Dementia with Lewy bodies: Emerging drug targets and therapeutics

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Abstract

Introduction—Dementia with Lewy bodies (DLB) is characterized by the toxic accumulation of α-synuclein protein inside neural cells; this results in neurodegeneration which is clinically accompanied by behavioral and psychological changes. DLB shares features with Parkinson's disease (PD) and Parkinson's disease dementia (PDD), but also overlaps neurochemically and pathologically with Alzheimer's disease. Symptomatic treatments for LBD differ in their effectiveness while disease-modifying and curative approaches are much needed.

Areas covered: We explore emerging therapeutics for DLB through the lens of repurposing approved drugs and survey their potential for disease modifying actions in DLB. Given the complexity of DLB with multiple pathologies, potential therapeutic targets that could affect Lewy body pathology, or metabolism or neurotransmitters or immunomodulation were surveyed. We queried PubMed and ClinicalTrials.gov searches 2017 – 2020.

Expert opinion: DLB is not simply a redux of AD or PD; hence, treatments should not be exclusively duplicative of AD or PD directed treatments. This opens a myriad of possibilities of therapeutic approaches that are disease specific or repurposed.

Keywords

Clinical trials; dementia with Lewy bodies; drug repurposing; drug development; Lewy body dementia; Parkinson's disease; dementia; synucleinopathy; drug targets

1. Introduction

Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), are neurological diseases that share in common α-synuclein (α-syn) pathology that accumulates

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into Lewy Body pathology, characterized by the toxic accumulation of α-syn protein inside neural cells. Accumulation in α-syn seen in synucleinopathies include Parkinson's disease (PD), DLB and multiple system atrophy (MSA). α-syn contributes to the fibrilization of β-amyloid and tau, two pathological hallmarks of AD [1,2]. Patients with DLB have more neuropsychiatric symptoms such as dementia related psychosis (hallucinations and delusions [3]. A 2020 study by Smirnov et al. demonstrated that both DLB and PDD patients experienced more severe impairment and a more rapid decline in visuospatial function than AD patients. Patients with PDD demonstrated higher impairment and a more rapid decline in executive functions than patients with DLB or AD. Patients with DLB also demonstrated a more rapid clinical decline than patients with AD, who, in reverse, demonstrated higher memory impairment than patients with DLB. Importantly, the rate of decline was similar for all three groups [4]. DLB patients had more fluctuations, hallucinations, and excessive daytime sleepiness [5].

2. Methods

The agents/compounds (or classes, as where two drugs have similar modes of action we group them together) that were clearly prioritized by the group for putative disease modifying actions were: monoclonal antibodies against α-synuclein, ambroxol, metformin, nilotinib/ bosutinib, rasagiline, salbutamol, liraglutide/exenatide, candesartan/telmisartan, etanercept, fasudil, and immunomodulators (Table 1.). Our basis for selection of evidence to present were PubMed and ClinicalTrials.gov searches 2017 – 2020 (Table 1.). For relevant clinical trials that include drugs of interest to our group, we used the search term "Dementia with Lewy bodies" on ClinicalTrials.gov. Status search field selections included "Completed", "Recruiting" and "Active, not recruiting". All other advanced search fields, such as study type, phase, and funder type were left blank. The balance between animal versus clinical studies was determined by availability of clinical data supporting animal studies.

3. Monoclonal Antibodies Against α-synuclein

Intuitively, the overlap between symptoms marking PDD and DLB can complicate the early clinical diagnosis essential to a more positive clinical outcome. However, Lewy bodies in PD can be identified by their association with the majority of phosphorylated α-syn accumulated specifically at serine 129 (pS129-α-syn) [6]. Thus, targeting α-syn may offer promise for the development of therapeutics to ameliorate the neuropathological symptoms of these diseases. In recent years, monoclonal antibodies against α-syn have been developed as a preferable, front-line defense against α-syn and as novel, reliable tools for research, diagnostics, and clinical treatment of dementias related to neuropathology [7]. These antibodies have thus far proven to be safe and effective therapeutic interventions for impeding α-syn aggregation and reducing the cytotoxic effects of α-syn, and further development of antibodies targeting α-syn remains an ongoing endeavor. A recent randomized phase I clinical trial (2019) by Brys et al. (NCT02459886) interrogated the safety and efficacy of BIIB054, a human-derived monoclonal antibody that targets and binds to α-syn. Both normal control subjects and participants with PPD demonstrated a high tolerability and minimal side effects when given BIIB054. Based on the results of this study,

further investigation is warranted to verify the potential of this particular antibody as a powerful biomarker and safe, effective therapeutic [8].

