered on ClinicalTrials.gov. These studies were identified through a literature search via PubMed and by examining reference lists of relevant systematic reviews.

We used the search term “Dementia with Lewy bodies” with no time restrictions on ClinicalTrials.gov. All other advanced search fields, such as study type, status, phase, and funder type were left blank. The search yielded a total of 87 trials registered on the government website. From the result, we excluded trials of behavioral interventions (e.g., caregiver interventions), cognitive therapies, and biomarker, diagnostic, and imaging studies. We included only trials of pharmacologic agents and devices for treatment purposes. Trials were also excluded if they did not specify the type of dementia being treated and only trials with DLB or DLB and PDD listed as the specific subject population were included. One relevant trial () did not show up in our search even though DLB was listed as one of the inclusion criteria. This trial was added to our final results. The following information was collected from ClinicalTrials.gov: trial title, ClinicalTrials.gov identifier, start date, estimated end date, primary outcome completion date, duration of treatment exposure, number of subjects planned for enrollment, number of arms, subject characteristics, outcome measures, whether a biomarker was used as an outcome measure, and sponsorship. Drug targets and mechanisms of action (MOA) were determined from the information on ClinicalTrials.gov or from a comprehensive search of the literature. We classified the mechanisms as symptomatic agents or DMTs based on the most likely MOA as presented on the website and associated information identified through searches. The distinction between symptomatic and disease-modifying agents can be arbitrary, and some agents may have both properties. For purposes of this review, we chose what appears to be the principal MOA.

We divided the identified trials into two groups: past and current pipeline. Past trials include trials listed as completed, terminated, suspended, unknown, or withdrawn on ClinicalTrials.gov (Table. 1). Trials in the current pipeline include trials listed as recruiting, active not recruiting (e.g., trials that have completed recruiting and are continuing with the exposure portion of the trial), and not yet recruiting (Table. 2). Small observational studies or case series are not registered on ClinicalTrials.gov and are not reflected in Table. 1, however, these studies are described in the following sections when relevant to the current pharmacological management.

3. RESULTS

As of August 1, 2019, there were 30 trials identified for the treatment of DLB on ClinicalTrials.gov. The first trial registered was in 2002 (galantamine), and since then a total of eight agents and one device in 22 trials have been completed, terminated, suspended, withdrawn, or the status became unknown (Table. 1). There are currently eight agents in eight clinical trials that are ongoing and actively recruiting (Table. 2).

All trials in the past for DLB have been for symptomatic treatment. There were nine Phase 2 trials, three Phase 2/3 trials, two pilot device studies, and eight post-marketing or

exploratory studies. Most of the trials addressed cognitive and neuropsychiatric symptoms (14 trials; 64%). There were three trials targeting hypersomnia and wakefulness, and three trials for both visual hallucinations and RBD. There was one trial for RBD and one for motor symptoms. Most of the trials were sponsored by the pharmaceutical industry or in collaboration with industry.

The current pipeline includes symptomatic agents as well as DMTs. There are seven Phase 2 trials and one trial in Phase 3. Five agents were identified as disease-modifying small molecules (62.5%). There are three symptomatic agents (37.5%); two targeting psychotic symptoms and one targeting cognition. The trials included an average of 149 participants and a mean trial duration of 124 weeks. The average duration of treatment exposure was 14 weeks. The mean trial duration includes the recruitment and the treatment period. The mean period from trial initiation to primary completion date (final data collection date for primary outcome measures) is 120 weeks. This indicates that approximately 106 weeks is the average anticipated recruitment time. Across all trials, 62.5% are sponsored by the biopharma industry and 37.5% by academic medical centers in collaboration with industry, NIH, or a philanthropic organization.

In the following sections, we review agents currently used in the treatment of DLB, studies that have failed or been suspended, and agents currently in the DLB drug development pipeline.

4. CURRENT PHARMACOLOGICAL MANAGEMENT

Current pharmacological treatment strategies involve targeting specific symptoms [43–46]. No DMTs exist for the treatment of DLB, and there are currently no drugs approved by the FDA for the symptomatic treatment of DLB. Drugs approved for other indications, such as AD and PD, are often utilized and most pharmacological treatments have not been studied in the DLB population. Psychotropic agents used in DLB are derived from studies in major depressive disorder, schizophrenia, or sleep disorders in patients without known neurological disorders. There is very little high-level evidence available in the DLB population for the drugs currently used, and no long-term safety and efficacy data exist.

4.1 Cognitive Symptoms

Cholinesterase inhibitors are the mainstay of treatment options for DLB and have been shown to improve cognitive and neuropsychiatric symptoms in DLB patients without worsening motor function [47,48]. Cholinesterase inhibitors increase brain acetylcholine levels, which affects cognition, function, and behavior [49]. They have been extensively studied in AD and are approved for the symptomatic treatment of AD. Although cholinergic deficit in DLB is well known, even to a greater extent than in AD, no cholinesterase inhibitor has been approved for DLB [50,51].

Donepezil is the most widely used and has the most evidence in DLB among the cholinesterase inhibitors. It was approved for the treatment of DLB in Japan in 2014 [52] and in the Philippines in 2016 [53]. Donepezil has the greatest number of clinical trials registered on ClinicalTrials.gov with two large RCTs and one open-label extension study.

There are three post-marketing studies with donepezil listed as completed. In the first large (n=140) RCT in DLB patients (), donepezil significantly improved cognition, behavior, and global function, as well as reduced caregiver burden [54]. The open-label extension study () confirmed the long-term safety and efficacy of donepezil in improving cognitive function and behavioral symptoms [55]. In a confirmatory, Phase 3 trial and its long-term extension study (), donepezil did not significantly improve psychiatric symptoms but improved cognitive function in the higher dose (10 mg) group [56,57].

