

Review Article

The Comorbidity of Alzheimer's Disease and Bipolar Disorder and the Potential of Lithium as Drug Therapy

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Abstract

Bipolar disorder is characterized by having pathological fluctuations in mood and energy that result in severe psychological issues and an increased risk of suicide. More than 4% of the adult population is affected by this disorder and as a result is at a higher risk of developing certain neurodegenerative disorders, such as Alzheimer's disease. Alzheimer's disease affects more than 6.2 million Americans over the age of 65 and is currently the sixth leading cause of death in the United States. There is currently no approved therapeutic approach to treat Alzheimer's disease, however, the comorbidity of bipolar and Alzheimer's disease has encouraged the investigation of lithium as a possible method of treatment. Lithium has been used to treat bipolar disorder for years and has recently been shown to increase gray matter density in the brain as well as encourage stem cell proliferation in areas where cell dysfunction and death have occurred. Research has shown chronic lithium usage can decrease the rate that dementia develops in high-risk individuals, such as individuals with bipolar disorder.

Keywords: Alzheimer's Disease; Stem Cell Proliferation; Bipolar Disorder; Lithium; Dementia

Abbreviations

AD: Alzheimer's Disease; HIV: Human Immunodeficiency Virus; BD: Bipolar Disorder; A β : Amyloid-Beta Peptide; SP: Senile Plaques; NFT: Neurofibrillary Tangles; DG: Dentate Gyrus; SGZ: Subgranular Zone; SVZ: Subventricular Zone; CNS: Central Nervous System; TAIs: Tau Aggregation Inhibitors; WHO: World Health Organization; GSK-3: Glycogen Synthase Kinase 3; MSC: Mesenchymal Stem Cells; NSC: Neural Stem Cells

Introduction

Epidemiology of Alzheimer's Disease

Neurodegeneration is a natural process that occurs with aging. The intensity of this degeneration varies between individuals and can be influenced by a combination of environmental factors and genetic factors [1]. However, neurodegenerative diseases, such as Alzheimer's Disease (AD), can expedite and intensify this process. Alzheimer's is a progressive neurodegenerative disease that physically alters the composition of the brain to the point where neurons and their connections are lost, resulting in a loss of memory and body function and thus, the ability to live independently [2]. Alzheimer's affects the lives of more than an estimated 6.2 million Americans over the age of 65 [3]. Without the institution of a medical breakthrough in the prevention of this neurodegenerative disease, this number could increase to 13.8 million Americans over the age of 65 by 2060. In the year 2019, 121,499 deaths were attributed to Alzheimer's, making AD the sixth-leading cause of death in the over 65 age demographics [3]. In contrast to other chronic illnesses such as heart disease or Human Immunodeficiency Virus (HIV) where the overall death count has decreased, the number of reported deaths from Alzheimer's has increased by over 145% [3,4]. The public health impact extends past the mortality and morbidity counts, into the lives of affected family members. Unpaid caregivers provide upwards of 16 billion hours of care to individuals diagnosed with dementia in 2021, with unpaid dementia

care estimated at around \$271.6 billion [3,5]. These numbers will only increase unless means of treatment and prevention are developed.

Pathophysiology of Alzheimer's Disease

To move forward in the understanding of the complex neurodegenerative disease that is Alzheimer's Disease, it is imperative to recognize the genetic and molecular biology behind this disease (Fig. 1) [6]. The overall cause for the development of this disease can be characterized by neuronal cell types being altered, causing cell dysfunction and death [6,7]. Neurotic plaques and neurofibrillary tangles because of Amyloid-beta peptide's ($A\beta$) accumulation in certain areas of the brain can contribute to these cell abnormalities that will ultimately cause AD [7-9]. Various types of neuropathological changes offer insight into disease progression. Positive lesions on the brain can occur due to accumulation of $A\beta$; these lesions are characterized by neurofibrillary tangles, amyloid plaques, dystrophic neurites, and neutrophil threads along with other deposits [10]. Negative lesions can form from brain matter atrophy that has been attributed to neural, neutrophil, and synaptic loss [10]. Both types of neuropathological changes cause the cell dysfunction that allows for the progression of AD.

