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Novel Genetic Therapeutic Strategies for Lewy Body Dementia

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Abstract

Lewy Body Dementia (LBD) is a neurodegenerative disorder in which the brain has abundant misfolded alpha-synuclein proteins. While LBD has similar symptoms to other degenerative neurological disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD), they are not the same medical diagnosis. LBD is characterized by all the motor deficit symptoms of Parkinson's disease (PD), but the opposite cannot be said, as PD is more complex and has more underlying symptoms. Clinical trials and in vivo experiments have shown that specific genes related to these misfolded proteins are potentially good genetic treatment and therapeutic targets. This review article seeks to provide an overview of the current state of novel therapeutic, genetic strategies to reduce the effects of Lewy Body Dementia.

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1. Introduction

There are three main goals we would like to achieve with this review paper. The first is to lay out a list of possible and current treatments available for Lewy Body Dementia (LBD) to reduce its effects. Next, we aim to understand how LBD can affect other conditions, such as Parkinson's Disease (PD) and Alzheimer's Disease (AD), and the connection between such diseases. Lastly, we seek to understand the molecular mechanism of the initiation of LBD.

Due to limited research and investigation on the topic, there is currently no cure for LBD. Because of the related symptoms among LBD, AD, and PD, some medications used to treat AD and PD can be used for LBD. One medication is an FDA-approved drug to treat AD called rivastigmine (Exelon). It is a reversible cholinesterase inhibitor that acts on a chemical in the brain critical for memory formation and cognitive thinking[1,2]. This is a reversible cholinesterase inhibitor that is known chemically as (S)- 3- [1-(dimethylamino) ethyl]phenyl ethyl methyl carbamate[3]. Another medication, carbidopa-levodopa, is used to treat PD and could be used for LBD movement-related treatment[1,2]. Levodopa is the precursor of dopamine and can cross the blood-brain barrier to create more dopamine in dopamine-deficient areas in the brain[4].

Some clinical features of LBD include visual hallucinations and Parkinsonism. Recurrent, complex visual hallucinations occur in up to 80% of patients with LBD and are a frequent clinical signpost to diagnosis[5]. They are typically well-formed, featuring people, children, or animals, sometimes accompanied by related phenomena including passage hallucinations, sense of presence, and visual illusions. Spontaneous parkinsonian features are common in LBD, eventually occurring in over 85% (Parkinsonism in Parkinson's disease (PD) is defined as bradykinesia in combination with rest tremor, rigidity, or both)[5].

LBD is defined as a progressive disease in which symptoms worsen as one ages. [1,2] Hallucinations are common in the early stages of LBD, as are restlessness, acting out dreams during sleep (called REM sleep disorder), and

movement difficulties[5]. Others may develop urinary urgency and incontinence. Unlike AD, memory is usually still fairly intact in the early stages. However, confusion and some mild cognitive changes may be present. As LBD progresses, symptoms develop and more strongly resemble Parkinson's disease[5]. These symptoms include increased problems with motor functions, difficulty with speech, swallowing problems, and greater paranoia and delusions[6]. Cognition also continues to decline, with shorter attention and significant periods of confusion occurring. In the later stages of LBD, extreme muscle rigidity and sensitivity to touch develops. Patients need assistance with almost all activities of daily living. Speech is often very difficult and may be whispered. Some LBD patients stop talking altogether[7].

Both LBD and PD are quite similar and have overlapping characteristics, but there are specific key differences that can differentiate LBD and PD in the spectrum[1,2]. There is a frequent coexistence of the pathology of amyloid plaques and neurofibrillary tangles in LBD compared with Parkinson's disease dementia. Amyloid plaque are misfolded proteins in the synaptic clefts of neurons. This would effectively block the transmission of neurotransmitters from neuron to neuron. Additionally, the accumulation of the protein *tau* within neurons are called neurofibrillary tangles. The *tau* protein works to help the neuron's microtubules which help guide nutrients and vitamins move in the neuron. Particularly, because *tau* proteins are 'sticky' in character they will bind to each other while they are connected to microtubules and create tangles of the microtubules inside neurons. This can harm the synaptic communication and internal cell communication of the neuron[31]. Alzheimer's differs from LBD clinically because of its unique cognitive profile and its lack of parkinsonian features except in the late stages[2].

