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REVIEW ARTICLE

Current Therapies and Drug Development Pipeline in Lewy Body Dementia: An Update

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Abstract
The term Lewy body dementia refers to either of two related diagnoses: dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD). Clinical management of Lewy body dementia is challenging. The current treatment options focus on relieving symptoms; no disease-modifying therapies are available. There are currently no US Food and Drug Administration (FDA) approved drugs for the treatment of DLB, and there are only a few for PDD. Cholinesterase inhibitors are shown to be beneficial in improving cognitive symptoms in Lewy body dementia. Rivastigmine was approved by the FDA to treat PDD. Donepezil was approved in Japan as a treatment for DLB. Levodopa may provide modest benefit in treating motor symptoms and zonisamide in adjunct to low-dose levodopa helps with parkinsonism. Treatment of autonomic symptoms are based on symptomatic treatment with off-label agents. Our main objective in this article is to present an overview of the current pharmacological options available to treat the clinical features of DLB and PDD. When evaluating the existing management options for Lewy body dementia, it is difficult to fully separate PDD from DLB. However, we have attempted to identify whether the cited studies include patients with PDD and/or DLB. Moreover, we have provided an overview of the current drug pipeline in Lewy body dementia. All currently active trials are in phase I or II and most are focused on disease modification rather than symptomatic treatment. Phase II trial results for neflamapimod show promising results. Due to heterogeneity of symptoms and underlying pathophysiology, there is a need for new biomarker strategies and improved definitions of outcome measures for Lewy body dementia drug trials.

1 Introduction

Lewy body dementia (LBD) is an umbrella term describing a range of clinical symptoms that are characterized pathologically by Lewy-related pathology (LRP), including both Lewy bodies and Lewy neurites. The clinical diagnoses associated with LRP include Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB), as well as multiple system atrophy (MSA).

In terms of clinical phenotypes, PDD and DLB may represent different points along a Lewy body disease continuum but have similar pathological aspects. While PDD and DLB each have separate diagnostic criteria, there is considerable

Key Points

Most of the commonly prescribed drugs for Lewy body dementia are derived from clinical trials in Alzheimer's or Parkinson's diseases.

A major focus of the management of neurobehavioral symptoms of Lewy body dementia is the discontinuation of medications with the greatest anticholinergic effect without worsening motor symptoms.

Various therapies are being developed to address the heterogeneity of the Lewy body dementia pathology, but there are inconsistent outcome measures between these studies.

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overlap between the two in symptomatology and treatment. The two diseases are clinically distinguished by the arbitrary 1-year rule based on the temporal onset of motor symptoms relative to cognitive symptoms. In PDD, the motor symptoms appear at least a year before the onset of dementia.

The diagnosis and clinical management of LBD can be challenging for physicians. As will be discussed later, patients with LBD present with varying degrees and combinations of dementia pathology, motor changes, and neuropsychiatric disturbances. DIAMOND-Lewy is a collaborative research program between Cambridge and Newcastle University that has developed a checklist to assist physicians in diagnosing and managing DLB and PDD patients based on 2017 consensus criteria [1, 2]. The checklist improved diagnostic rates of DLB, but not PDD, at two geographical regions in England [3]. A primary analysis found some benefits for patients and caregivers based on global outcome measures and caregiver burden, when the toolkit was used in comparison with standard therapy [4].

Management options are currently directed towards alleviation of symptoms; a disease-modifying therapy does not currently exist. However, appropriate use of available treatments can significantly reduce symptom burden and improve quality of life.

The primary focus of this article is to review the current pharmacological options available to treat the clinical features of DLB and PDD. Lewy body dementia describes a spectrum of conditions; it is difficult to fully separate PDD and DLB when reviewing the existing management options. However, we have attempted to identify if the cited studies involve patients with PDD and/or DLB. We also provide an overview of the current investigational drug pipeline in LBD.

2 Dementia with Lewy Bodies

DLB is a relatively common cause of dementia. In a 2014 meta-analysis by Vann Jones and O'Brien, DLB accounted for 4.2% of all community-based diagnoses of dementia, and increased to 7.5% of diagnoses in a secondary care setting [5]. It is commonly accepted that DLB is the third most common cause of dementia behind only Alzheimer's disease (AD) and vascular dementia.

Pathologically, DLB is characterized by the presence of Lewy bodies, which are scattered throughout the limbic system, neocortex, brainstem, and peripheral autonomic nervous system [1]. Lewy bodies are round, eosinophilic intraneuronal cytoplasmic inclusions consisting primarily of α-synuclein (SCNA). In addition, Lewy neurites are also present, typically in the transentorhinal cortex, amygdala, the CA2 and CA3 regions of the hippocampus, the nucleus basalis of Meynert, and additional brainstem nuclei [6]. In addition to LRP, up to 80% of patients with DLB will have concomitant Alzheimer's disease pathological changes and many meet the pathological criteria for AD [7].

From a biochemical perspective, DLB is associated with marked dopaminergic and cholinergic deficiencies. Particularly, there is a loss of cholinergic neurons in the nucleus basalis of Meynert and reductions in markers of cholinergic activity in the parietal and temporal cortices [8]. Additionally, the reduction in post-synaptic D2 receptor density in the striatum is more pronounced in DLB than in healthy controls [9].

It should be mentioned that there is considerable convergence of the neuropathologic features of DLB and PDD. The distinguishing features that may separate DLB and PDD from a neuropathological perspective are variable and somewhat unreliable, making it difficult to separate them into two separate pathologic entities. Because of this, a single Lewy body disorder research model has been proposed and accepted, with abnormal SCNA aggregation being the defining process common to both [10].

In 2017, revised clinical diagnostic criteria for DLB were published by the DLB consortium. Required for the diagnosis is the establishment of cognitive changes significant enough that they impact an individual's level of function, or, in other words, the presence of dementia. Additional core criteria include fluctuations in cognition, recurrent visual hallucinations, rapid eye movement sleep behavior disorder (RBD), and spontaneous motor features of Parkinsonism (one or more cardinal features of bradykinesia, rest tremor, and/or rigidity). There are several features that are supportive of a diagnosis of DLB, including (i) severe antipsychotic sensitivity, (ii) postural instability, (iii) repeated falls, (iv) hypersomnia, (v) hyposmia, (vi) syncope or transient episodes of unresponsiveness, (vii) non-visual hallucinations, (viii) systematized delusions, and (ix) apathy, anxiety, and depression [1].

In addition to these clinical features, the updated diagnostic criteria outline various indicative and supportive biomarkers [1]. There are currently no blood or cerebrospinal fluid biomarkers that can reliably diagnose DLB. Multiple previous studies have reported low β-amyloid 40–42 in DLB compared with those in PDD and controls, but they have not been validated to be able to reliably differentiate DLB from other neurodegenerative conditions [11, 12]. Along with there being no blood or spinal fluid biomarkers, direct imaging of α-synuclein pathological changes is also not available.