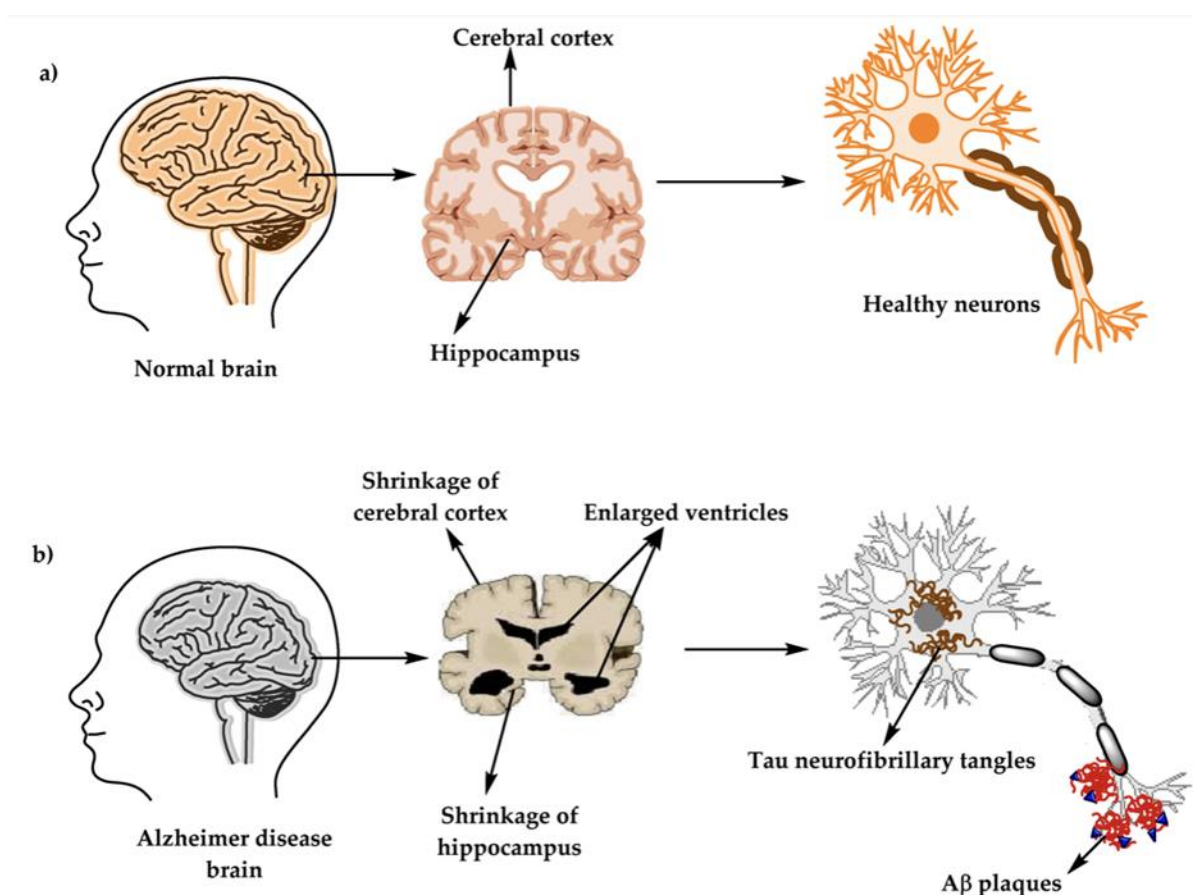


Figure 1: The physiological structure of the brain and neurons in (a) healthy brain and (b) Alzheimer's Disease (AD) brain [6].

Senile Plaques (SP) have been regarded as a defining characteristic of AD since the first descriptions of AD in 1907 [11]. SP can exist in several different forms, most of which include a variety of $A\beta$ peptides that result from secretase cleavage of a transmembrane glycoprotein known as APP [11]. $A\beta_{42/43}$ is most common, while $A\beta_{40}$ is found more in blood vessels of patients who's AD has progressed past early stages [11]. Animal models suggest that $A\beta$ peptides are formed in response to cell degradation [11]. APP shares its structures with precursors of epidermal growth factors, suggesting that APP is a protectant that is activated by injury to brain cells [12,13]. SP may also contain degenerating neuronal perikarya and acetylcholinesterase rich neurites which may be degenerating neurons found in the nBM, and a variety of other constituents that aid in the overall degradation and loss of function in neural cells [14]. Neurofibrillary Tangles (NFT) may form as the result of injury; neurons respond to degradation by increasing the synthesis of the protein tau [15]. In healthy individuals, tau carries multiple phosphate

groups in its microtubule assembly domain [15]. Individuals with AD have elevated phosphorylation and aggregation of Tau which causes abnormalities in glycosylation, ubiquitination, glycation, and other post translational modifications that causes the aggregation of tau in the synaptic loci in AD patients (Fig. 2-3) [15].