Rivastigmine is another cholinesterase inhibitor with positive evidence in DLB. It was the first drug to be tested in DLB in a large randomized, double-blind, placebo-controlled study. This trial was conducted in the UK, Spain, and Italy, and was not registered on ClinicalTrials.gov. In this trial of 120 patients, rivastigmine significantly improved delusions, hallucinations, and cognition [58]. A small, open-label study of long-term rivastigmine use in DLB reported that rivastigmine was effective in improving cognition and neuropsychiatric symptoms initially, but no further significant improvements were seen long-term [59]. Rivastigmine is approved for the treatment of PDD. Galantamine has only been studied in a small (n=50) open-label study (). This study showed that galantamine improved neuropsychiatric symptoms and sleep disturbances but did not improve cognition [60]. Further studies in large patient groups are needed to consider its use in DLB. Cholinesterase inhibitors are generally well-tolerated in the DLB population without worsening motor symptoms. However, because of the disease-associated autonomic dysfunction in this patient group, caution is warranted when starting treatment. Side effects related to the gastrointestinal system (e.g., nausea, diarrhea, vomiting, weight loss), sleep disorders, and cardiac function may be more prominent in DLB patients [46].

Memantine, a glutaminergic N-methyl-D-aspartate (NMDA) receptor antagonist approved for the treatment of moderate to severe AD, lacks evidence in DLB compared to donepezil and rivastigmine. It is proposed that memantine works in dementia by preventing the toxic effects of glutamate in the brain [45]. The first large (n=199) RCT of memantine in DLB () showed that memantine is mildly beneficial in improving global clinical status and neuropsychiatric symptoms [61]. A small (n=75) Phase 2 RCT () confirmed that memantine may be effective in improving global clinical status in DLB [62], and a further analysis of this trial showed improvements in attention and episodic memory [63]. However, a meta-analysis of six studies of memantine in PDD and DLB showed that memantine has minimal clinical effects in this population [64].

Two device studies of deep brain stimulation (DBS) for the treatment of cognitive symptoms in DLB were identified on ClinicalTrials.gov (,). The results of these trials were not available. DBS is widely used in PD for motor symptoms, and there is some evidence of positive cognitive effects in AD patients after stimulation of the cholinergic nucleus basalis of Meynert [65]. Cholinergic deficit has been linked to cognitive decline in DLB, and DBS may be beneficial in DLB patients.

4.2 Neuropsychiatric Symptoms

Neuropsychiatric symptoms, such as hallucinations, delusions, depression, anxiety, agitation, and aggression are common in DLB patients with visual hallucinations being the

most prevalent. Drugs for the treatment of neuropsychiatric symptoms are limited due to the high risk of neuroleptic sensitivity in this patient population. In general, neuroleptic agents are known to have significant toxicity and limited evidence of efficacy in the dementia population. Antipsychotics are associated with high risk of extrapyramidal symptoms, worsening cognition, falls, stroke, and metabolic syndrome [66]. They are also linked to significant increase in mortality in patients with dementia, leading to a Black Box Warning from the FDA [66]. DLB patients are more susceptible to experiencing antipsychotic toxicity due to neuroleptic hypersensitivity and can experience severe adverse reactions after even a single dose [17]. In fact, poor tolerance of antipsychotics is one of the diagnostic criteria for DLB.

When considering treatment for neuropsychiatric symptoms in DLB, non-pharmacological interventions should be tried first [67]; cessation of medications that can exacerbate neuropsychiatric symptoms, such as dopamine agonists and anticholinergics, may also resolve some symptoms. For mild-to-moderate and non-threatening neuropsychiatric symptoms, cholinesterase inhibitors are often effective and should be tried prior to initiating psychotropic medications [13]. Several studies suggest that donepezil, rivastigmine, and galantamine are effective in reducing delusions and visual hallucinations without worsening motor function [58,68,69]. There is some evidence that memantine can improve neuropsychiatric symptoms [61]. When psychotic symptoms become severe and threatening with significant impact on patient safety and quality of life, atypical antipsychotics can be tried. As noted, antipsychotics should be used with extreme caution in DLB patients to avoid the risk of NMS and worsening of motor symptoms and cognition. Typical antipsychotics have a higher risk of NMS and should be avoided in DLB patients. Despite limited evidence of efficacy, low doses of atypical antipsychotics are utilized with quetiapine being the most widely used. In one case series, quetiapine showed reduction of psychotic symptoms and agitation [70], while another small trial did not show significant improvement in agitation and hallucinations though it was well tolerated without worsening parkinsonism [71]. There is supportive evidence for efficacy of clozapine in PD psychosis [72], but it has not been studied in DLB patients. Clozapine is typically used as second line after quetiapine. The selection of quetiapine versus clozapine is not evidence-based with regard to efficacy; rather one is chosen based on its side effect profile [46]. Clozapine has potential to cause agranulocytosis and requires extensive monitoring, while quetiapine does not require intensive monitoring and is easier for the patient and the clinician to use. There is mixed evidence regarding olanzapine use in DLB patients. One study showed that olanzapine was effective in reducing hallucinations and delusions in DLB patients without worsening parkinsonism [73]. However, olanzapine is associated with a higher risk of developing NMS, worsening motor symptoms (due to its strong dopamine D2 receptor antagonism), and cerebrovascular events than other atypical antipsychotics [74]. One small RCT of citalopram and risperidone for the treatment of neuropsychiatric symptoms in a mixed DLB and AD population showed symptomatic improvement in the AD group but not in the DLB group. DLB patients experienced significantly more side effects with risperidone than AD patients [75,76]. More data are needed to justify the use of atypical antipsychotics in DLB patients.