Using ligands specific for dopamine transporters, both positron emission tomography (PET) and single photon emission computed tomography (SPECT) demonstrate decreased dopaminergic activity in the basal ganglia in patients with parkinsonian disorders. This finding cannot be used to distinguish between other parkinsonian conditions. Therefore, its utility is most relevant when attempting

to differentiate between DLB and other neurodegenerative conditions that typically lack parkinsonism such as AD. A 2007 study involving 326 patients with dementia reported a sensitivity of 78% and specificity of 90% in using DAT SPECT imaging to diagnose DLB [13]. This imaging finding of reduced dopaminergic activity in the striatum is considered to be an indicative biomarker of DLB [1].

A second indicative biomarker, which is discussed in more depth later in the treatment section of our discussion, is the presence of REM sleep without atonia or RBD on polysomnography [1]. Polysomnography-confirmed RBD has a specificity of 98% for Lewy body disease [14].

Lewy body disease is associated with cardiac autonomic denervation which can be quantified using metaiodobenzylguanidine (MIBG) myocardial scintigraphy [1]. A third indicative biomarker for DLB is the finding of reduced sympathetic innervation on MIBG myocardial scintigraphy, with previous studies demonstrating a sensitivity of 69% and specificity of 89% [15].

In addition to indicative biomarkers, supportive biomarkers have also been identified. In structural magnetic resonance imaging (MRI), the medial temporal structures and hippocampi are typically well preserved without significant atrophy. Additionally, a quantitative electroencephalogram (EEG) showing prominent posterior slow-wave activity with periodic fluctuations in the pre-alpha and theta range is currently categorized as an indicative biomarker. Finally, fludeoxyglucose PET imaging demonstrating either occipital hypometabolism and/or the presence of the cingulate island sign are also supportive findings [1].

Based on the 2017 revised clinical criteria for DLB, the presence of two or more core clinical features or one core clinical feature and at least one indicative biomarker is sufficient for a diagnosis of probable dementia with Lewy bodies. Possible dementia with Lewy bodies is diagnosed in the context of one core clinical feature with no indicative biomarker or the presence of one or more indicative biomarkers but no core clinical features [1].

3 Parkinson's Disease Dementia

PDD is defined as the presence of dementia which occurs in the setting of an established diagnosis of Parkinson's disease (PD). From a historical perspective, the chief feature that previously separated PD and DLB was the timing of onset of cognitive symptoms relative to the appearance of motor changes. The '1-year rule' refers to the well accepted idea that the presence of dementia within the first year of onset of parkinsonism was exclusionary for PD and more suggestive of underlying DLB. DLB Consortium has remained supportive of the 1-year rule distinguishing DLB from PDD in 2017 consensus criteria, as it continues to be useful in clinical practice [1]. The International Parkinson and Movements Disorder Society deleted the 1-year rule with the release of new clinical diagnostic criteria for PD in 2015 [16]. With their new criteria, individuals may be diagnosed with PD regardless of their cognitive impairment. Those with significant cognitive impairment are assigned the label of PD, dementia with Lewy bodies subtype [16].

Dementia is a common feature of PD, with the prevalence estimated to be around 25–30% of patients with PD [17]. Older age and the duration of disease are both risk factors for PDD. In a study published in 2005 by Hely et al., at 15 years of disease duration, 48% of their cohort of PD patients met criteria for a diagnosis of dementia, and 36% fulfilled criteria for PD mild cognitive impairment [18].

Consensus criteria for the diagnosis of PDD were developed in 2007. The core features of these criteria include the requirement of a diagnosis of PD according to the Queen Square Brain Bank criteria, along with the presence of dementia with impairment in more than one cognitive domain (attention, memory, executive function, visuospatial function) [19].

4 Treatment of Cognitive Impairment and Cognitive Fluctuations

One of the primary features of both DLB and PDD is a progressive decline of cognitive function resulting in a loss of the ability to function independently. The cognitive deficits seen in DLB and PDD are similar, both with notable deficiencies in executive function, attention, and visuospatial function with relatively milder deficits in memory retrieval. Additionally, patients with DLB often have pronounced fluctuations in alertness and attention. Caregivers will describe drastic changes ranging from seemingly normal cognitive performance followed by periods of severe confusion and impairment that may raise concern for seizures or strokes. Bradshaw et al. demonstrated that the cognitive fluctuations in DLB differ qualitatively from the normal variations seen in other types of neurodegenerative disease [20]. Additionally, a study done in 2000 involving attention and vigilance tasks showed that the fluctuating cognition in DLB occurs on a second-to-second basis [21].

When it comes to the management of the cognitive symptoms of DLB, cholinesterase inhibitors are the mainstay of treatment. Similarly to those with Alzheimer's disease, profound degeneration of cholinergic neurons of the basal forebrain is seen in both DLB and PDD [22]. Cholinesterase inhibitors exert their effect by blocking the enzymatic breakdown and increasing the availability of the central nervous system acetylcholine. It should be noted that no head-to-head comparison trials of the different cholinesterase inhibitors have ever been performed. In regards to the specific

cholinesterase inhibitors, donepezil and rivastigmine appear to be equally efficacious. Rivastigmine is the only cholinesterase inhibitor that is US Food and Drug Administration (FDA) approved for use in PDD.

In a placebo-controlled, double-blinded multicenter study involving 120 patients with LBD, participants were randomized to either 6–12 mg/day of rivastigmine or placebo for 20 weeks. Patients who received the rivastigmine demonstrated a significant improvement on a computerized cognitive assessment, particularly on tasks related to attention. Patients on rivastigmine also demonstrated reduced apathy and anxiety, along with experiencing a reduction in delusions and hallucinations [23].

In another randomized study involving 140 DLB patients, 12 weeks of treatment with either 5 or 10 mg of donepezil were significantly superior to placebo on Mini Mental Status Examination (MMSE) scores (5 mg: mean difference 3.8; 95% confidence interval [CI] 2.3–5.3; $p < 0.001$; 10 mg: mean difference 2.4; 95% CI 0.9–3.9; $p = 0.001$) and CIBIC-plus. Improvements were also noted in behavioral measures and caregiver burden [24]. A second, double-blind, randomized controlled trial in 2015 showed a statistically significant improvement in MMSE scores only with the 10-mg dose compared with placebo. The change in the 5-mg group was not significant [25].

Evidence for galantamine is limited only to open-label studies. In one such study by Edwards et al. in 2007 involving oral galantamine, there were statistically significant changes noted in the Neuropsychiatric Inventory (NPI-12) which improved by 8.24 points from baseline. Additionally, scores on the Clinician's Global Impression of Change improved by 0.5 points from baseline [26].

The most common side effects of cholinesterase inhibitors are primarily gastrointestinal in nature. Additionally, because they enhance vagal tone, they may lead to cardiac issues such as bradycardia, syncope, or heart block. For those unable to tolerate oral formulations, it is reasonable to switch to the patch formulation of rivastigmine to see if it is better tolerated.