This paper provides an overview of novel therapeutic genetic strategies to reduce the effect of LBD by targeting topics of epigenetics, cognitive enhancers, non-coding RNAs, micronutrients, making alterations of central cholinergic (ACh) and dopaminergic (DA) systems, and looking at current drugs and treatments. This review will also be discussing how factors such as age, diet, and underlying health conditions can affect the intensity of Lewy Body Dementia in a patient.

2. Molecular Components of LBD

While there are many molecular pathways of LBD, research has shown that alpha-synuclein(AS)-positive inclusions are the main indicator of Lewy Body[8,9], causing the impairment of protein degradation pathways, including both the ubiquitin-proteasome system and the autophagy-lysosome pathway. The ubiquitin-proteasome pathway (UPP) is the main pathway that destroys unneeded proteins and eliminates misfolded or misguided proteins that are in the wrong locations within the cell with the use of a protease or proteasome[32]. This mechanism works through the formation of a polyubiquitinated protein, which serves as a recognition signal for the eventual action of the proteasome to degrade the proteins into peptides, as shown in *Figure 1*. This is an important mechanism as this can decrease the number of unnecessary proteins and debris in the body that is unneeded. Defects in the UPP can be detrimental to the homeostasis of the amounts of *tau* protein in the neuron. A possibility of the amount of extra *tau* protein in the neuron can be due to a mishap of the UPP.

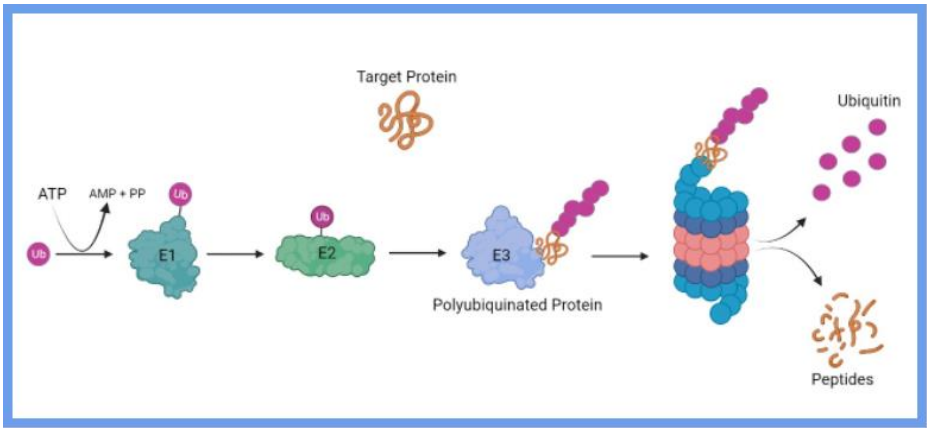

Figure 1. The ubiquitin-proteasome pathway (UPP)*. Ubiquitin, a 76 amino acid protein, marks the molecule to be degraded by attaching itself to a substrate protein. In this process, E1–the ubiquitin-activating enzyme, E2–the ubiquitin-conjugating enzyme, and E3–the ubiquitin-protein ligase, cause a cascade of reactions, the result of which is the linkage of one molecule of ubiquitin to the protein (mono-ubiquitination). Polyubiquitination occurs when additional molecules attach to the seven lysine residues or the N-terminus of the ubiquitin molecule to form a chain. Polyubiquitination is the recognition signal for the proteasome to degrade the target protein into peptides.*