4. Antihyperglycemic Medications

4.1 Metformin

Metformin has been untethered from its original purpose of treating type 2 diabetes mellitus and deployed as a potential therapeutic agent against neurodegeneration. Farr et al. showed that metformin reduces AD pathology in senescence accelerated (SAMP8) mouse models by decreasing accumulation of the neurotoxic proteins APPc99 and pTau, both of which have been implicated as significant risk factors for AD [9]. The group also noted that metformin has the ability to improve learning and memory in mice. Wang et al. theorized that the mechanism by which metformin acts is through inhibition of cyclin-dependent kinase 5 (Cdk5), an enzyme which, when activated, can lead to synaptic depression and mimic AD pathology [10]. Diabetes has a deleterious effect on the hippocampus, thereby leading to the cessation of cytogenesis within the brain [11]. Metformin may stimulate neural cell growth, thus enabling the preservation of memory function and the mitigation of cellular damage to neurons [11]. These benefits can also be seen in patients with PD, by allowing astrocytes to alter the expression of genes related to neurodegeneration [12].

4.2 GLP-1 agonists

Liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist used for the management of type 2 diabetes mellitus, has shown neuroprotective benefits in APP/PS1 mice, a transgenic mouse model of AD [13]. Seven-month-old APP/PS1 mice administered liraglutide showed improved performance object recognition and maze navigation tasks, while mice in the normal control group showed no improvements, suggesting that liraglutide is effective only when given to subjects with these genetic risk factors. APP/PS1 mice also showed higher degrees of neural plasticity, but these effects were seen in mice in the at-risk group. Duarte et al. recently (2020) studied the benefits of peripheral liraglutide treatment in AD female mice by administering 0.2 mg/kg, once daily for 28 days [14]. The following parameters affected in AD were evaluated: Aβ and p-tau, motor and cognitive function, glucose metabolism, inflammation and oxidative/nitrosative stress. Ultimately, liraglutide only reduced cortical $A\beta_{1-42}$ levels in the mice. Further research appears necessary to discern the role of genetics in the etiology of synucleinopathies.

Exenatide, a synthetic, long-lasting GLP-1 analogue, is another antihyperglycemic medication under investigation for treatment in neurodegenerative diseases. In a mouse model of amyloid-independent neuronal dysfunction, exenatide promoted improvement in short- and long-term memory performances [15]. Similarly, An et al. demonstrated that exenatide prevented cognitive decline, alleviated $A\beta_{1-42}$ deposition and hippocampal synapse damage, and improved mitochondrial morphology after 16 weeks of subcutaneous injections in a transgenic mouse model of AD [16]. A randomized, placebo-controlled clinical trial in patients with moderate stage PD evaluated effects of exenatide on PD disease progression [17]. Patients were given 2mg orally once weekly over 60 weeks. Notably, positive effects on motor severity of PD remained 12 weeks following the last exenatide

exposure. These results, coupled with the paucity of research applied specifically to DLB, support the need for further investigation of exenatide as a viable therapeutic in the DLB population.

5. Angiotensin Receptor Blockers

The angiotensin receptor blocker candesartan also appears to improve cognition. In a study by Trigiani et al., transgenic mouse models of AD administered candesartan showed reduced neuroinflammation, but no change in cerebral blood flow [18]. These findings suggest that candesartan may be most effective for AD, PDD, and DLB patients with hypertension, but of little benefit to patients with normal blood pressure. Preclinical evidence for potential benefits includes protection against cognitive decline partly due to peroxisome proliferator-activated receptor gamma activation. Moreover, candesartan has demonstrated anti-inflammatory properties [19], which may offer protection against neurodegeneration and potentially slow disease progression.