The benefits of memantine are much less clear compared with the benefits of cholinesterase inhibitors. Memantine is an *N*-methyl D-aspartate (NMDA) receptor antagonist that limits the neurotoxicity of glutamate. Previous animal model studies of parkinsonism have suggested evidence for glutamatergic overactivity, which explains the theoretical rationale for use of memantine in DLB [27]. However, the actual data for the efficacy of memantine in treating the cognitive symptoms of DLB is mixed and further studies are required.

A 24-week, randomized, placebo-controlled study of memantine 20 mg per day involving 72 patients with PDD or DLB showed that the memantine group performed better on the AD Cooperative Study—Clinical Global Impression of Change scale (ADCS-CGIC) compared with those receiving placebo (mean difference 0.7, 95% CI 0.04–1.39; $p = 0.03$). No significant differences were noted in secondary outcome measures [28]. Another larger study involving 199 patients with either DLB or PDD who were treated with memantine 20 mg per day again demonstrated a significant improvement in ADCS-CGIC scores in patients with DLB but not those with PDD [29]. The studies were somewhat limited by small sample sizes.

A phase II randomized controlled trial of neflamapimod, a p38αkinase inhibitor, in patients with DLB showed a statistically significant improvement on a custom battery of six cognitive tests over 16 weeks compared with placebo (AscenD-LB; ClinicalTrials.gov identifier: NCT04001517). The sponsor reported, in a press release, an improvement in gait as captured by timed up-and-go test [30]. The researchers attributed the result of the study as an indication of positive effect on basal forebrain cholinergic dysfunction [31].

5 Treatment of Motor Symptoms/Parkinsonism

The cardinal parkinsonian symptoms, including bradykinesia, resting tremor, rigidity, and postural instability, are observed in approximately 70% of patients with DLB [32]. The frequency and distribution of motor symptoms differ from those seen in idiopathic PD. Patients with DLB often experience fairly symmetric rigidity and bradykinesia, though a tremor is less common and less severe than in idiopathic PD [33, 34]. The reason for this difference has not been fully elucidated, though it has been postulated to be secondary to differences in the degree and distribution of Lewy body-related pathology [10].

While not necessarily supported by extensive or rigorous clinical trials, levodopa's benefit on motor symptoms in patients with DLB is generally considered modest and less robust than the response in patients with idiopathic PD. In one study of levodopa treatment for extrapyramidal symptoms in DLB, a significant motor response was noted in only about one third of patients. Four out of 14 patients withdrew due to side effects, with two dropping out because of gastrointestinal symptoms and the other two due to worsening confusion [35]. In another study published in 2008, motor benefit defined as > 10% improvement over baseline UPDRS III scores was achieved in only one-third of study subjects with DLB without exacerbation of psychotic symptoms [36]. A suggested approach would be to start with a low dose of one-half tablet of carbidopa-levodopa 25–100 mg three times daily, with slow increases according to the motor response and tolerance of side effects. Alternatively, while dopamine agonists such as a pramipexole and ropinirole are good options for younger patients with mild parkinsonism secondary to PD, they are generally avoided in patients with

DLB because of their propensity to cause somnolence and worsen hallucinations.

Various therapies are available to treat Parkinsonism in people with Parkinson's disease. DLB patients are less likely to be treated with these drugs than those with Parkinson's disease.

Zonisamide, an anticonvulsant medication that inhibits sodium and T-type calcium channels, has been approved in Japan for the treatment of PD [37]. The dosage typically studied in PD is 25–50 mg/day, much lower than the doses used to treat seizures. The exact mechanism through which it exerts its effect is unclear, though several theories have been proposed. In 2016, Murata et al. explored the efficacy and safety of zonisamide 25–50 mg/day taken once daily as compared with placebo. Both zonisamide 25 mg/day and 50 mg/day demonstrated a statistically significant reduction in UPDRS III scores [38]. More recently, Murata et al. published their results of a phase III randomized trial assessing the benefit of zonisamide for parkinsonism in patients with DLB [39]. Patients with parkinsonism who were diagnosed with probable DLB were randomized to receive oral zonisamide (25 or 50 mg/day) or placebo for a 12-week period, followed by a 40-week open-label extension. At week 12, the group difference (least squares mean ± SEM) for changes from baseline versus placebo in UPDRS III total score was − 2.7 ± 0.9 (95% CI − 4.4 to − 0.9; $p = 0.005$) in the zonisamide 25 mg/day group and − 2.6 ± 0.9 (95% CI − 4.4 to − 0.8; $p = 0.005$) in the zonisamide 50 mg/day group [39]. Following these trials, Japanese regulators approved zonisamide for the indication of parkinsonism in DLB in 2018 [40].

Zonisamide had a moderate effect on parkinsonism, but was still achieved with a relatively low dose of levodopa (254 mg/day), which is an alternative to increasing levodopa dosage. In DLB patients, the adverse effect of mental slowing, which can occur with epilepsy patients, may also occur if they are at a more advanced stage or taking higher doses [41]. The side effect of loss of appetite is relatively common, and it may put a burden on patients and their families [39].

Zonisamide 25–50 mg once a day may be a safe and effective adjunct to levodopa for the management of parkinsonism in PD and DLB. DLB patients who cannot tolerate an increase in the dose of levodopa because of gastrointestinal side effects or the development of hallucinations might benefit from zonisamide [42].

It has a mild therapeutic benefit, but its effects on cognition may limit its maximum dosage.

In addition to the pharmacological measures discussed above, it is also important to consider the importance of non-pharmacological interventions to help with motor symptoms. There are multiple studies demonstrating that regular aerobic exercise has a positive impact in patients with PD [43, 44]. A meta-analysis published in 2017 by Song et al. found that tai chi was associated with improvements in motor outcomes, including in the Timed Up and Go testing, the Unified Parkinson's Disease Rating Scale III score, balance, fall frequency, and 6-min walk [45].

6 Treatment of Neuropsychiatric Symptoms

Neuropsychiatric symptoms such as delusions, hallucinations, apathy, and anxiety are common in DLB and PDD. While relatively rare for other types of neurodegenerative disease such as Alzheimer's disease, recurrent visual hallucinations are one of the core clinical features for DLB. When compared with Alzheimer's disease, hallucinations, depression, and delusions occurred earlier and were more frequent in patients with DLB [46]. It is more common to see neuropsychiatric symptoms early on in LBD than in AD. The symptoms of hallucinations, delusions, sleep disorders, and irritability tend to remain more frequent over time in LBD, contributing significantly to personal strain [47]. Generally, neuropsychiatric symptoms play a similar role in other dementias, such as AD. However, in cases of LBD where the prevalence of these symptoms may be high, they may be especially important, requiring changes in treatment based on caregiver's report. DLB caregivers' subjective burden scores were higher than those typically reported by caregivers of AD or mixed diagnoses. Falling is a significant problem for patients with LBD, but it was not a significant predictor of any burden dimension [47].