The autophagy-lysosome pathway is another important catabolic pathway that regulates the quality and the number of proteins made within the body's cells. There are three common mechanisms of lysosomal autophagy which are macroautophagy, microautophagy, and chaperon-protein mediated autophagy. Macroautophagy is where an autophagosome is created containing the surplus amount of protein and a lysosome will bind to the organelle-like structure to degrade the particles within it. All these pathways separately are important to degrade an excess number of large proteins. In the case of smaller proteins, a bigger lysosome will use phagocytosis to degrade the need proteins. Similarly, chaperon -mediated pathway will utilize a longer way to degrade proteins including another chaperon protein which connects the excess amount of protein to a channel that leads to the lysosome. This lysosomal pathway uses a lysosome to engulf the autophagosome and destroy its contents with enzymes[33]. These pathways then will degrade the neurons present in the brain.

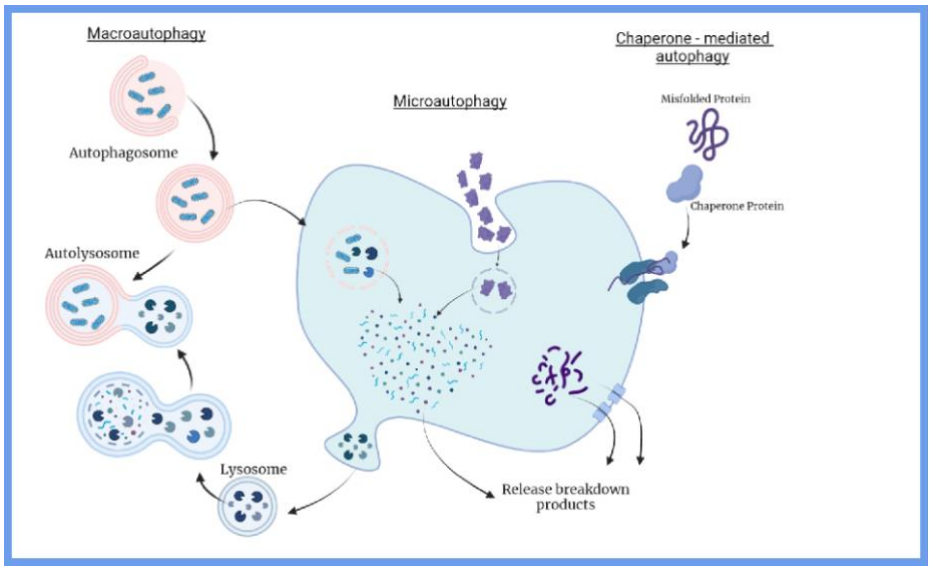

Figure 2. The three different autophagy-lysosome pathways–macroautophagy, microautophagy, and chaperone-mediated autophagy.

Alpha-synuclein also is a major component of the filamentous glial cell inclusions (GCIs) that are abundant in the white matter oligodendroglial cells of multiple system atrophy (MSA) brains. Accumulation of alpha-synuclein into filamentous inclusions could play a mechanistic role in the pathogenesis of several progressive neurological disorders, such as Parkinson's disease, LBD, Familial Alzheimer's disease, Lewy body disease variant of Alzheimer's disease, sporadic Alzheimer's disease, and multiple system atrophy[10]. This path is obscure, but UPP and autosomal-lysosomal pathways are the commonly known pathways that LBD is categorized into. LBD specifically affects the thalamus structurally and functionally[8,9].

Additionally, a study suspected there are five specific important and targeted genes from LBD patients: BIN1 and TMEM175, SNCA, APOE, and GBA-5[10]. This was done by uncovering participant samples from 44 different European ancestry banks; specifically, 17 in Europe and 27 across North America. When the sequences from LBD patients and control patients were compared, they found 5 consistent different genes that were among the LBD patients. To confirm their results and conclusions, the researchers also compared those 5 genes to another 970 LBD patients with a new control set of 8,928 control subjects[10].