6. Monoamine Oxidase Inhibitors

The monoamine oxidase inhibitor, rasagaline, has been used to treat depression, and its benefits to cognitive functioning may be applicable to DLB, PDD, and AD. Rasagaline may delay the onset and decrease symptoms such as tremors and muscular rigidity of PD. A 2018 Japanese study demonstrated that rasagaline 1mg per day was well tolerated by study subjects with PD, and treatment-emergent adverse effects (TEAE) ranged 52.4–62.4% for both normal controls and PD subjects [20]. Preclinical evidence in treatment of PD showed that rasagaline causes an increase in extracellular levels of dopamine in brain striatum, effectively easing the most severe symptoms typically experienced by patients with PD. The inhibition of monoamine oxidase by rasagaline appeared to contribute to decreased dopamine reuptake and neuroprotective benefits the drug has demonstrated in clinical trials [21].

7. Tyrosine Kinase Inhibitors

Nilotinib is a chemotherapeutic agent typically used to treat leukemia. This tyrosine kinase inhibitor may prove to be efficacious in the treatment of DLB, PDD, and AD. A small proof of concept study by Pagan et al. found that nilotinib can dramatically alter the course of PD in humans, with little to no harmful adverse events [22]. Nilotinib disintegrates α-syn and hyper-phosphorylated Tau (p-Tau) in PD mouse models, ameliorating the neurodegenerative effects induced by these harmful proteins on the brain and cognitive functioning [23]. Preclinical evidence for potential benefits include autophagic clearance of neurotoxic proteins (α-synuclein, tau, amyloid-β) and protective effects on neural cells. Nilotinib doses between 150–300 mg have been shown to be safe and tolerable when tested by both normal controls and PD subjects in clinical studies for PD [24]. Nilotinib targets kinases involved in the hyperphosphorylization of tau in order to clear them from neurons [25]. In addition, nilotinib has demonstrated the ability to reduce neuroinflammation accompanying neurodegenerative disease. Working in concert with bosutinib, another tyrosine kinase inhibitor, pre-plaques associated with AD, DLB, and PDD were cleared from neurons

in transgenic mice, thereby delaying the onset of these neurodegenerative diseases and ameliorating their damage to neurons [26].

8. Immunomodulators

Lenalidomide, a pleitropic immunomodulator, is used to treat relapsed and refractory multiple myeloma. One of its principal mechanisms of action is destabilization of TNFα mRNA and inhibition of IL-1, IL-6, and IL-12 production from human peripheral blood mononuclear cells [27]. A 2015 study by Valera et al. demonstrated the ability of lenalidomide to reduce motor behavioral deficits, reduced microglial activation, and ameliorated dopaminergic fiber loss in the striatum of a transgenic mouse model of PD [28]. Expanding on their previous conclusions, Valera et al. more recently showed that combining lenalidomide with an α-syn-reducing immunotherapy, CD5-D5, reduced astrogliosis, microgliosis, and α-syn accumulation in the brain of a transgenic mouse model of MSA [29]. Building on data gathered from such findings, our group has initiated a phase II, proof of mechanism, clinical study to investigate the safety, tolerability, and efficacy of lenalidomide on cognition in individuals with amnesic mild cognitive impairment due to AD [30]. We hypothesize that modulating inflammation via lenalinomide may alter the progression of AD. Further preclinical research along with results from our clinical trial will contribute imperative information regarding the effectiveness of lenalidomide as a potential therapeutic for synucleinopathies. Notwithstanding, studies specific to DLB are critical in evaluating lenalidomide and other immunomodulators as definitive disease modifying therapies for this population.