Visual hallucinations are comparatively less common in PDD, and often are more prevalent later in the disease course [48].The visual hallucinations in DLB are typically detailed and well formed. Most are benign and not distressing to the patient. Descriptions are often centered on well-formed images of animals or people, or alternatively as the visualization of non-specific shapes or flashes of color. Visual illusions, misperceptions, illusions of presence, or the observation of the movement of shadows in the peripheral vision are also common. Auditory hallucinations are less specific and less frequent for DLB and PDD, and often go underreported.

Delusions are also common in DLB. These delusions are typically complex and bizarre, often involving entrenched thoughts related to visual hallucinations that a patient has experienced [49]. The delusions in DLB are contrasted with those experienced in AD, which are more frequently related to misidentification or their own memory impairment. Of note, a study done in 2010 showed that the frequency of somatoform disorder was higher in DLB and PD than in other types of neurodegenerative diseases. These somatoform disorders consisted of non-physiological sensory or motor symptoms frequently accompanied by delusional thought content [50].

Depression and anxiety are common in both DLB and PDD. In a 2007 study by Borroni et al., 61.9% of their cohort of DLB patients had depression, 67.4% experienced significant anxiety, and 57.6% had apathy [51]. An additional study in 2017 demonstrated that co-morbid depression was more common in patients with DLB versus those with Alzheimer's disease [52].

It bears mention that antipsychotic sensitivity is considered to be clinical feature supportive of DLB, and also occurs in patients with PDD. Previous studies have shown that approximately 50% of patients with DLB will have severe sensitivity to antipsychotic medications [53]. The mechanism of this phenomenon is thought to be mediated by dopamine-2 receptor blockade. Adverse reactions occur more commonly with older, first-generation antipsychotics, though reactions to newer agents are also frequently encountered.

In patients with LBD, treatment of hallucinations and psychotic symptoms is challenging since dopaminergic medications are the main option for treating motor impairments. To achieve optimal outcomes, it is helpful to follow a stepwise approach. The initial step should focus on identifying systemic disorders that may aggravate neuropsychiatric symptoms based on the history and physical examination, such as urinary tract infection, followed by discontinuing anticholinergics. In the next step, relatively low-potency antiparkinsonian medications can be stopped first, including monoamine oxidase B inhibitors or amantadine, which may worsen neurobehavioral symptoms. Next, dopamine agonists should be reduced or discontinued. In one randomized controlled trial of patients with LBD, rivastigmine 6–12 mg daily significantly and clinically improved apathy and anxiety, with fewer delusions and hallucinations compared with the control group [23]. Because of the significant safety concerns and the aforementioned antipsychotic sensitivity, antipsychotics are typically a last resort for more severe behavioral symptoms after other measures have been attempted. Additionally, dopaminergic blockade may result in worsening of pre-existing motor symptoms, so it should be used with caution in patients with more pronounced parkinsonism.

In clinical trials of antipsychotics for patients with DLB or PDD, there has been no strong evidence of efficacy. Typical antipsychotics such as haloperidol should be avoided. In a small case series published in 2003, Takahashi et al. demonstrated that five out of nine DLB patients who received quetiapine 25–75 mg/day had a decline of > 50% in the sum of scores measuring agitation, hallucinations, and delusions on the Neuropsychiatric Inventory scale [54]. However, in a multicenter, randomized, double-blind, placebo-controlled study in 2007 involving 23 patients with DLB and nine with PDD, quetiapine did not show a benefit for treating agitation or psychosis when compared with placebo [55].

In another study done in 2002, patients receiving olanzapine 5 mg showed significant reductions in delusions and hallucinations without worsening of motor symptoms [56]. There is supportive evidence for the use of clozapine for patients with psychotic symptoms in the setting of PD. In a 4-week, randomized, double-blind, placebo-controlled study, patients receiving clozapine demonstrated improved psychotic symptom assessment scores, with no change in motor and cognitive function compared with those receiving placebo [57]. The use of clozapine is limited by its potential to cause serious hematological side effects such as granulocytopenia, and the need for close laboratory monitoring. There are relatively few randomized clinical trials of high quality regarding LBD treatment, as most pharmacological studies focus on uncontrolled clinical trials. Consequently, there are no direct comparisons of pharmacotherapies for LBD randomized clinical trials. Network meta-analysis (NMA) is a technique for comparing multiple treatments simultaneously in a single analysis by incorporating direct and indirect evidence within a network of randomized controlled trials. NMA can generate estimates with precision and accuracy [58, 59]. A recent NMA of nine randomized controlled trials found that none of the treatments (olanzapine, quetiapine, memantine, rivastigmine, donepezil, or zonisamide) had statistical significance for managing neuropsychiatric symptoms ($k = 6$, $n = 653$). According to a second network meta-analysis of randomized clinical trials and single-arm studies, aripiprazole, olanzapine, and yokukansan (an eastern Asian herbal supplement) were associated with improvements in symptoms based on NPI-10 scores ($k = 27$, $n = 1073$) [59].

Pimavanserin, a selective serotonin 5-HT2A receptor inverse agonist, has been approved by the US FDA for use in patients with PD psychosis. Due to its lack of effects on both dopaminergic and histaminergic receptors, there are less of the problematic side effects seen with other antipsychotics. In a 6-week, randomized, double-blind, placebo-controlled study of pimavanserin published in 2013, a subgroup of patients with cognitive impairment had an improvement in a psychosis score that was better than the change observed in patients who had normal cognition [60].

The HARMONY trial was a relapse-prevention study evaluating the efficacy and safety of pimavanserin for treating hallucinations and delusions associated with dementia-related psychosis. The study showed efficacy when a prespecified interim analysis revealed > 2.8-fold reduction in risk of relapse with pimavanserin (hazard ratio 0.353; 95% CI 0.172–0.727; 1-sided $p = 0.0023$). Patients with dementia-related psychosis who had a response to pimavanserin had a lower risk of relapse with continuation of the drug (13%) than with discontinuation (28%) [61]. The FDA has rejected the manufacturer's request that pimavanserin be the first approved treatment of hallucinations and delusions associated with dementia-related psychosis due to the absence of statistically significant changes in some of the

dementia subgroups, and low numbers of patients with less common dementia subtypes [62]. The efficacy of pimavanserin in DLB has not been fully established.

The results of a meta-analysis of four randomized clinical trials, including 680 patients with PDD, showed that pimavanserin significantly reduced delusions and hallucinations [63]. A retrospective cohort study compared patients with PD or DLB who started on quetiapine or pimavanserin for psychosis and assessed time to discontinuation of the medication using a Kaplan-Meier study [64]. Analyzing time to discontinuation accounted for efficacy, safety, and tolerability. The pimavanserin group had a lower discontinuation rate at early stage compared with the quetiapine group but a higher discontinuation rate at late stage. Lower early discontinuation rates in the pimavanserin cohort may indicate better results when it comes to promptly treating psychosis. In fact, more patients remain on quetiapine long term because of its delayed effects, possibly as a result of improvement in secondary indications such as agitation or insomnia [64].