Anxiety and depression are common in DLB patients—but no RCTs have been conducted for agents purported to treat these symptoms, and efficacy evidence is limited. Standard of

care with selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) is used despite insufficient evidence of efficacy in DLB patients. Sertraline is considered to be the safest antidepressant in the elderly population due to its relatively lower cardiac risk compared to other SSRIs. Escitalopram and citalopram are recommended for patients with difficulty sleeping [44]. Some studies suggest that donepezil may be effective in improving depression [56]. There is emerging evidence suggesting that the underlying cause of depression in DLB is different from that seen in AD and people without dementia [17]. This suggests the need for studying antidepressants specifically in the DLB population.

4.3 Parkinsonism

Medications used for movement symptoms in PD are typically used in DLB, however DLB patients are often less responsive to dopaminergic treatments than those with PD [77]. Treatment is often limited because dopaminergic agents can cause visual hallucinations and other psychotic symptoms, exacerbating existing symptoms in DLB patients [78]. Furthermore, when used in DLB, neuroleptics can worsen parkinsonism.

Levodopa, a dopamine precursor agent, is preferred over dopamine agonists, such as pramipexole and ropinirole, since dopamine agonists have been found to have a higher risk of producing neuropsychiatric symptoms and sleep disturbances [79]. Low dose levodopa is often used in clinical practice despite limited evidence of benefit and an absence of RCTs for motor symptoms in DLB patients. One small observational, open-label study of levodopa use in DLB found that levodopa has limited efficacy in reducing parkinsonism in DLB patients, although it was generally well tolerated in moderate doses [79]. In general, levodopa doses should be kept low to avoid worsening of hallucinations and neuropsychiatric symptoms. Other PD medications, such as selegiline, amantadine, and anticholinergics, are not recommended in DLB. Similar to dopamine agonists, they are associated with a higher risk of neuropsychiatric symptoms and should be avoided when possible.

4.4 Sleep Disorders

Patients with DLB often experience sleep disturbances such as excessive daytime sleepiness and RBD. The latter is highly prevalent in DLB and was added as a core clinical feature to the revised diagnostic criteria. RBD is typically treated with clonazepam, a long-acting benzodiazepine, and melatonin, even though no specific evidence exists for their use in the DLB population [18]. Clonazepam is considered as first line therapy for RBD; however, cautious use is warranted as benzodiazepines are associated with an increased risk of falls and cognitive impairment in older patients. The lowest possible dose should be used with augmentation with melatonin; in case of severe adverse events with clonazepam, melatonin should be used alone [80]. No RCTs for RBD in DLB patients have been conducted and current treatment recommendations are based on available practice guidelines for managing RBD [81]. Per ClinicalTrials.gov, two trials of ramelteon, a selective agonist of melatonin receptors MT1 and MT2, were terminated due to low subject recruitment and enrollment (,). Ramelteon is marketed as a non-habit forming hypnotic for insomnia, and was being studied for the treatment of RBD and sleep/wake cycle disturbances in DLB.

Modafinil and armodafinil are wake-promoting agents approved for excessive sleepiness associated with narcolepsy and shift work sleep disorder. They have been shown to increase dopamine in the brain by blocking dopamine transporters; however their precise MOA related to sleep/wake regulation is unknown [82]. Interestingly, they are considered to have limited interaction with dopamine receptors, and thus are of interest for excessive daytime somnolence in DLB [82]. An open-label pilot study () of armodafinil in DLB showed improvements in hypersomnia and wakefulness with reasonable tolerability and no worsening of parkinsonism [82]. Modafinil did not show improvement and exacerbated psychotic symptoms in a small case study [83]. A recent Phase 3 trial of suvorexant showed a benefit in AD patients with insomnia [84]; trials of the dual orexin receptor antagonist class are warranted in DLB [85].

4.5 Autonomic Dysfunction

Autonomic nervous system dysfunction is an under-recognized complication of synucleinopathy, and can occur in any stage of the disease, even years before the diagnosis of DLB is made [24]. Symptoms include constipation, urinary dysfunction, sexual dysfunction, and postural hypotension. The symptoms may respond to the standard of care [86], however, drugs that can exacerbate existing DLB symptoms should be avoided or used cautiously. For example, dopamine receptor blockers (e.g., metoclopramide) and anticholinergics can induce or exacerbate parkinsonism.

5. FAILED OR SUSPENDED TRIALS

Axovant Sciences was developing two agents, intepiridine (RVT-101; a 5-TH6 antagonist) and nelotanserin (a 5-HT2A inverse agonist), for various symptoms in DLB, and have recently reported negative results for both agents. 5-HT6 receptor antagonists may improve cognition by decreasing gamma-amino butyric acid (GABA) and increasing glutamate levels, consequently facilitating the release of other neurotransmitters such as dopamine, noradrenaline, and acetylcholine, all of which are found to be compromised in dementia [87]. The HEADWAY-DLB study was a Phase 2, multinational, placebo-controlled study evaluating the safety and efficacy of intepirdine in patients with DLB (,). The study enrolled a total of 269 participants with a diagnosis of DLB and a Mini-Mental State Examination (MMSE) score between 14 and 26 [88]. The primary outcome measure of motor function as measured by Unified Parkinson's Disease Rating Scale (UPDRS)-III did not meet statistical significance after 24 weeks of treatment compared to placebo. There was no significant improvement in cognition and global function as measured by Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)-11 and Clinical Interview-Based Impression of Change with caregiver input (CIBIC+) [88]. A Phase 2 pilot study of intepirdine () in patients with dementia and gait impairment did not show any improvement in gait speed [86]. Based on these results, Axovant discontinued the interpridine development program including the Phase 3 MINDSET study in AD [89].