9. Other Targets

Etanercept is an anti-TNFα drug used for treating autoimmune disorders also demonstrated potential anti-neuroinflammatory properties. Gocmez et al. investigated cognitive and endothelial function in male Wistar albino rats divided into three groups: young, aged, and aged that received subcutaneous etanercept at 0.8 mg/kg weekly for 8 weeks [31]. All groups performed identical cognitive tasks, and upon completion of these tasks, blood pressure of each rat was measured. Aged rats not administered etanercept showed a decline in cognition, while aged rats that received etanercept showed lowered blood pressure and increased cognitive performance. Findings from this study indicate that in elderly human patients with cognitive decline, etanercept could offer protection against neuroinflammation and vascular damage A randomized, placebo-controlled, double-blind, phase 2 trial studying subjects with mild to moderate AD showed that subcutaneous etanercept given once weekly at 50 mg was well tolerated [32]. However, studies encompassing a broader population are necessary for more accurately determining the safety and efficacy of etanercept on the DLB population exclusively. Preclinical evidence for the potential benefits of the drug include its potential to act on dysregulation of TNFα expression that contributes to inflammation and dementia [32].

The bronchodilator salbutamol is a beta2-agonist that also has shown promise as an effective therapeutic against PDD, DLB, and AD. Salbutamol acts by inhibiting uptake of testosterone, a hormone which can adversely affect hippocampal function and emotional

memory. In animal models of memory disorders, memory function has shown marked improvement following exposure to beta-blocking drugs [33]. Targeting adrenergic pathways may be a key to preserving memory function in patients suffering neurodegenerative diseases. However, further investigation is required to determine the precise mechanisms underpinning the ability of salbutamol and other beta-adrenoceptors to decrease neuronal death and Aβ accumulation. Although hormone-blocking agents can offer benefits for brain health, it must also be noted that users of β2-agonists such as propranolol and salbutamol also face an elevated risk of PD [34]. Preclinical evidence for potential benefits are the presence of the compound epinephrine, which effectively stabilizes harmful proteins and prevents them from forming into tangles and plaques indicative of neurodegeneration [34].

Ambroxol (Ax) has been used since 1979 as a method for clearing excess mucus from the lungs, and, in recent years, the mechanism of action has been examined as a means by which α-syn may be cleared from neural cells [35]. This potential therapeutic may improve function of glucocerebrosidase in neurons, which helps reduce the accumulation of α-syn. A 2015 study by Fois et al. found that Ax accumulates in lamellar bodies and acts similarly to a bond-breaking solvent [35]. The group concluded that Ax may dissolve the bond between α-syn and neural cells, clearing α-syn as safely and effectively as it clears excess phlegm from alveoli. A recent single-center open-label non-controlled clinical trial by Mullin et al. found that Ax therapy may modify PD pathogenesis by increasing β-glucocerebrosidase (GCase) enzyme activity and reducing α-syn levels [36]. Although mutations of the glucocerebrosidase gene, GBA1 (OMIM 606463), are the dominant risk factor for PD, Ax may significantly reduce the genetic risk factor intrinsic to PD. Magalhaes et al. point out that mutations to GBA1 may be responsible for the overexpression of α-syn found in patients with PD, and Ax can reverse the effects of GBA1 by increasing the activity of the lysosomal enzyme cathepsin D, thereby facilitating the clearance of α-syn [37]. Although this genetic mutation is a relevant risk factor, Ax can decrease this risk by dislodging α-syn from neural cells.

Fasudil, a Rho-kinase inhibitor and vasodilator, may block feedback loops in which beta-amyloid drives its own production, thus impeding the accumulation of tau and other neurologically destructive amyloids. Yu et al. studied the effects of fasudil on transgenic AD mice and found a reduction in Aβ deposition and tau protein phosphorylation in the brains of APP/PS1 mice, thereby suggesting protective effects on subjects with an elevated genetic risk of neurodegenerative dementia [38]. A study by Gao et al. supported these findings by demonstrating the ability of fasudil to increase neurite outgrowth by 52.84%, decrease Aβ burden by 46.65%, and decrease tau phosphorylation by 96.84% [39].