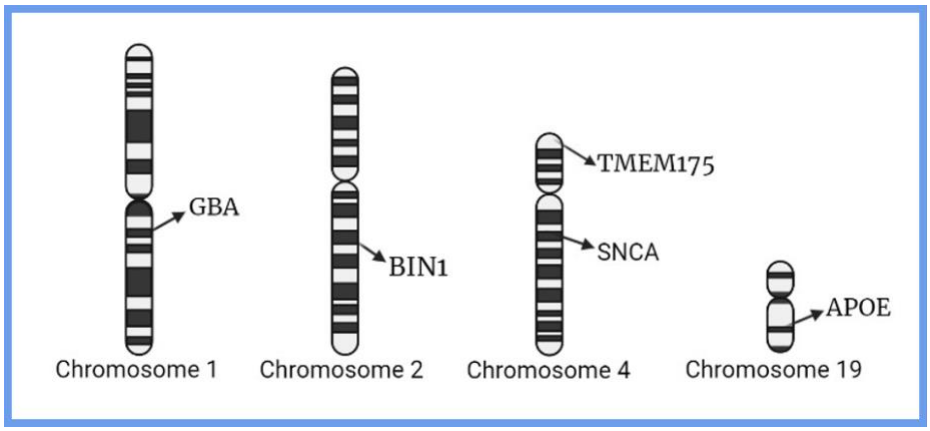

Figure 3. The 5 genes GBA, BIN1, TMEM175, SNCA, and APOE on their respective chromosomes.

Widespread mitochondrial dysfunction is very closely related to disease development as well. The impairment of protein degradation pathways, including both the ubiquitin-proteasome system and the autophagy-lysosome pathway, also plays an important role during the development of Lewy body diseases[11]. Differential expression changes of isoforms corresponding to genes primarily involved in Lewy body formation point to alternative splicing as another important mechanism in the development of dementia with Lewy bodies[11].

3. Epigenetics

Parkinson's disease and dementia with Lewy bodies are deemed similar based on a neurological overlap between them. Both PD and LBD are distinguished by an abnormal accumulation and deposition of misfolded and aggregated alpha-synuclein which gives rise to Lewy bodies and Lewy neurites.

The diversity and complexity of LBD make them complex multifactorial disorders. Thus, many LBD cases originate from the interaction of multiple genetic and environmental, epigenetic factors. There are many genes of interest that are involved in LBD, one of them being SNCA, which is a rare gene involved in LBD. It has two distinct profiles within its locus, one pertaining to PD, located in the 3' SNCA portion, and the other to LBD, located in the 5' SNCA portion[12]. SNCA was the first and is one of the most studied genes identified as an LBD-causing gene. SNCB, like SNCA, has been detected in some LBD cases.

The b-syn, from the synuclein family, has shown to be a regulator of the a-syn aggregation. Common variants, like rare variants, that could increase the risk of developing LBD have been found to be located in genes associated with PD or AD. One of these well recognized risk variants is the allele ε4 of the apolipoprotein E gene (APOE). APOE poses a risk in LBD patients because the allele ε4 accumulates and accelerates the disease which leads to a shorter lifespan for the patient[13]. On the other hand, APOEε2 has been shown to have protective effects against the development of LBD[12].

Epigenetics regulate gene expression through methods that are independent of the primary DNA sequence, even though they can be heritable. Without altering the DNA sequence, epigenetic mechanisms moderate reversible changes in gene expression and cell phenotype.

There are two major mechanisms pertaining to epigenetics modifications, shown in *Figure 4*. The first is DNA methylation, a biochemical process by which a methyl group is added to DNA, thereby modifying the function of the gene. It occurs at cytosines located 5' to guanine (CpG), and it is mediated by methyltransferases. In the promoter regions, DNA methylation can either repress gene expression, hypermethylated CpG, or increase gene expression, hypomethylated CpG. This mechanism plays a big role in aging and development.