Pimavanserin does not have negative impacts on cognitive function in patients with neurodegenerative diseases compared with those on placebo and is thought to be well tolerated without worsening parkinsonian symptoms. Pimavanserin may be clinically useful for promptly managing psychosis in LBD patients, but it is not recommended for patients with preexisting QT prolongation.

No specific treatment or guideline has been defined for treating depression and anxiety in patients with DLB and PDD. To address the gaps in the treatment of LBD, an expert opinion consensus has been developed [65]. However, further trials are needed. The International Parkinson and Movement Disorder Society Evidence-Based Medicine Committee recommended venlafaxine as clinically useful treatment for depressive symptoms in PD [66]. Despite conflicting studies on paroxetine, citalopram, and sertraline for treatment of depression in PD, the committee considered these SSRIs as possibly useful due to established efficacy outside of PD [66]. However, these drugs should be used with caution in those with rapid eye movement (REM) sleep behavior disorder due to the risk of exacerbation. In a 2010 study, 71% of patients with DLB treated with citalopram discontinued therapy because of intolerable side effects [67]. Tricyclic antidepressants are widely known to be anticholinergic and, therefore, should be avoided.

7 Treatment of Rapid Eye Movement Sleep Behavior Disorder

RBD is a common symptom in all synucleinopathies and is one of the core clinical criteria of DLB [1]. In normal REM sleep, the skeletal musculature is atonic, leading to absence of motor activity. This absence of motor function is thought to be mediated by a network of inhibitory projections originating in the brainstem which then terminate in the motor neurons of the spinal cord [68].

In RBD, the normal atonia during REM sleep is lost, resulting in recurrent episodes of complex motor behavior and/or vocalizations during sleep, often accompanied by vivid dreams of being attacked or chased [69]. These episodes most typically occur in the second half of sleep when REM sleep is most prevalent. This differs in relation to other parasomnias such as sleep walking, confusional arousals, and sleep terrors which typically occur in earlier sleep periods. The movements of RBD are described as purposeful, ranging in severity from violent punching of the limbs to more subtle, benign gesturing of the hands. Patients with RBD are at a high risk of injury due to falling or jumping out of the bed.

RBD has been shown to be associated with an increased risk of development of an α-synucleinopathy. The estimated 10-year risk for developing a neurodegenerative disease in patients with idiopathic RBD is 40.6% [70]. In another series, 81% of patients diagnosed with idiopathic RBD eventually developed a parkinsonian or dementia syndrome, with the mean interval being 14 years from the onset of RBD [71].

The evaluation of RBD often involves corroboration from a partner or informant but definitive diagnosis of RBD requires a video polysomnography which will demonstrate REM sleep without atonia (RSWA) measured using surface electromyography [72].

In regards to the treatment of RBD, the first and most essential priority should be ensuring a safe sleep environment. Dangerous items such as knives and firearms should be made inaccessible. The immediate sleeping environment should be modified with removal of all items that may be easily broken. In extreme cases, more restrictive measures such as bed alarms and padded railings may be utilized.

Pharmacologically, melatonin is often considered to be the first-line therapy. Melatonin is an endogenous hormone secreted by the pineal gland which helps regulate circadian rhythms. Melatonin production is reduced in PD with a reported association between slow-wave sleep and melatonin area under curve in PD patients [73]. The exact mechanism through which melatonin improves RBD symptoms is unknown. However, multiple studies have demonstrated that melatonin decreases the severity and frequency of RBD. In a 2013 study by McCarter et al., 12% of patients using melatonin 6 mg had complete resolution of their RBD. Approximately 48% reported moderate or greater subjective improvement in their episodes. Additionally, melatonin treatment was also associated with decreased reported severity of injuries [74]. McGrane et al. reviewed multiple prospective and retrospective studies involving the use of melatonin in the range of 3–9 mg [75]. The authors found that each of the studies demonstrated that melatonin again

reduced both the severity and frequency of RBD. As mentioned, melatonin is often an ideal first-line treatment due to its favorable safety and tolerability profile when compared with other medications used to treat RBD. It tends to be well tolerated, with most side effects (GI upset, headaches, fatigue, and dizziness) usually being fairly mild [75]. The dose of melatonin required to suppress RBD often varies, with a typical starting dose of 3 mg prior to bedtime that may be increased periodically in similar increments until the symptoms have improved or ceased.

Clonazepam is a long-acting benzodiazepine that has been shown to be efficacious in treating RBD. Much like melatonin, the exact mechanism through which clonazepam affects RBD is unknown. Clonazepam is often effective in doses as small as 0.25 mg/night, though doses above 1 mg/night may be necessary in certain cases [76]. The main limitations of clonazepam are related to its problematic side effect profile, particularly as it pertains to elderly patients with dementia. These side effects may include increased confusion, drowsiness, and dizziness. Clonazepam should also be used with caution in those with pre-existing sleep apnea and gait disorders.

There have been multiple case series which have demonstrated the effectiveness of clonazepam on RBD. A study by Olson et al. demonstrated that clonazepam treatment was completely or partially successful in approximately 87% of patients who were given the medication [77]. Similarly, a study done in 1996 by Schenck and Mahowald followed 170 patients with RBD for a 12-year period who were treated with nightly clonazepam. In that cohort, complete or substantial control of RBD was achieved in 86% of patients [78].

Melatonin and clonazepam can be used together in cases where either one alone is not sufficient to treat RBD. In addition to melatonin and clonazepam, other treatments for RBD have also been investigated. A small crossover study done in 2012 showed a benefit in reducing the frequency of RBD episodes with the use of a rivastigmine patch at a dose of 4.6 mg/24 h [79]. Similarly, a case series involving three patients with RBD demonstrated some improvement with the use of donepezil [80].

Of note, there are several classes of medications that have been shown to induce or potentially exacerbate the symptoms of RBD and should be avoided if possible. These include tricyclic antidepressants, monoamine oxidase inhibitors, noradrenergic antagonists, and SSRIs [81].

8 Treatment of Autonomic Symptoms

As previously discussed, there are several associated features often encountered in patients with underlying Lewy body disease, including autonomic dysfunction, which may manifest as orthostatic hypotension, urinary issues, erectile dysfunction, and/or constipation. Dysautonomia occurs commonly in α-synucleinopathies, occurring in up to 60% of patients [82]. The distribution of Lewy body pathology is not strictly confined to the central nervous system, being found also in the peripheral sympathetic autonomic ganglia and the myenteric plexus of the gastrointestinal tract [83]. I-123 metaiodobenzylguanidine (MIBG) scans will demonstrate reduction of uptake in the peripheral sympathetic nervous system in both patients with DLB and PD regardless of whether they are experiencing symptoms of dysautonomia or not [84].