Elliott et al showed that fasudil can balance two neural pathways for the canonical Wnt inhibitor Dickkopf-1 (Dkk1) and non-canonical Wnt signaling [40]. Canonical (Wnt-β-catenin) signaling stabilizes synapses, and non-canonical (Wnt-PCP) signaling retracts synapses. Activation of non-canonical Wnt signaling enhances Aβ production, while activation of canonical signaling suppresses Aβ production. Aβ triggers Dkk1 expression, which triggers the activation of non-canonical Wnt signaling to stimulate further Aβ production. According to this group, fasudil breaks this feedback loop, thus reducing the expression of Aβ in mice with advanced amyloid pathology [40].

In these studies, fasudil performed strongly as a promising new therapeutic for neurodegenerative diseases. However, the extent to which fasudil can ameliorate symptoms or delay the onset of disease remains in further need of examination.

10. Conclusion

DLB is the second most common neurodegenerative disease that has a faster rate of decline than AD and remains undertreated [41]. It remains an area of unmet need in neurological diseases. Why is the rate of decline faster? This is unclear, but it could be the result of multiple pathologies, the presence of neuropsychiatric symptoms or the worse neurotransmitter deficit. Repurposing drugs originally designed for treating a broad spectrum of diseases and disorders to specifically target the underlying pathology driving DLB development and progressions a growing and exciting avenue of exploration. Applying a wide range of currently available therapeutics to neurodegenerative diseases holds the potential promise of finally localizing their underlying root causes and perhaps significantly altering disease progression. However, robust data must be obtained to ensure that we are, in fact, applying the safest and most effective alternatives if we are to achieve this long-desired goal. The drugs discussed above, however, remain in need of further, intensive preclinical and clinical investigation to assess their suitability as therapeutics for these diseases. Accurate diagnose of patients is paramount in ensuring the most optimal clinical treatment possible. To that end, research into these specific therapeutic possibilities must continue advancing so that all of the benefits and drawbacks to patients, and to their caregivers, can be fully understood in their proper context and to provide accurate information to patients and caregivers so that they may engage with the treatment plan which offers the highest probability of providing to them the highest quality of care possible.

11. Expert Opinion

DLB is categorized as a synucleinopathy as well as a tauopathy and amyloidopathy. Belonging to these three separate neurodegenerative disease categories make DLB identification more complicated from a pathological standpoint, yet alsopresents potential novel treatment targets. In addition to targeting a-synuclein with mABs, there are opportunities to target inflammation via GLP1, immunomodulation, tyrosine kinase and other targets. Additionally, the traditional targets that overlap with AD including neurotransmitter loss and amyloid could have added value in DLB.

Recent studies have been undertaken to investigate possible linkages between the pathologies of diabetes mellitus and neurodegenerative diseases. Findings from these studies could benefit the DLB community by uncovering the neuroprotective mechanisms in FDA approved antihyperglycemic therapeutic agents such as metformin, liraglutide, and exenatide. Identifying mechanisms by which alterations in glucose metabolism affects cognition and behavior in the DLB population may result in more potential therapeutic targets. Furthermore, establishing dosing requirements of antihyperglycemics in patients with DLB will make way for more advancements in treatment regimens.

As more anticancer drugs are identified with anti-inflammatory and neuroprotective effects, more potential therapeutics against neurodegenerative diseases will be identified for repurposing. The potential of tyrosine kinase inhibitors such as nilotinib and bosutinib to prevent or significantly reduce hyperphosporylation of the neurophysiological signatures (tau, α-syn, and Aβ) of neurodegenerative diseases shows promise in effectively preventing or treating DLB. Lenalidomide and other immunomodulators offer opportunities to repurpose drugs proven to alter either the innate or adaptive immune response. With the MCLENA-1 phase II trial, our group aims to determine whether lenalidomide is safe in AD subjects and whether it can alter the clinical progression of AD when administered before dementia onset. Additionally, we hope to determine if lenalidomide improves behavioral and cognitive deficits in AD. Future studies by our group will apply knowledge acquired from AD trials involving lenalidomide and other immunomodulators to DLB.