The second mechanism is Histone tail modification which either loosens or encompasses the tail to turn a gene "off" or "on" or deactivate or activate a gene, respectively. The proteic part of chromatin is referred to the histones which allow the compaction of DNA. These two mechanisms have a fundamental part in learning and memory processes because they are dynamically controlled in neurons. Epigenetic mechanisms mediate gene-environment interactions because they can often be provoked by environmental risk factors. This emphasized the importance of certain factors in patients with LBD, such as diet, physical activity, and lifestyle[13].

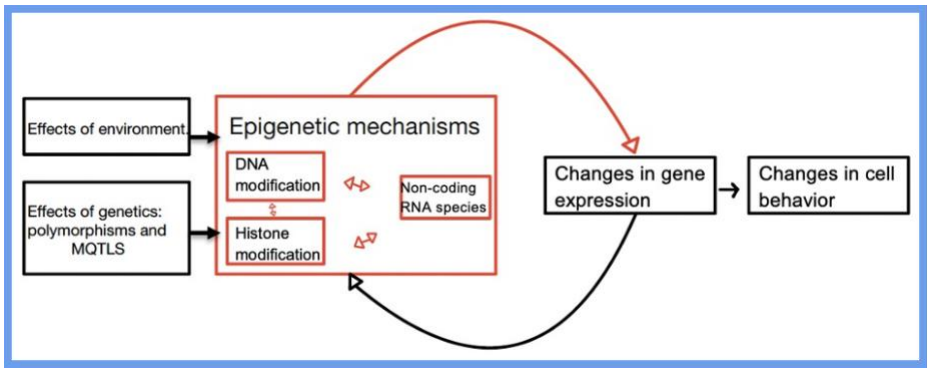

Figure 4. The process of the epigenetic mechanisms. *The effects of the environment and genetics may have an influence on changes in gene expression and cell behavior.*

LBD studies have mostly been focused on genetics rather than epigenetics; however, epigenetic mechanisms and regulation have proved to play an important role in the pathophysiology of the disease and genome. Even though there are scarce studies on epigenetics in LBD, there is evidence of an overlap of APOE and SNCA from their genetic and epigenetic regulation (*Figure 5*)[13]. Transcriptomic and proteomic studies analyzing the genetic pathway have shown clinical and neurological correlates to the disorder through the synaptic function, lysosomal processing, and circadian rhythm[13]. The origin of the cause of these changes has not yet been determined. There are a few limitations in the evidence that exists including small sample sizes, tissue specificity, and lack of information. As more technologies are developed, more will be discovered regarding this topic.

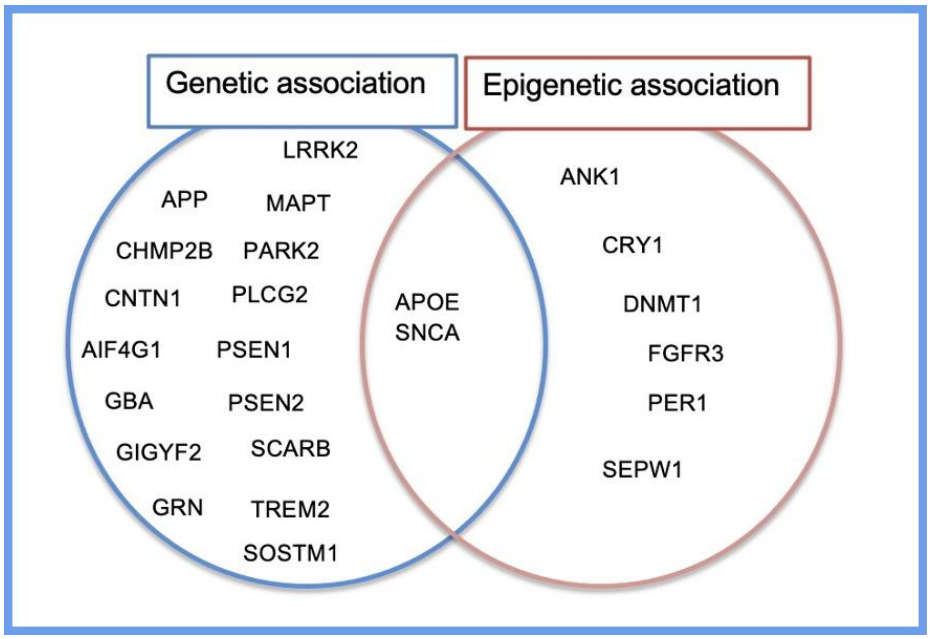

Figure 5. Genetic Association and Epigenetic Association in LBD. *This figure shows the different genes involved in LBD and how they are associated with genetics or epigenetics. As seen, APOE and SNCA have both genetic and epigenetic associations.*