Nelotanserin was being developed for visual hallucinations and RBD in DLB. It was originally in development for the treatment of insomnia based on the fact that 5-HT2A receptors are implicated in the regulation of sleep and waking [90]. In PD, 5-HT2A

receptors have been suggested to have a role in mediating visual hallucinations [91]. In 2016, pimavanserin, also a 5-HT2A inverse agonist, was approved for the treatment of hallucinations and delusions in PD psychosis. In the first pilot Phase 2 trial of nelotanserin in 30 patients with DLB or PDD with visual hallucinations (), the agent was well tolerated but did not produce benefit in any outcome measures except a trend toward improved motor function as measured by UPDRS-III. In a subgroup analysis of DLB patients, there was statistically significant improvement in UPDRS-III and Axovant planned a larger study of nelotanserin focused on patients with DLB with motor deficits [89,92]. However, a Phase 2 trial of nelotanserin for RBD in DLB patients failed to meet the primary efficacy endpoint of reduction in frequency of RBD events, and the development program was suspended [93].

HTL0018318 is a muscarinic M1 receptor agonist that is being developed by Heptares Therapeutics. It is thought to improve cognition by enhancing acetylcholine neurotransmission. A Phase 2 trial evaluating its use in cognition and psychosis in DLB was planned to begin in 2018 (). However, the trial was suspended due to a toxicology finding showing that some animals developed tumors at doses higher than those used in humans [94]. The estimated study start date is listed as July 2019 on ClinicalTrials.gov.

6. CURRENT DRUG DEVELOPMENT PIPELINE

The current DLB drug pipeline is small compared to the AD pipeline with only eight agents compared to 132 agents in clinical trials for AD [42]. However, compared to the past, this is a notable improvement in drug development activity for DLB. Increasingly, more trials are looking at DLB populations alone rather than combining DLB and PDD patients in a trial. There are now DMTs being studied in DLB whereas only symptomatic agents have been tested in the past.

6.1 Tyrosine Kinase Inhibitors—Bosutinib, Nilotinib, K0706

Of the eight agents in the current pipeline, three are tyrosine kinase inhibitors—bosutinib, K0706, and nilotinib—being studied by the same investigators from Georgetown University. Tyrosine kinase inhibitors induce autophagy, a mechanism whereby cells degrade their own contents, and have been proven useful in several diseases including chronic myeloid leukemia (CML) [95]. There is evidence suggesting that autophagy is impaired in neurodegenerative diseases, leading to failure of degradation of neurotoxic proteins including α-synuclein, amyoid-β and tau [96,97]. In DLB patients, tyrosine kinase inhibitors may offer neuroprotection by clearing these neurotoxic proteins.

Nilotinib is a c-Abelson (Abl) tyrosine kinase inhibitor approved for the treatment of CML. In animal studies, nilotinib facilitated autophagic clearance of α-synuclein by decreasing Abl tyrosine kinase activity and reduced the loss of dopaminergic neurons [98]. These findings showed nilotinib's potential to be a DMT for α-synucleinopathies, and a small open-label, proof-of-concept study in PD and DLB was conducted [99]. The study suggested that nilotinib is relatively safe in patients with PD and DLB, and that it may have a beneficial effect on motor and cognitive outcomes [99]. A Phase 2 RCT to confirm these findings is currently recruiting participants (). The study is expected to enroll 60 participants with the diagnosis of DLB. Participants will be treated with nilotinib for 24 weeks. In

addition to safety and tolerability, changes in DLB-related cerebrospinal fluid (CSF) and plasma biomarkers will be measured; specific biomarkers are not listed on ClinicalTrials.gov

Bosutinib is another tyrosine kinase inhibitor targeting Abl and Src tyrosine kinases and is also an approved drug for CML. Similar to nilotinib, the proposed mechanism in DLB is induction of autophagy to promote clearance of neurotoxic proteins. A Phase 2 trial () is currently recruiting 30 participants with mild to moderate DLB with an abnormal DaT scan. As in the nilotinib study, the investigators will assess DLB-related CSF and plasma biomarkers as outcomes including homovanillic acid (HVA), 3,4-dihydroxyphenylacetic acid (DOPAC), amyloid-β, tau, and α-synuclein, and TREM-2, an inflammatory biomarker.

K0706 is a novel Abl tyrosine kinase inhibitor being developed by Sun Pharma. It has been shown in animal models to reduce dopaminergic cell death and improve behavioral outcomes, and a recent Phase 1 study showed that K0706 was well tolerated in PD patients [100]. A Phase 2 trial of K0706 was recently started in participants with a diagnosis of DLB with dementia and parkinsonism, and at least one other core symptom such as fluctuation, visual hallucinations, or RBD (). The study plans to enroll 45 participants, and the treatment period will be 12 weeks. Outcome measures include cognitive, behavioral, and motor functions, and DLB-related CSF and plasma biomarkers.

6.2 Nelfamapimod (VX-745)

Neflamapimod (VX-745) is a selective inhibitor of the p38 mitogen activated protein (MAP) kinase alpha enzyme being developed by EIP Pharma. It completed a successful Phase 2a trial in early AD (REVERSE-SD trial) and a Phase 2b trial was recently completed. It is also being studied for cognition in Huntington's disease. P38 MAP alpha kinase is an intracellular enzyme that is involved in inflammation and Aβ-induced and age-related synaptic dysfunction, which may be a driver of learning and memory deficits [101,102]. The AD study concluded that neflamapimod may improve episodic memory by mediating synaptic dysfunction and may have the potential to improve amyloid plaque burden [102,103]. DLB shares similar pathophysiology to AD and DLB patients may also benefit from improvement of synaptic plasticity. EIP Pharma recently started a Phase 2 trial of neflamapimod in DLB (). The primary objective is to study neflamapimod's effect on cognition, attention, and executive and visuospatial functions. Other outcome measures include neuropsychiatric symptoms and EEG as a potential biomarker for DLB. Eighty participants with probable DLB with at least one core clinical feature and a positive DaT scan will be enrolled.