Challenges faced by the DLB researchers and clinicians include the unique symptomatic manifestation in DLB which leads to under-diagnosis or misdiagnosis of patients, a lack of biomarker and genetic markers, and the traditional symptomatic treatment focus in DLB-specific clinical trials. Clinical trials in DLB have unique challenges. First, since the symptoms are cognitive and motoric and neuropsychiatric, which should be the primary outcome measure? Second, can outcome measures from AD trials such as ADAS, CDR CGIC, etc or UPDRS from movement disorder trials be used in a clinically meaningful manner to determine efficacy or do new instruments that are DLB-centric need to be created and validated? Third, what is the appropriate period of time for a DLB related clinical trial? The typical symptomatic RCT in AD is 6 months. Might a DLB study be shorter (16 weeks)? Fourth, DLB patients have significant fluctuations clinically. How does one capture severity of clinical fluctuations? How is that factored as a covariate? What measures can be in place to ensure that the clinical observation of efficacy is not a measure of fluctuations? What relationships between these fluctuations and other observable symptoms might exist that could constitute reliable biomarkers for future study and the development of safe and effective therapeutics to help pinpoint and aleviate or delay these symptoms?

The paucity in translational studies has created a substantial gap in knowledge that should be addressed with haste. Continued collaboration between basic scientists and clinicians will lead to improved diagnostic biomarker development and increased identification of potential drugs for repurposing, which will in turn lead to monumental breakthroughs in the clinic. Rapid and accurate diagnosis is imperative to ensuring the selection of an appropriate disease management plan. Many potential therapeutic agents have been tested in AD, PD, or PDD, but not in DLB. The likely strategy for DLB, similar to AD will be a multi-modal, multi-targeted approach. Confounding treatment is the variability of DLB which makes interpretation of drug effects difficult. Future trial design for DLB will likely not duplicate AD outcomes such that objective measures of efficacy might be better able to determine clinical efficacy. Pragmatic randomized controlled trials enrolling large numbers of patients with DLB will streamline the approval process for repurposed and newly developed drugs targeting DLB in the near future.

Acknowledgements

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Article Highlights

- Drugs developed for purposes excluding treatment of neurodegenerative diseases have demonstrated the potential to serve as disease modifying treatments for DLB and PDD

- Several drugs, compounds, and drug classes have demonstrated efficacy, safety, and tolerability in neurodegenerative diseases: monoclonal antibodies against α-synuclein, ambroxol, metformin, nilotinib/ bosutinib, rasagiline, salbutamol, liraglutide, exenatide, candesartan/telmisartan, etanercept, fasudil, and immunomodulators

- Although these drugs have thus far demonstrated the potential as effective therapeutics, their clinical benefits and side effects in the DLB population require further inquiry

- Genetic risk factors can be ameliorated by these drugs, though further research is necessary to fully understand their mechanisms of action in neurodegenerative diseases

- Monoclonal antibodies against α-synuclein have been proven safe and effective and may delay or impede the development of DLB and PD

Table 1.

Selected FDA approved agents with potential for repurposing for disease modifying action in DLB

Agent	Mechanism of action	Clinical trials for DLB
Ambroxol	Mucolytic agent; inhibits the NO-dependent activation of soluble guanylate cyclase	None
Metformin	Indirectly activates AMPK through inhibition of the mitochondrial respiration chain complex 1	None
Nilotinib	Tyrosine kinase inhibitor	ClinicalTrials.gov Identifier: NCT04002674
Bosutinib	Tyrosine kinase inhibitor	ClinicalTrials.gov Identifier: NCT03888222
Rasagiline	Monoamine oxidase inhibitor	None
Salbutamol	Beta2-agonist	None
Liraglutide	Glucagon-like peptide-1 (GLP-1) receptor agonist	None
Exenatide	Glucacon-like peptide-1(GLP-1) receptor agonist	None
Candesartan	Angiotensin II receptor antagonist	None
Telmisartan	Angiotensin II receptor antagonist	None
Etanercept	Biologic tumor necrosis factor (TNF) inhibitor	None
Fasudil	Rho-kinase inhibitor	None
Lenalidomide	Cyclooxygenase-2 (COX-2) inhibitor	None