With the appropriate information, epigenetics are an important tool and strategy that can be used to battle a variety of different diseases. There are tactics that would delay the onset and progression of neurodegenerative diseases, such as LBD. One of these tactics includes targeting the epigenome[14]. This can be done using small drugs, such as HDACi, that are able to cross the blood brain barrier[14]. Even though studies are scarce and there are concerns with using this type of drug, there are potential targets for drug development that could have a promising result for potential epigenetic preventive factors for neurodegeneration. As more is discovered about this disease, epigenetics will serve as a fundamental factor in either delaying the onset or helping in the stratification and improvement of the diagnosis.

4. Cognitive Enhancers

Cognitive enhancers, also called nootropics, are neuroprotective or extremely nontoxic in consideration to neurodegenerative diseases like LBD. Nootropics can be naturally found or synthetically made which can enhance attentional control and memory. There are various mechanisms by which nootropics acts, which are as follows: 1) increasing circulation to the brain, 2) providing precursors to neurotransmitters (chemical messengers in the

brain), 3) improving neuron function, 4) preventing free radical and oxidative damage to brain cells, and 5) providing usable energy to the brain[15].

Nootropics exist in three main categories: supplements, racetams, and stimulants. Supplements or dietary sources of nootropics are mainly natural and can be found in fruits and vegetables. Natural nootropics come in the form of vitamins like Omega-3, iron, antioxidants, amino acids, and caffeine. Racetams are positive allosteric modulators of AMPA receptors in the brain and include piracetam and nefiracetam. Racetams are categorized and claimed as "pharmacologically safe" drugs[15]. The amnesia reversal effect with racetams is compared with scopolamine, electroconvulsive shock, and hypoxia, which are more invasive strategies considering the safe nature of racetams[16]. Specifically, nefiracetam has been proven to have more affinity for muscarinic receptors at the nanomolar range than other aniracetam and nebracetam. Most racetams are safe but can cause adverse reactions to males than women if used incorrectly or in excessive amounts[15]. Lastly, stimulants are another type of smart drug under nootropics that enhance productivity in the brain. Some examples include methylphenidate and amphetamines and are specifically known to improve ADHD symptoms in patients with ADHD[15]. Amphetamine salts contained primarily of dextroamphetamine (d-AMP) are known by the trade name Adderall that help patients with ADHD[17]. Unlike racetams, stimulants can enhance cognitive abilities in impaired or unprescribed patients without causing adverse effects. Similar to racetams, they can be found in natural and synthetic forms that affect neurotransmitter levels, neurogenesis, and blood flow to the brain[17]. Some stimulants are known to improve symptoms of LBD and reverse the progression of dementia. Additional categories of nootropics include dopaminergics, specifically work to raise levels of dopamine, and serotonergics, specifically work to raise levels of serotonin, which can also raise treatments to reverse symptoms of LBD[15].