Orthostatic hypotension is defined as a reduction of 20 mmHg or more in systolic blood pressure and/or a reduction of 10 mmHg or more in diastolic blood pressure within 2–5 min of standing. In DLB, the orthostatic hypotension is often delayed, and may occur outside of the 5-min requirement [85]. Approximately 68% of patients with DLB experience orthostatic hypotension, and roughly 28% experience an episode of syncope [86, 87]. When orthostatic hypotension is verified in DLB, a thorough screening should be undertaken for possible medications that could be exacerbating the symptoms. These include diuretics, medications that induce vasodilation such as sildenafil, α-blockers, and tricyclic antidepressants. Levodopa and dopamine agonists may also worsen orthostatic hypotension. Non-pharmacological, supportive measures such as raising the head of the bed, increasing fluid and salt intake, and the use of support stockings or an abdominal binder should be initiated. If conservative measures fail, pharmacological agents such as fludrocortisone, midodrine, or droxidopa may be utilized. Fludrocortisone works to expand intravascular volume, while midodrine and droxidopa increase peripheral vascular resistance [88].

In addition to orthostatic hypotension, urinary issues are common in both PDD and DLB. In a Japanese study published in 2015 involving 32 patients with DLB, 91% had urinary symptoms [89]. Commonly encountered issues include urinary urgency, frequency, and incontinence. Antimuscarinic medications such as oxybutynin and trospium are generally avoided due to their potential for worsening cognitive deficits. In one case series involving 50 patients with PD using mirabegron (a β-3 adrenoceptor agonist) 50 mg daily, 50% reported improvement in their urinary symptoms, including 11.4% who had complete resolution [90].

Patients with α-synucleinopathies have widespread gastrointestinal disturbances at all levels. Dysphagia and drooling are common, occurring in 50–60% of patients with PD [91]. Patients with sialorrhea/drooling may benefit from multiple treatment options. Oral glycopyrrolate 1 mg twice daily has been shown to be beneficial. In a 4-week, randomized, double-blind, placebo-controlled crossover trial with oral glycopyrrolate in 23 patients with PD, the mean

sialorrhea score improved from 4.6 with the placebo to 3.8 with glycopyrrolate ($p = 0.011$) [92]. Additionally, botulinum toxic injections into the salivary glands have been shown to be beneficial in reducing sialorrhea in PD [93].

Along with the aforementioned dysphagia and drooling, previous studies have also shown that up to 90% of patients with PD may have constipation [94]. In patients with DLB, similar studies have shown a frequency of approximately 30% [95]. When patients with Lewy body disease experience constipation, aggravating medications such as opiates should be discontinued if possible. Although not formally studied in clinical trials, dietary modifications such as increasing fiber and ensuring adequate hydration are usually recommended. Oral bulking agents such as psyllium may be beneficial. A previous study published in 1997 showed the psyllium increased stool frequency in PD patients with constipation [96]. Finally, another study involving the osmotic laxative polyethylene glycol showed efficacy in increasing bowel movement frequency in a placebo-controlled study involving patients with PD [97]. According to the evidence-based medicine committee of the Movement Disorder Society, lubiprostone and macrogol are possibly useful in treating constipation in PD [57]. In a high quality randomized clinical trial of PD patients with constipation, consumption of fermented milk containing probiotics and prebiotic fiber was superior to placebo in increasing bowel movements [98]. Linaclotide (guanylate cyclase C agonist) and prucalopride (selective 5-HT4 receptor agonist) are both FDA approved for treatment of chronic idiopathic constipation. In a retrospective study of patients with neurodegenerative parkinsonism and constipation who failed to respond to initial treatment for constipation, linaclotide (145 or 290 μg/day) or prucalopride (1–4mg/day) significantly increased the number of bowel movements [99]. A higher proportion of patients reported subjective satisfaction in controlling their constipation symptoms with the use of linaclotide as compared with prucalopride [99].

9 Lewy Body Dementia Drug Pipeline in 2022

There is an insufficient number of medications approved for the treatment of LBD. Rivastigmine is the only prescription drug approved by the US FDA in 2000 to treat mild to moderate dementia in people with PD. Japanese regulators have approved donepezil and zonisamide for treating cognition-related and motor symptoms in DLB, respectively [37, 100]. The failed phase IIb clinical study of intepirdine in 2016 was the first multi-continental trial involving patients with DLB [101]. There is currently no disease-modifying treatment for LBD. There has been a significant increase in interest in conducting clinical trials for patients with LBD over the past decade.

The ClinicalTrials.gov site was examined in March 2022. Dementia with Lewy bodies was the disease specified, as was Lewy body disease and Lewy body dementia. The review includes only drug-related interventional trials. There were four types of recruitment status included: not yet recruiting, recruiting, enrolling by invitation, and active but not recruiting. Trials not included were completed, terminated, suspended, or withdrawn, or the subjects did not have dementia. In total, 10 drug trials were identified. The trials of all of the agents presented were listed as phase I ($N = 1$) or phase II ($N = 9$) in the database and there were multiple key topics entered: agent, condition, beginning date, projected end date, number of subjects planned to enroll, number of arms of the study, whether a biomarker was described, mechanism of action, primary outcome, sponsorship by biopharma companies or NIH or academic medical center, ClinicalTrials.gov identifier (NCT number), and phase of the study (Table 1). Another topic entered was the mechanism of action (MOA); all but one of the current trials were disease-modifying treatments (DMTs). DMTs were arranged by mechanisms of action. We also included one agent (irsenontrine, E2027) after discussion as the trial was recently completed, and therefore would not have fallen under our defined search criteria for 2022.

9.1 Tyrosine Kinase Inhibitors

Currently, three of the medications under investigation for DLB are tyrosine kinase inhibitors. These trials are being conducted on a single trial site.

9.1.1 Nilotinib

Nilotinib is approved for treating certain types of leukemia by the FDA. Studies were conducted to determine if this compound can break down abnormal α-synuclein proteins found in DLB or decrease phosphorylated tau levels in the brain as reported in animal models [102, 103].

Nilotinib appeared to promote the clearance of α-synuclein by autophagy in animal models [104]. Phase II trials in PD and PDD failed to demonstrate benefits. Georgetown University's first trial showed that the group that received 300 mg daily had a decline in activities of daily living from baseline to 12 months. A multicenter trial found no effect of the drug on dopamine biomarkers [105].

Another trial of nilotinib in AD failed to report any benefit, and participants taking 300 mg daily experienced significantly worse behavioral symptoms [106].