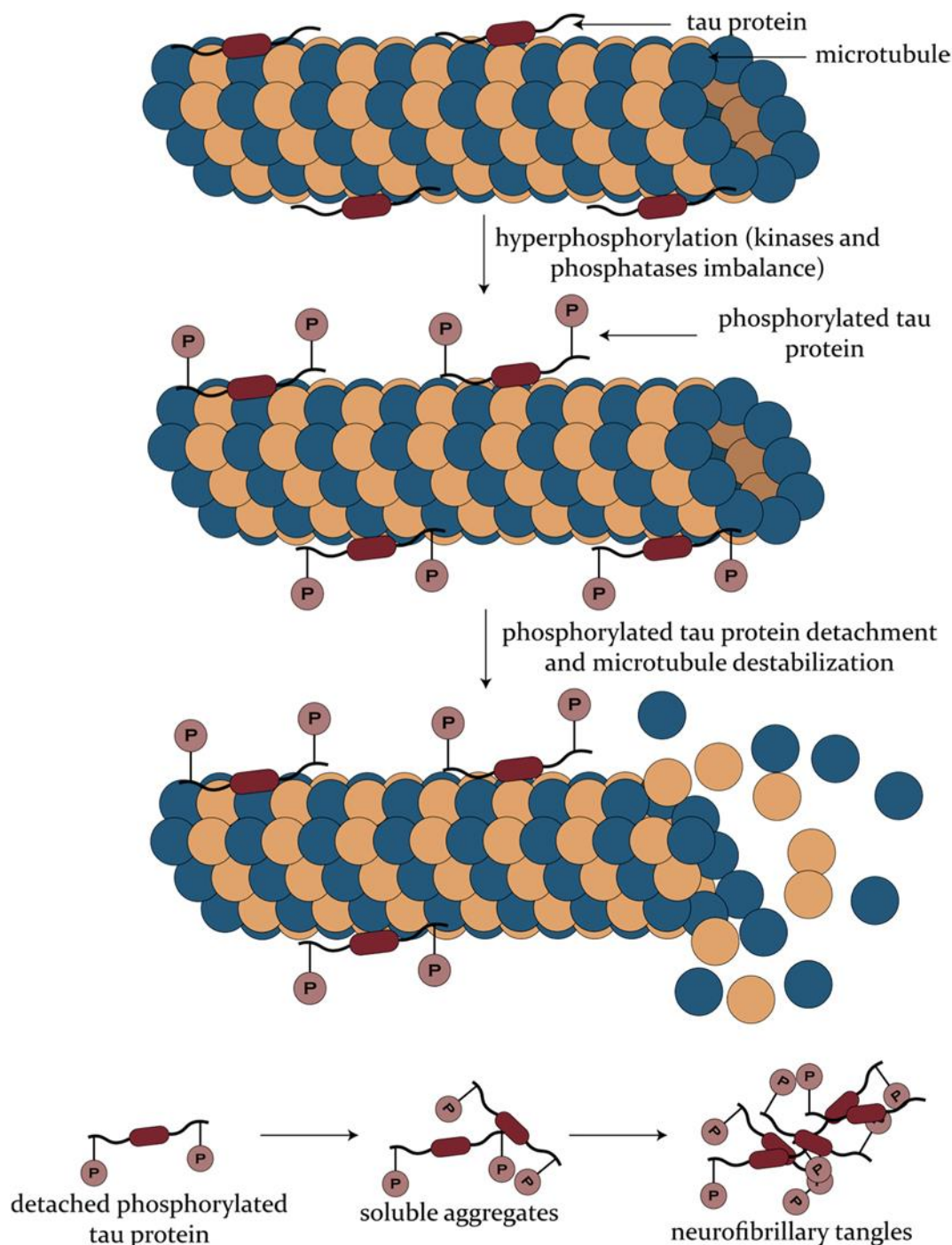


Figure 2: The formation of neurofibrillary tangles through tau protein hyperphosphorylation [16].