One clinical trial study of nootropics has been done on patients with AD. Researchers were particularly interested in comparing the effects of specific nootropics that affected behavioral and psychological symptoms of dementia which is how LBD can also be affected in the study. Specifically, the study looked at cholinesterase inhibitors and memantine or a N-methyl-

D-aspartic acid (NMDA) receptor antagonist. Cholinesterase inhibitors of donepezil and rivastigmine increase the concentration of acetylcholine at the neurotransmitter sites. The other cholinesterase inhibitor tested was Galantamine which is a double action that not only increases acetylcholine at neurotransmitter sites like donepezil and rivastigmine, but also acts by modulating activity at nicotinic receptors. Memantine is a NMDA receptor antagonist modulates glutamate in the glutamic system of the brain. The study had selected patients with AD and had given a placebo to some patients and others received a cognitive enhancer. Observations were made with the efficacy and reversal of dementia in these patients. This clinical trial has potential to show that more than 100,000 patients are eligible for cognitive enhancers in Canada alone as 30% of the AD patients have moderate dementia. These medications have been approved for the treatment of Alzheimer's disease in many countries as well[18].

Another facet to consider is the administration of such effective nootropics. In a clinical trial led by Dr. Murat Emre from Istanbul and published in the prestigious New England Journal of Medicine in 2005 had shown that rivastigmine, as previously mentioned, a cholinesterase inhibitor that enhances ACh concentration in neurotransmitter sites was effective in Parkinson's disease (PDD). Although this drug is not approved for LBD patients in the Dr. Emre's trial[19]. However, many doctors and providers consider both disorders to have similar enough symptoms for the rivastigmine medication to be effective in both conditions. In this study both the patch, developed and approved for use in 2007, and the pill of rivastigmine were given along with the placebo to patients with PDD. The patch and pill of rivastigmine were proven to be more effective than the placebo and showed the same effectivity. However, one trial of Dr. Emre's study declared the patch was more effective than the pill of rivastigmine mainly because of the lower recurrence of side effects of nausea and vomiting in the patch than in the pill. Because medications were taken by the skin in comparison to the mouth, GI issues decreased in patients who used the patch[19].

5. Non-coding RNAs

As previously described, LBD is very complex and has become an increasing

demand on global health care systems. Because it is so complex, there are many factors that need to be researched to create possible therapies or treatments. Non-coding RNAs (ncRNAs) are RNA sequences that cannot be translated into proteins. There is a vast variety of different ncRNA families; however, the two most valuable to this topic are the miRNA and lncRNA families. These two families have the capacity to provoke gene regulation across cellular physiological pathways. Since miRNAs and lncRNAs influence disease pathways, it is important to research ncRNAs for possible therapies and for more information on the pathogenesis[20]. miRNA and lncRNA families have different influences on dementia[20]. miRNA, short for microRNA, refers to a small single stranded ncRNA molecule. It comprises 22 nucleotides and functions in RNA silencing and post-transcriptional regulation of gene expression. miRNA inhibits the translation of proteins coded by mRNA transcript by acting as a physical obstruction for ribosomal action. There are many studies attributing and demonstrating the effects of miRNA defects on multiple forms of dementia, however because LBD has not been deeply studied there are no details on the influence of miRNA on LBD[21]. Specifically, lncRNA, short for long non-coding RNA, refers to a single RNA sequence composed of at least 200 nucleotides. lncRNA regulates gene expression in several levels such as epigenetics and transcriptional levels. Most lncRNAs are detrimental to pathways in neurodegenerative diseases[21]. Just as in miRNA, there are no studies on the specific effect of lncRNAs on LBD.

As stated previously, small molecule drugs show potential for the future of this disease. One of the few studies that has been done using ncRNAs is the use of small molecule drugs targeting ncRNAs as treatments for dementias[22]. ncRNAs could function as therapeutic targets because they are enriched in the central nervous system. A small molecule can bind to ncRNA, changing its conformation, to regulate it. There has been extensive work in developing oligonucleotides to target mRNAs and ncRNAs, however there are many obstacles that have not yet been researched which block the entry, specifically in the blood brain barrier. Another tactic that needs further studying is the use of gene therapy. Using gene therapy with viral vectors can edit ncRNAs and can allow for more durable ncRNA modulation. However, this also

comes with obstacles regarding the delivery and expression of the target genes, making the therapy ineffective.

More research and knowledge could lead to identifying novel diagnostic procedures and/or drug targets. While these possible therapies or drugs may not be able to cure a patient, they can help with the control of the patient's mental condition, disease progression, and cognitive decline.