Previous phase II trials of nilotinib in PD, PDD, and AD did not show any benefit. Nilotinib is currently being tested

Table 1 Agents currently in clinical trials for Lewy body dementia

Agent name	Start date	Projected end date	No. of subjects planned	Biomarker described	Sponsor	Mechanism of action	Identifier	Primary outcome	Phase
Terazosin	1 Oct 2021	Oct 2022	40	Not specified	Qiang Zhang; University of Iowa	DMT: stimulates glycolysis and increases ATP	NCT04760860	Tolerability Brain [ATP] as measured by 31P- MR spectrometry	II
CT1812	Mar 2022	Apr 2024	120	Plasma and CSF	Cognition Therapeutics	DMT: inhibits α-synuclein oligomer- and Aβ oligomer-induced toxicity and regulates autophagy	NCT05225415	Safety and tolerability	II
K0706	Sep 2019	Jun 2023	45	Plasma and CSF: HVA, DOPAC, Aβ40/42, t-tau, p-tau231/181, α-synuclein	Georgetown; Sun Pharma Advanced Research Company	DMT: induces autophagy	NCT03996460	Safety and tolerability	II
Nilotinib	Jan 2020	Jun 2024	60	CSF and plasma	Georgetown; NIH	DMT: induces autophagy and clears α-synuclein	NCT04002674	Safety and tolerability	II
Bosutinib	Apr 2019	Aug 2021	30	Plasma	Georgetown; Alzheimer's Association	DMT: clears α-synuclein, tau and β-amyloid	NCT03888222	Safety and tolerability	II
ATH-1017	20 Jan 2022	Oct 2023	75	Not specified	Athira Pharma	DMT: activates HGF and synaptic activity	NCT04831281	Composite GST	II
Ambroxol	Sep 2020	Sep 2023	15	CSF and plasma biomarkers: α-synuclein tau, p-tau, Aβ-42	Lawson Health Research Institute	DMT: raises glucocerebrosidase levels	NCT04405596	Change in MMSE safety and tolerability	I/II
Ambroxol	4 May 2021	1 Apr 2022	172	Blood and CSF biomarkers: α-synuclein MRI EEG ECG DaTSCAN	Helse Fonna, Klinbeforsk, Helse-Bergen HF	DMT: raises glucocerebrosidase levels	NCT04588285	Safety and tolerability ECG changes MMSE-NR3 ADCS-CGIC CDR-SB NPI GDS	II
NYX-458	14 Nov 2019	Dec 2022	100	Not specified	Aptinyx; CogState Ltd; Worldwide Clinical Trials	Symptomatic: modulates NMDA receptor	NCT04148391	Change from baseline in physical examination rates of AEs Early termination due to AE NPI-12 S-STS MDS-UPDRS	II

Table 1 (continued)

Agent name	Start date	Projected end date	No. of subjects planned	Biomarker described	Sponsor	Mechanism of action	Identifier	Primary outcome	Phase
CST-103	28 Jun 2021	Mar 2022	40	EEG	CuraSen Therapeutics	DMT: improves cerebral blood flow	NCT04739423	FERT EEG Activity tracking Pupil measurements DCFS	II

Nine agents in ten clinical trials currently ongoing according to ClinicalTrials.gov, assessed on March 31, 2022

ADCS-CGIC Clinician's Global Impression of Change, *AE* adverse event, *CDR-SB* Clinical Dementia Rating–Sum of Boxes, *CSF* cerebrospinal fluid, *DCFS* Dementia Cognitive Fluctuation Scale, *DMT* disease-modifying treatment, *ECG* electrocardiogram, *EEG* electroencephalogram, *FERT* Facial Expression Recognition Task, *GDS* Geriatric Depression Scale, *GST* Global Statistical Test, *MDS-UPDRS* Movement Disorder Society Unified Parkinson's Disease Rating Scale, *MMSE-NR3* Mini Mental Status Examination, Norwegian revised version, *NMDA* N-methyl D-aspartate, *NPI-12* Neuropsychiatric Inventory, *S-STS* Sheehan Suicidality Tracking Scale

in a phase II trial at Georgetown University in patients with DLB (NCT04002674).

9.1.2 Bosutinib

Bosutinib is an oral inhibitor of Abl and Src tyrosine kinases approved by the FDA for the treatment of chronic myeloid leukemia. Bosutinib reduced levels of α-synuclein in mouse models expressing human synucleinopathy.

Bosutinib enhanced dopaminergic neuron survival, modulated the immune response to α-synuclein, and helped with α-amyloid and tau clearance and cognitive improvement [103, 107].

One open-label study of bosutinib in patients with AD or PD found that after 1 year of treatment, bosutinib resulted in less decline in both Clinical Dementia Rating (CDR) scores and Repeatable Battery Assessment of Neuropsychological Status (RBANS) performance than predicted population-based decline [108].

A single-site, phase II study is underway to assess safety tolerability, biomarkers, and clinical outcomes of bosutinib in DLB (NCT03888222).

9.1.3 K0706

K0706 is under development for treatment of chronic myeloid leukemia (CML) and Philadelphia positive acute lymphoblastic leukemia that is resistant or intolerant to prior tyrosine kinase inhibitor therapy. Tyrosine kinase inhibitors induce autophagy, which degrades neurotoxic proteins such as α-synuclein, β-amyloid, and tau in PD and AD models. The current study will serve as a proof of concept for future trials in DLB and PD (NCT03996460).

9.2 Irsenontrine (E2027)

E2027 is a highly selective and potent inhibitor of phosphodiesterase 9 (PDE9) [109]. PDE9 breaks down cyclic guanosine monophosphate (cGMP), which serves as a second messenger in synaptic function and cognitive function. PDE9 inhibition by E2027 increases cGMP levels which may protect against α-synuclein toxicity in DLB [109, 110]. In 2018, a phase II/III trial enrolled 206 participants with DLB for 12 weeks of treatment with E2027 50 mg daily, or placebo. The results have not been published yet. The sponsor has followed with an open-label trial of E2027 in four groups of participants with DLB or PDD with or without amyloid co-pathology. The results are expected to be released in 2022.

9.3 Terazosin

Terazosin is an α-blocker, approved for management of benign prostate hypertrophy symptoms by relaxing the muscles of the bladder and prostate. It is proposed that terazosin also enhances the activity of phosphoglycerate kinase 1 (PGK1), stimulating glycolysis and increases cellular brain ATP levels and slowed neuron loss in mouse and rat models of PD. Dopamine level was also increased with partial restoration of mobility [111].

A cohort database study from Denmark and the United States showed that men taking terazosin were between 12% and 37% less likely to develop PD during the follow-up period than men taking tamsulosin, another α_1-adrenergic receptor antagonist which does not activate phosphoglycerate kinase [112].

Lack of ATP production is a common feature of Parkinson's and other neurodegenerative conditions. The above studies are encouraging, and suggest that terazosin can be a good candidate to repurpose in clinical trials across the PD spectrum. The current randomized clinical trial in DLB explores tolerability and changes in cognition, mobility, and behavior. The secondary outcome also explore changes in fluorodeoxyglucose (FDG)-PET, a surrogate for glucose metabolism, serum ATP, and terazosin level (NCT04760860).