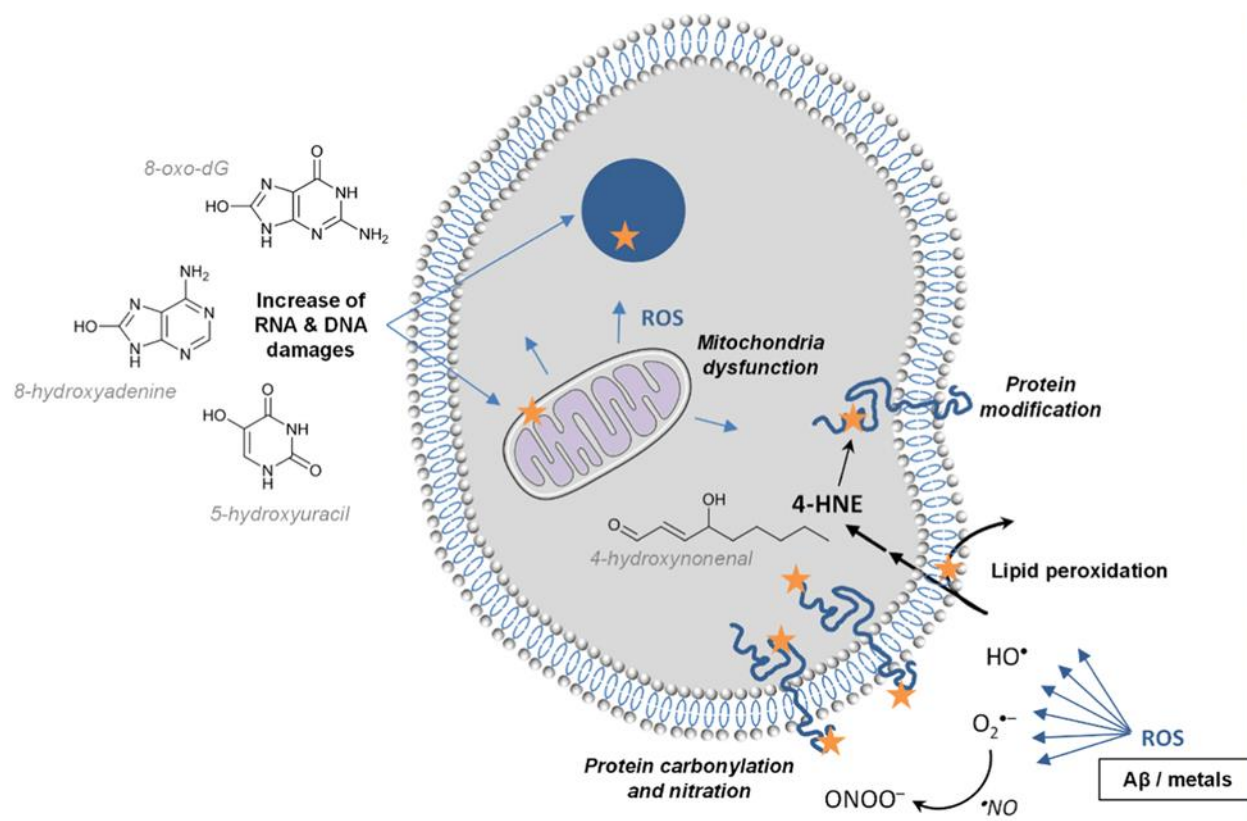


Figure 3: Induced oxidative stress in AD brain regions of high Aβ levels [8].

History of Alzheimer's Disease Treatment

Even though AD is the leading cause of dementia, there have been little to no advances in treatment options for individuals with AD [17]. Current treatment options include cholinesterase inhibitors and memantine [17]. The objective of the treatments designed for AD are to ameliorate cognitive symptoms as well as slow the progression of the disease [17,18]. Many drug trials conducted to date have been monotherapy trials focusing on a comparison of results between an active agent and a placebo [18]. The complexity of the diverse pathology and interactive network that is AD has led to the more recent belief that a combination therapy may be needed to target this neurodegenerative disease [19]. Success with combination therapy regarding other chronic diseases, such as cancer and HIV, have paved the way for future research of potential treatment for AD [19]. There are two types of treatment combinations-pharmacodynamic combinations designed to exert multiple effects of the biology of the disease, and pharmacokinetic combinations which affect the way a drug is absorbed, distributed, and metabolized [19]. The benefits of combination therapy include flexibility in delivering the drug to the target, as well as the delivery method and delivery timing [20]. Currently, the disease-modifying therapies are add-ons to cholinesterase inhibitors or memantines because of the background of standard-of-care therapy that allows for various experimental agents to be studied [19,20]. Unfortunately, many phase III trials have failed. BACE 1 inhibitors that originally showed good promise in previous phase trials failed due to a failed safety analysis [21]. Another potential therapy, Verubecestat, did not have enough positive impact to pass the phase III trial [22]. A noteworthy characteristic of AD is the formation of intracellular neurofibrillary tangles composed of hyperphosphorylated tau [23]. The abnormal phosphorylation of tau that leads to the formation of tau protein aggregates that are associated with cell dysfunction and dementia have led to the investigation of Tau Aggregation Inhibitors (TAIs) that could have the ability to prevent or reverse tau aggregate formation and therefore prevent any behavioral changes that would occur as a result [23]. The challenges with AD drug therapy development and clinical trial failures suggest a need for innovation in the development of treatment of this disease (Fig. 4).