6. Other Factors in Effect

6.1 Inflammation

As LBD and AD have similar symptoms and neuroinflammatory mechanisms involving the activation of microglia, overexpression of interleukin-1 and other inflammatory mediators, and inflammatory toxicity to neurons. The activation of microglia are also resultants from the overexpression with α-synuclein-containing neurons and glia in PD. These connections are also associated with the microglial associations with neurofibrillary tangle-containing neurons in AD. It is shown that there is a reciprocal induction between α-synuclein and injured neurons on one hand and activated microglia and cytokine overexpression with in vivo and in vitro experiments. This mechanism of inflammation can lead to more injured neurons which can activate microglia and cause a cycle of inflammation beneficial to the neuron which can cause neuronal death. This concept can show the progression and overlap between both AD and LBD[25].

6.2 Risk Factors

There are several factors that contribute to a person's risk for developing LBD. A history of high caffeine intake, for example, is associated with a lower risk of LBD. Research has suggested that the benefits increase in tandem with the amount of caffeine a person drinks per day and may reduce the risk of LBD by as much as 29%[26]. Genetics and heredity appear to play a role in the risk of LBD as well. Generally, if you have a first-degree family member with Lewy body dementia or PD, your risk of Lewy body dementia increases. Additionally, for reasons not entirely clear, a history of depression and anxiety is linked to an increased risk of Lewy body dementia[27]. Metabolic

Disorders Hypertension (high blood pressure) is linked to an increased risk of Lewy body dementia. The incidence of hypertension among people with Lewy body dementia is roughly 65%. Having high blood pressure, in turn, increases the risk of Lewy body dementia by 60.5%. Type 2 diabetes, a form of diabetes strongly linked to lifestyle, is associated with a 25% increased risk of Lewy body dementia. High cholesterol also increases the risk of Lewy body dementia by roughly 25%[28].

6.3 Micronutrients

Micronutrients are a fundamental part to healthy development, disease prevention, and a good lifestyle. No micronutrients, except vitamin D, are produced in the body therefore they must come from a person's diet and intake. Micronutrients are important for healthy people but even more important for those who have a disease or are genetically prone to developing a disease[23]. Those who do not supply their body with sufficient nutrients can suffer from malnutrition, which has been found to be tied to cognitive function. Deficiency of nutrients, specifically vitamin B12 and folate, can lead to decreased cognitive function. In addition, weight loss associated with malnutrition will often occur prior to the onset of dementia[23]. As the disease progresses, weight loss can also progress and vice versa. While there are several diets that are said to prevent, or help with, cognitive decline and dementia, there are no studies that directly prove one diet to help with LBD[24]. Finding the correct micronutrients that could help patients who have LBD or are predisposed to it could have a huge impact on this area of health.

7. Conclusion

From the progression of research of LBD in clinical trials, in vivo, and in vitro experiments, the potential of epigenetic therapy should be examined more thoroughly. Future directions of the use of deep brain stimulation[29] and repetitive transcranial magnetic stimulation (rTMS) has shown potential in other neurodegenerative diseases and could be applicable to LBD[30]. The effects of epigenetics, age, diet, and inflammation within the body can enhance other scientists' knowledge when designing therapies for LBD in the future. As this article has mentioned many current therapies and potential therapies it is important to note the limitations and drawbacks of the research

presented. One drawback is that many of the clinical trials are research alongside Alzheimer's disease and or Parkinson's disease so there is no precise way to isolate LBD research and progression. Additionally, many of the clinical trials and experimental data found were said to be inconclusive as the data was little or had little to no value of measurement. Protocols on how to measure the data obtained in experimental trials are still being researched upon. To combat these terms, this article took a holistic review of each article and applied most information back to LBD with reason. Nevertheless, the research presented is to enhance the knowledge of other scientists researching LBD therapies to give a foundation about the current and probable therapies available.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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