6.3 Pimavanserin

Pimavanserin is a selective serotonin 5-HT2A inverse agonist that was approved by the FDA in 2016 for the treatment of delusions and hallucinations in PD psychosis [104]. Its novel mechanism avoids significant activity at dopamine receptors, thereby avoiding motor side effects associated with current antipsychotics [105]. In a Phase 3 RCT (n=199) in participants with PD psychosis, pimavanserin significantly reduced psychotic symptoms as measured by Schedule for the Assessment of Positive Symptoms (SAPS)-PD without worsening motor function [106]. It also showed benefits on sleep and caregiver burden

[106]. Preliminary data from open-label extension studies further supports its use [107]. Several studies suggest that hallucinations and delusions in DLB, PDD, and AD are linked to alterations in the 5-HT system [37], suggesting that treating this common mechanism may produce benefit across different dementias. As with other antipsychotics, there is still a risk of QT prolongation and an increased risk of death in dementia with pimavanserin. Nonetheless, the current treatment options for psychosis in DLB are limited, and pimavanserin should be explored in the DLB population. Currently, a Phase 3 trial of pimavanserin for relapse of dementia-related psychosis is ongoing (). Participants with DLB, PDD, AD, and other dementias with psychotic symptoms (delusions, hallucinations) are treated with pimavanserin for 12 weeks and those responding are randomly assigned to pimavanserin or placebo; time to relapse in psychotic symptoms will be measured as the primary outcome.

6.4 MP-101

MP-101 is being developed by Mediti Pharma for the treatment of dementia-related psychosis, agitation, and aggression. MP-101 is an agonist of metabotropic glutamate receptors (mGluRs) 2 and 3. Glutamate is the main excitatory neurotransmitter in the central nervous system, and mGluRs regulate glutamate neuronal transmission by altering the release of neurotransmitters or by modulating the post-synaptic responses to glutamate [108]. Abnormal glutamatergic activity in the brain may be present in psychiatric disorders, and normalizing this aberrant activity has been studied as a therapeutic target in bipolar disorder [109] and schizophrenia [110]. The activation of mGluR2 and mGluR3 decreases neuronal excitability by inhibiting glutamate release and modulates synaptic plasticity [111]. A Phase 2 trial of MP-101 in participants with dementia-related psychosis and/or agitation and aggression is currently ongoing (). Participants must have a clinical diagnosis of DLB, PDD, AD, frontotemporal degeneration spectrum disorders, or vascular dementia. Approximately 100 participants are treated with MP-101 for 10 weeks. The primary outcome measure of delusions, hallucinations, and/or agitation and aggression is assessed by the Neuropsychiatric Inventory (NPI) psychosis subscale.

6.5 E2027

E2027 is a selective phosphodiesterase-9 (PDE-9) inhibitor being developed by Eisai for the treatment of DLB. PDE inhibitors may have neuroprotective properties and improve neuronal plasticity in neurodegenerative diseases [112]; they have been explored as disease-modifying therapies in AD [42]. PDE-9 is a cyclic guanosine monophosphate (cGMP)-degrading enzyme that is highly expressed in the brain [113]. cGMP is critical to cell signaling, and is involved in synaptic plasticity and cognitive function. In animal models, E2027 has been shown to inhibit the degradation of cGMP and increased CSF cGMP levels with positive effects on cognitive function [113]. A Phase 2 trial is currently ongoing in participants with probable DLB (). The study will examine the effect of E2027 on cognition and clinical and caregiver impressions as measured by Montreal Cognitive Assessment (MoCA) and CIBIC+ after 12 weeks of treatment. Assessments of neuropsychiatric and motor symptoms will also be explored as secondary outcome measures.

6.6 LY3154207

LY3154207, in development by Eli Lilly, is a selective positive allosteric modulator of the dopamine D1 receptor subtype being studied for cognition in participants with DLB or PDD. Dopamine is linked to various symptoms associated with DLB including cognitive function, motor deficits, behavioral symptoms, and daytime somnolence [36] and D1 receptors, specifically, are essential in attention, memory and executive function [114]. The proposed mechanism suggests that LY3154207 increases the affinity of dopamine for the D1 receptor, which in turn increases the dopamine D1 receptor tone at the site of dopamine release and amplifies response to endogenous dopamine [114]. This may be beneficial in patients with insufficient physiologic dopamine, such as DLB patients. Direct D1 receptor agonists may cause rapid tolerance development due to overstimulation of the D1 receptor, and LY3154207 may enhance D1 activity without these limitations [115]. A Phase 2 trial is currently being conducted to study the effects of LY3154207 on cognitive function in participants with mild to moderate dementia due to DLB or PDD (). Primary outcome measure is improvement in the ability to maintain concentration for a period of time without error, and is assessed by the Continuity of Attention (CoA) composite score of the Cognitive Drug Research Computerized Cognition Battery (CDR-CCB) [116]. Secondary outcomes will evaluate improvements in cognitive function and attention, parkinsonism, daytime sleepiness, and neuropsychiatric symptoms.

6.7 Zonisamide

Zonisamide is an antiepileptic being studied as adjunct therapy to levodopa for the treatment of Parkinsonism in DLB. It is currently approved in Japan as adjunct therapy to levodopa in PD patients. Results of a recent Phase 2 trial (n=158) showed that zonisamide is effective in improving DLB-related parkinsonism, as measured by UPDRS-III, without worsening cognitive function or psychiatric symptoms [117]. The trial was conducted only in Japan and was not registered on ClinicalTrials.gov. Current study was conducted based on the positive results from previous trials that showed zonisamide improved motor symptoms and the “wearing-off” phenomenon without worsening psychiatric symptoms in PD patients and a small number of DLB patients [118,119]. Zonisamide has the potential to reduce the levodopa dose needed, therefore reducing the risk of neuropsychiatric side effects. A Phase 3 trial is currently pending.