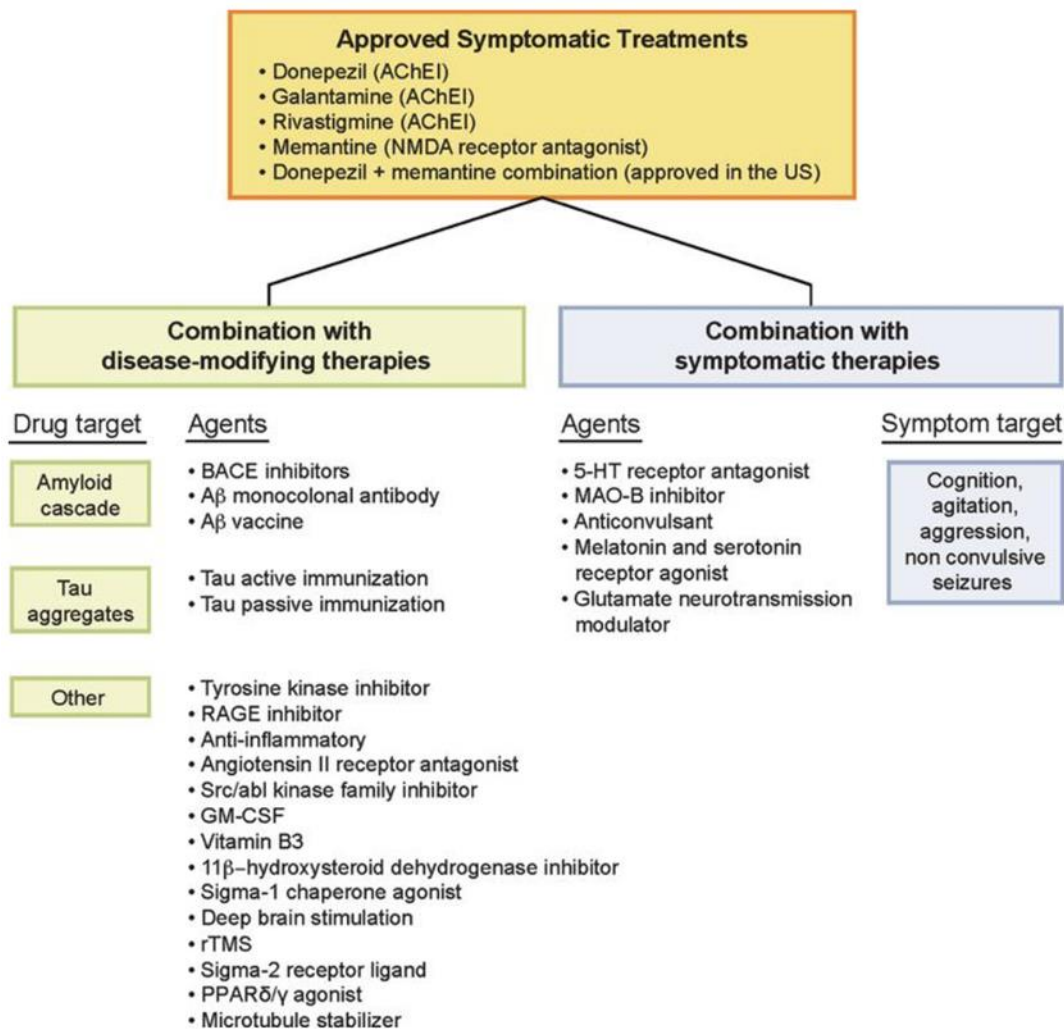


Figure 4: Combination therapies in the development of a therapeutic approach for AD [19].