A carrier for a pathological mutation in β-glucocerebrosidase gene (*GBA1*) has a strong genetic risk factors for PD, PDD, and LBD [113]. Animal models have shown that raising the levels of glucocerebrosidase can decrease levels of α-synuclein. Ambroxol is able to raise the levels glucocerebrosidase and is proposed as a disease-modifying treatment for PDD [114]. A phase II, single-center, double-blind, randomized placebo-controlled trial involving 75 individuals with mild to moderate PDD was designed (NCT02914366). Primary outcome measures were the Alzheimer's Disease Assessment Scale—cognitive subscale (ADAS-Cog) and the ADCS-CGIC. Secondary measures included different cognitive and mobility scales. Markers of neurodegeneration will include MRI and CSF measures [114]. The results are not published yet. The current phase II trial investigates the effects of ambroxol on cognition, functional decline, and on neuropsychiatric symptoms of the glucocerebrosidase-enhancing chaperone ambroxol in 172 participants diagnosed with prodromal and early DLB (NCT04588285). Another clinical trial is underway for 15 participants with LBD (NCT04405596). The participants will be randomized to placebo or ambroxol 450 mg/day with titration to a maximum of 1350 mg/day.

9.4 CT1812

CT1812 is a small molecule receptor antagonist designed to inhibit synaptic binding and signaling by soluble Aβ oligomers [115]. CT1812 does not appear to interact directly with β-amyloid protein. Instead, CT1812 binds to the σ-2 receptor complex, which is a key oligomer binding site regulator, displacing Aβ oligomers from their receptor targets at the synapses in preclinical AD models, which facilitates oligomer clearance into the CSF [116]. A small study in patients with mild AD showed the CT1812-treated group had significantly lower levels of neurogranin, a marker of synaptic damage [116].

A randomized clinical trial (NCT05225415) is underway for DLB patients at doses of 300 and 100 mg over a 24-week period based on the hypothesis that σ-2 receptors regulate autophagy, which is impaired in synucleinopathy [117]. Additionally, DLB patients often have both amyloid pathology and synucleinopathy in the brain. It has been hypothesized that σ-2 receptor modulators may inhibit α-synuclein oligomer and Aβ oligomer-induced toxicity to neurons, thereby restoring normal neuronal function.

9.5 NYX-458

NYX-458 is an NMDA receptor modulator. In primate models of PD, NYX-458 improved attention, working memory, and executive function rapidly and continuously [118].

The current trial is being conducted on subjects with MCI or mild dementia associated with PD or DLB (NCT04148391).

9.6 CST-103 (Clenbuterol)

Clenbuterol (CST-103) is a β2-agonist that was reported to increase cerebral blood flow in patients with MCI or PD [119].

The reduction of noradrenergic signaling from neurons in the locus coeruleus may result in reduced activity of neurons in the prefrontal cortex, thalamus, hippocampus, and amygdala. In neurodegenerative disorders, activation of excitatory receptors of the ascending noradrenergic system by β2-adrenergic receptors could serve as an attractive therapeutic target. Long-term exposure to β2-agonists may cause undesirable peripheral effects, such as tachycardia, hyperglycemia, and hypokalemia. To counter the adverse effects of chronic therapy on cardiovascular and metabolic systems, co-administration of a peripherally restricted β-blocker, nadolol, was studied [120].

A small study with seven patients with MCI and one with PD was conducted. The patients received a first dose of

clenbuterol 80 g at the beginning of the study and a second dose following a 7-day washout. In the second visit, half of the patients were pre-treated with nadolol 1 mg 2.5 h before receiving clenbuterol. Following clenbuterol administration, the hippocampus, the thalamus, and the amygdala showed significant increases in cerebral blood flow. Nadolol administered before clenbuterol did not alter the central effect of clenbuterol on cerebral blood flow [120].

The current trial is a two-period, two-way crossover trial to evaluate clenbuterol in four subject populations of PD patients with RBD and depression, MCI with depression, DLB with cognitive fluctuations, and PDD with cognitive fluctuations. Clenbuterol will be co-administered with nadolol for a 14-day period (NCT04739423) [121].

9.7 ATH-1017 (Fosgonimeton)

Fosgonimeton (ATH-1017, formerly known as NDX-1017), is a small molecule designed to affect neurodegeneration by activating hepatocyte growth factor (HGF) signaling and its tyrosine kinase receptor, MET. Activation of the HGF/MET system promotes survival and regeneration [122].

A phase I (NCT03298672) safety study of single subcutaneous daily injections of fosgonimeton in healthy people and AD patients raised no safety issues, with dose-proportional pharmacokinetics in all groups [123]. Quantitative electroencephalography (qEEG) and event-related potential (ERP) measured neurophysiological signals as indicative of brain penetration and target engagement. People with AD have prolonged P300 latency. P300 refers to the spike in activity following the presentation of a stimulus as measured during EEG. In the trial, fosgonimeton improved p300 latency in the AD group. The fast-onset normalization of ERP P300 latency in AD subjects was hypothesized to enhance synaptic function and potential cognitive effects [123]. In addition to two ongoing phase II trials for participants with mild to moderate AD, a current trial intends to enroll 75 patients with LBD to receive fosgonimeton or placebo over the course of 26 weeks (NCT04831281).

10 Conclusions

DLB and PDD are complex disorders with heterogeneous and often overlapping clinical and pathological findings. The treatment of these disorders is primarily symptomatic, as disease-modifying therapies do not currently exist. There is some evidence to support the benefit of cholinesterase inhibitors for treating cognitive and neuropsychiatric symptoms in LBD. Additionally, rivastigmine is FDA-approved for use in PDD. The benefits of memantine for treating the cognitive symptoms of LBD are not as well established and further studies are required. The motor symptoms of DLB are often less responsive to levodopa when compared with patients with PD. More recently, a phase III clinical trial demonstrated the benefit of zonisamide in improving the motor symptoms of DLB. In patients with significant neuropsychiatric symptoms, typical antipsychotics should be avoided. There is some data to suggest possible efficacy of atypical antipsychotics, quetiapine, clozapine, and olanzapine. For PD psychosis, pimavanserin has been shown to be beneficial, though its efficacy in DLB patients has not been fully established. Both melatonin and clonazepam are effective in decreasing the frequency and severity of RBD. Symptoms of dysautonomia are common in DLB and PDD, and include orthostatic hypotension, constipation, and urinary symptoms. Medications such as fludrocortisone, midodrine, or droxidopa may be utilized for orthostatic hypotension if conservative measures are insufficient. For urinary issues, mirabegron may be beneficial in decreasing symptoms. And finally, psyllium and polyethylene glycol, lubiprostone, linaclotide, or prucalopride have demonstrated efficacy when constipation is present.

LBD drug development has improved noticeably over the past few years. Neflamapimod may be the first new drug to advance toward a phase III trial for LBD in the near future. With nine agents currently in clinical trials looking to find a disease-modifying treatment, the landscape of LBD drug development is moving more towards disease-modifying therapies. Given the heterogeneous nature of Lewy body dementia, new biomarker strategies and better definition of outcome measures are necessary to improve drug trial designs.

Declarations

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