7. OTHER POTENTIAL THERAPEUTIC STRATEGIES

DMTs including immunotherapy, stem cells, and gene therapy aimed at preventing, slowing or ameliorating the production and aggregation of pathological proteins are of interest as future treatments for DLB [65]. In animal models, both passive and active immunotherapy targeting α-synuclein reduced pathological and behavioral deficits induced by aggregated α-synuclein [120,121]. There are immunotherapies in RCTs for PD, such as AFFITOPE targeting aggregated α-synuclein [122]—however, none are being studied in DLB patients. Neural stem cells (NSCs) targeting α-synuclein have been studied in animal models, and a recent study showed that NSC transplantation into α-synuclein transgenic mice improved cognition and motor functions [123]. The results were ascribed to NSC-related expression of brain-derived neurotrophic factor (BDNF), which modulates dopaminergic and

glutamatergic systems [123]. Two agents, NPT200–11 and Ambroxol, have been shown to decrease the central levels of α-synuclein. NPT200–11 is an α-synuclein misfolding inhibitor, which has been shown to have cognitive and motor benefits in animal models of PD [124]. Ambroxol is currently being tested in PDD and has shown to improve cognition by raising the levels of beta-glucocerebrosidase and lowering alpha-synuclein [125]. However, neither agent is currently being tested in DLB, even though the MOAs suggest that they could be beneficial in DLB.

8. CONCLUSION

DLB patients have a poor prognosis, short lifespan and fast cognitive decline relative to patients with AD or PDD. There are only eight agents in clinical trials while currently used treatments address symptomatic manifestation using agents approved for other indications. There is limited evidence to support their use with most evidence being anecdotal case series. Only a small number of RCTs have been conducted in the DLB population and none have demonstrated a drug-placebo difference. Cholinesterase inhibitors, donepezil and rivastigmine, have the most evidence in the DLB population with support for benefit for cognition and neuropsychiatric symptoms. Memantine, a NMDA receptor antagonist, has been shown to be effective in a few studies, but the evidence is less robust than that supporting use of donepezil or rivastigmine. Treatment of visual hallucinations and delusions is challenging in DLB due to the high sensitivity of DLB patients to neuroleptic agents. Antipsychotics should be reserved for severe symptoms and only the lowest doses should be used and treatment period should be as short as possible. Agents should be chosen based on their side-effect profile with queitapine and clonazapine being the most widely used despite little evidence. Parkinsonism symptoms can be difficult to treat since levodopa can cause hallucinations and other neuropsychiatric symptoms. Recent study of zonisamide as adjunct therapy to levodopa has shown benefit and holds promise as potential treatment option for motor symptoms. RBD, now considered a core clinical feature of DLB, is managed with clonazepam and melatonin, although no RCTs in the DLB population have been conducted with these agents. Modafinil and armodafinil have potential to treat excessive daytime sleepiness; further RCTs of these agents are needed. Autonomic dysfunction is an under-recognized complication of synucleinopathy usually managed by standard of care.

Randomized controlled trials in DLB have only recently begun with two trials recently reporting negative results. Intepiridine (RVT-101), a 5-HT6 antagonist, failed to show significant improvement in motor function and cognition in the HEADWAY-DLB studies. Nelotanserin, a 5-HT2A inverse agonist, showed potential in improving motor function but its development was discontinued after another trial failed to show efficacy in reducing RBD events. Despite these setbacks, there are eight agents currently in the pipeline that hold promise. Tyrosine kinase inhibitors, bosutinib, nilotinib, and K0706, are currently in Phase 2 trials being studied as potential disease-modifying agents that work by inducing autophagy to degrade alpha-synuclein and other neurotoxic proteins. Neflamapimod, a p38 MAP kinase alpha inhibitor, is being studied for its potential to improve synaptic plasticity, thereby improving cognition. Pimavanserin, an agent already approved for the treatment of psychosis in PD, is currently being studied in dementia-related psychosis and its unique

mechanism holds promise in DLB patients. Another agent being developed for dementia-related psychosis, MP-101, targets glutamate neurotransmission. E2027, a selective PDE-1 inhibitor, and LY3154207, a dopamine D1 receptor modulator, are also being studied in Phase 2 trials testing their efficacy in improving cognition in DLB patients. Other disease-modifying approaches such as immunotherapy, stem cell therapy, and gene therapy are being tested in other α-synucleinopathies but not yet in DLB.

Identifying molecular targets specific to DLB and further understanding of the disease pathophysiology are critical for developing future therapeutic interventions as well as guiding current treatment management. Measuring clinical efficacy in rigorous clinical trials remains a challenge because of important confounders, such as fluctuations and psychomotor impairments. More RCTs in DLB patients and measures directed at the unique features of DLB are urgently needed.

9. EXPERT OPINION

Management of DLB patients is challenging due to the varied symptoms, limited treatment options, and high sensitivity to drug-induced adverse events. Current treatments aim at providing symptomatic relief using drugs off-label. Symptomatic treatments can potentially slow down the disease progression but do not reverse the disease pathology, and there are no DMTs available for DLB. Treatment strategies should follow a systemic approach with structured monitoring of efficacy and side effects. Drug selection should be evidence-based to the extent possible. DLB patients present with various types of symptoms, and treatment should begin by targeting the most troublesome symptoms. The risks and benefits of initiating treatment should be considered, especially in this patient population where drug intolerance is common.

Biomarkers play an important role in drug development. Participant selection, target engagement, disease course prediction, evidence of disease modification, and side effect monitoring all involve biomarkers [126]. The prevalence of DLB diagnosis has increased since the release of the revised diagnostic criteria for DLB. Still, no direct biomarkers and genetic markers have been identified to date. There is a need to identify reliable biomarkers and neuroimaging approaches to diagnose DLB. Developing CSF, plasma, and imaging biomarkers will be valuable to assess disease activity and risk factors, and to monitor treatment responses. The development of consensus diagnostic criteria, imaging support for the diagnosis such as a DaT scan, and improved clinical measures [127] provide the basis for clinical trials and will allow more rigorous assessment of emerging treatments in the future. Additionally, identifying novel drug targets is crucial to developing DLB specific disease-modifying therapies.

Most of the past and current trials include patients with either DLB or PDD. DLB and PDD share similarities in pathology and symptoms, however, may respond differently to treatments;for example, levodopa appears to be more effective in patients with PDD than DLB. Trials targeted specifically for DLB population are needed. Many agents are being tested in PD and PDD, but not in DLB patients. These agents may be shown to have benefit in DLB, which shares many of the biological features of PD and PDD. Clinical trial

methodology for DLB is not likely to be identical to instruments used in AD trials given the contrasting clinical features of the two illnesses. New measures may be needed as part of the development strategy for DLB therapeutics.

In the past, the majority of the studies in the DLB population have been small case series and the very few RCTs conducted have been for symptomatic treatments only. Since then the drug development activity for DLB has progressed considerably; especially national support and interest in centralizing research efforts have increased. However, the DLB drug pipeline is notably small compared to the AD pipeline, and still remains an area of unmet need. Conducting RCTs in DLB patients can be challenging since DLB is often under-diagnosed or misdiagnosed, and recruiting eligible subjects can be difficult. Also this vulnerable patient population is more prone to adverse events, which can affect the subject retention rate in trials. Two agents, intepiridine and nelotanserin, failed to show drug-placebo difference in DLB patients. Trials often fail to demonstrate drug benefit, however, all well-conducted trials provide learnings that can be applied to future trials. The AD pipeline has advanced every year and continues to grow despite the lack of success. Progress depends on innovation and learning from past experiences. Evaluating the DLB drug development landscape can provide insight into how best to optimize development practices.

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Article Highlights

- There is a need for novel therapeutics for dementia with Lewy bodies (DLB)
- There is a lack of randomized controlled trials (RCTs) for DLB therapeutics. Most studies in the past were case studies and open-label trials. RCTs for DLB have only recently been initiated.
- There are no drugs approved for DLB in the United States and Europe and current treatment strategies target symptomatic relief using drugs approved for other indications.
- There are eight agents currently in the DLB drug development pipeline and this includes two promising agents—pimavanserin and zonisamide. Symptom-specific targets are emerging as a therapeutic approach.
- Early trials of drugs for DLB have resulted in no demonstrable efficacy. Recent trials of two novel agents, intepiridine (RVT-101) and nelotanserin, failed to show drug-placebo difference in DLB patients.
- New biomarker strategies may enhance diagnostics and clinical trial designs, and new therapeutic targets may assist in the development of DLB specific disease-modifying therapies.

Table 1.

Agents in past clinical trials for Dementia with Lewy bodies

Agent	Mechanism of action	Target symptoms	Sponsor	Phase	Status	CT.gov ID	Primary outcome measures	Estimated end date
Intepirdine (RVT-101)	Selective 5-HT6 receptor antagonist	Cognition, motor function, neuropsychiatric symptoms	Axovant Sciences	2	Completed	(HEADWAY-DLB study)	UPDRS-III	Dec 2017
				2/3	Terminated	(HEADWAY-DLB extension)	Long-term safety and tolerability	Feb 2018
				2	Completed		Change in gait	Nov 2017
Nelotanserin	5-HT2A inverse agonist	Visual hallucinations, RBD	Axovant Sciences	2	Completed		UPDRS-Parts II and III	Nov 2017
				2	Completed		Frequency of REM sleep behaviors	May 2018
				2	Terminated		Long-term safety, tolerability, and efficacy	Jan 2019
HTL0018318	Muscarinic M1 receptor agonist	Cognition, psychosis	Heptares Therapeutics	2	Suspended		Safety and tolerability	Jan 2021
Donepezil	Acetylcholinesterase inhibitor	Cognition, neuropsychiatric symptoms	Eisai	3	Completed		MMSE, NPI-12	Apr 2013
				2	Completed		MMSE, NPI-10	Mar 2011
				2	Completed		MMSE, NPI-10, CIBIC+, J-ZBI	Feb 2010
				4	Completed		MMSE, HDS-R	Mar 2017
				4	Completed		CIBIC+	Mar 2018
			Osaka University	n/a	Completed		FDG-PET	Feb 2015
Galantamine	Acetylcholinesterase inhibitor	Cognition, neuropsychiatric symptoms	Neurological Research Center, Ortho-McNeil Neurologics	3	Completed		NPI-12, ADCS-CGIC, COGDRAS	Aug 2004
Memantine	NMDA receptor antagonist	Cognition, neuropsychiatric symptoms	Helse Stavanger HF	2	Completed		CIBIC	Mar 2009
			H. Lundbeck A/S	4	Completed		None (exploratory study)	Jan 2009
Armodafinil	CNS stimulant; increases dopamine	Hypersomnia, attention, wakefulness	Mayo Clinic, NIA	4	Completed		MWT	Mar 2012
			New York University	n/a	Unknown *		EEG	Unknown

Agent	Mechanism of action	Target symptoms	Sponsor	Phase	Status	CT.gov ID	Primary outcome measures	Estimated end date
Ramelteon	Selective agonist of melatonin receptors MT1 and MT2	RBD, sleep/wake cycle disturbances	Massachusetts General Hospital	n/a	Withdrawn		Sleep/wake patterns via activity monitors	Jul 2010
			Northwestern University, Takeda	n/a	Terminated		Frequency of RBD based on daily sleep diaries	Dec 2009
Deep Brain Stimulation (DBS)	Electrical stimulation of the Nucleus Basalis of Meynert	Cognition	University Hospital, Rouen	Pilot Device	Completed		FCSRT	Dec 2017
			University College, London	Pilot Device	Completed		HVLT, verbal fluency, SRT, CRT, WAIS-IV, Posner's Covert Attention test, CAF	Oct 2016

ADCS-CGIC: Alzheimer's Disease Cooperative Study Clinical Global Impression of Change, CAF: Clinician Assessment of Fluctuation, CIBIC+: Clinical Global Impression of Change - plus caregiver input, CNS: central nervous system, COGDRAS: Cognitive Drug Research Computerized Assessment System, CT.gov ID: ClinicalTrials.gov identifier, CRT: Choice Response Time task, EEG: electroencephalography, FCSRT: Free and Cued Selective Recall Reminding Test, FDG-PET: fluorodeoxyglucose positron emission tomography, HDS-R: Hasegawa's Dementia Scale, HVLT: Hopkins Verbal Learning Test, J-ZBI: Japanese-Zarit Caregiver Burden Interview, MMSE: Mini-Mental State Examination, MWT: Maintenance of Wakefulness Test, NIA: National Institute on Aging, NMDA: N-methyl-D-aspartate, RBD: REM sleep behavior disorder, SRT: Simple Response Time task, UPDRS-III: Unified Parkinson's Disease Rating Scale-Part III, WAIS-IV: Wechsler Adult Intelligence Scale

Note: Eight agents and one device in 22 clinical trials identified as completed, terminated, withdrawn, suspended, or with unknown status as of August 1, 2019 according to ClinicalTrials.gov.

* Trial status becomes "unknown" if the status has not been updated in the past 2 years and the trial completion date has passed.

Table 2.

Agents currently in clinical trials for Dementia with Lewy bodies

Agent	Mechanism of action	Therapeutic purpose	Sponsor	Phase	Status (CT.gov ID)	Subject characteristics	Primary outcome measures	Estimated end date
Bosutinib	Tyrosine kinase inhibitor	Autophagic clearance of neurotoxic proteins (α-synuclein, amyloid-β, tau) (DMT-SM)	Georgetown University, Alzheimer's Association	2	Recruiting ()	Mild to moderate DLB with abnormal DaT scan	Safety and tolerability	Aug 2021
E2027	Selective PDE-9 inhibitor	Reduce degradation of cGMP and improve cell signaling and synaptic plasticity (DMT-SM)	Eisai	2	Recruiting ()	Probable DLB	MoCA, CIBIC+	Mar 2020
Pimavanserin	Selective 5-HT2A inverse agonist	Symptomatic treatment of psychosis (hallucinations, delusions); relapse prevention of psychotic symptoms	Acadia, NIA	3	Recruiting ()	Dementia-related psychosis	Time to relapse	Aug 2020
LY3154207	Dopamine D1 receptor modulator	Symptomatic treatment of cognitive function; amplifies response to endogenous dopamine	Eli Lilly	2	Recruiting ()	Mild to moderate dementia due to DLB or PDD	Continuity of Attention score of CDR-CCB	Feb 2020
K0706	Tyrosine kinase inhibitor	Autophagic clearance of neurotoxic proteins (α-synuclein, amyloid-β, tau); reduce dopaminergic cell death (DMT-SM)	Georgetown University, Sun Pharma	2	Recruiting ()	DLB with fluctuations, visual hallucinations or RBD	Safety and tolerability	Aug 2021
Nilotinib	Tyrosine kinase inhibitor	Autophagic clearance of neurotoxic proteins (α-synuclein, amyloid-β, tau); reduce dopaminergic cell death (DMT-SM)	Georgetown University, NIH	2	Recruiting ()	DLB with fluctuations, visual hallucinations or RBD	Safety and tolerability	Aug 2023
Neflamapimod (VX-745)	P38 MAP kinase alpha inhibitor	Improve neuroinflammation and synaptic plasticity (DMT-SM)	EIP Pharma	2	Recruiting ()	Mild to moderate DLB with a positive DaT scan or polysomnography verified RBD	NTB	Jun 2020
MP-101	mGluRs 2/3 agonist	Symptomatic treatment of psychosis, agitation, and aggression; inhibits glutamate neurotransmission	Mediti Pharma	2	Recruiting ()	Dementia-related psychosis and/or agitation and aggression	NPI – psychosis subscale	Aug 2020

CDR-CCB: Cognitive Drug Research Computerized Cognition Battery, CIBIC+: Clinical Global Impression of Change - plus caregiver input, CT.gov ID: ClinicalTrials.gov identifier, DLB: dementia with Lewy bodies, DMT-SM: small molecule disease-modifying therapy, MAP: mitogen-activated protein, mGluRs: metabotropic glutamate receptors, MoCA: Montreal Cognitive Assessment, NIA: National Institute on Aging, NIH: National Institute of Health, NPI: Neuropsychiatric Inventory, NTB: Neuropsychological Test Battery, PDD: Parkinson's disease dementia, PDE: phosphodiesterase, 5-HT: 5-hydroxytryptamine (serotonin receptors), RBD: REM sleep behavior disorder.

Note: Eight agents in eight clinical trials currently ongoing as of August 1, 2019 according to ClinicalTrials.gov.

Note: Zonisamide is pending Phase 3 clinical trial in Japan for the treatment of Parkinsonism in DLB as adjunct therapy to levodopa; however is not registered on ClinicalTrials.gov.