Epidemiology of Bipolar Disorder

Bipolar Disorder (BD) is characterized by continually recurring episodes of severe depression and manic episodes separated by periods of remission known as euthymic episodes [24]. In between these episodes of pathological decreases and increases in mood and energy, normal moods and brain function are observed [24]. There are two types of bipolar disorder: bipolar disorder type I and bipolar disorder type II [25]. BP-I is defined as having intense manic episodes that result in psychiatric issues that may lead to social impairment and hospitalization [25]. BP-II is less severe in that affected individuals can likely remain functional while undergoing a hypomanic episode [25]. Epidemiological studies have revealed that around 1% of the adult population is affected by BP-I and more than 4% are affected by other mental disabilities on the bipolar spectrum such as BP-II and cyclothymia [26]. BD is considered a major public health problem because of its attribution to an increased risk of suicide in affected individuals [27]. The disease is typically early onset, developing between ages 15 and 25 years old [27]. Though this disease is rarely fatal, due to the significant functional impact it induces, this disease is a cause of a significant decrease in quality of life and is the sixth highest cause of medical disability worldwide for individuals between ages 15 and 44 according to the World Health Organization (WHO) [28]. From a public health standpoint, bipolar disorder costs the United States an estimated \$45 billion annually [29]. Over 60% of bipolar patients have an additional mental health or substance use disorder diagnosis, Axis I, such as abuse of alcohol or drugs [29]. While alternative methods of treatment such as therapeutic approaches can be used to treat bipolar disorder, the most effective manner of managing symptoms associated with the disorder is by use of medication, for example, lithium [29].

Biomarkers Associated with Bipolar Disorder

Currently, individuals with BD experience a diagnostic delay of about ten years which has a negative effect on the outcome of the disease [29]. There are not many current biomarkers for BD which makes diagnosis and prognosis of the disease difficult to assess [30,31]. It is imperative to be able to identify BD early on in an individual's life to ensure the individual undergoes as little distress as possible. This allows the individual the opportunity to find the best medication regime to treat the debilitating symptoms of the disorder to ameliorate the individual's quality of life and lessen the risk of suicide. A recent study conducted on electrophysiological data via ERG could be candidate markers of interest in the diagnosis of BD [32]. To understand why certain individuals are affected by bipolar disorder, efforts have been made to understand the genomics of BD. Two genes, CACNA1C and ANK3, have been identified as risk genes due to the six pathways that are associated with BD [33]. These pathways have shown to be involved with calcium signaling and hormones [33]. Based on *ex-vivo* studies conducted in 2018, a characteristic of BD is calcium dysregulation [34]. In individuals with bipolar disorder, intracellular calcium signaling appears to be increased independently of current mood state [34]. Lithium may help to regulate these abnormalities and is currently used to treat BD and other L-type voltage-gated calcium channel antagonists and antiepileptic drugs are currently being investigated as alternate treatments to BD [34].

Comorbidity of Alzheimer's and Bipolar Disorder

BD and AD can both be classified as neuropsychiatric disorders, or complex conditions that are poorly defined on a biological basis [35]. There is little known about the genetic aspects of these disorders and even less known about the specific loci that may affect the development of these disorders [35].

While neuropsychiatric disorders cannot be classified as neurodegenerative diseases, these disorders, like neurodegenerative diseases, also can cause cellular dysfunction and cell death. Psychiatric disorders can arise before or after neurodegenerative diseases are identified which leads to hypotheses regarding the comorbidity of these disorders and diseases [36]. An example of this correlation and a recent area of interest is studying the comorbidity of BD and AD. Epidemiological studies across the world have shown that BD patients may have an increased risk of developing dementia compared to controls of the same gender and age of the population [36]. Amongst BD patients there seems to be a positive correlation between the frequency of dementia and the number of affective episodes and the presence of BD symptoms [35]. To understand the neural, cellular, and molecular pathways of BD and AD, the human brain tissue must be compared between healthy individuals and those who are in a pathological state [36,37]. The creation and distribution of drugs to treat these conditions are based on the shared molecular pathways of disease, therefore more knowledge on these two disorders and the relationship between them is needed [37].

Hippocampal Alterations of Alzheimer's Disease and Bipolar Disorder

Many structural and functional abnormalities play a role in the development of both AD and BD. As seen in recent neuroimaging studies, the lateral ventricles and gray and white matter have an altered volume in BD and AD patients as compared to the control [38,39]. Both BD and AD are characterized by having changes in the hippocampal area [38,39]. The hippocampus is critical for memory acquisition and this region of the brain is divided into two hemispheres - the left hemisphere being responsible for episodic memory while the right hemisphere is imperative in task memory and recall [40].

The literature regarding changes in the hippocampal mass in patients suffering from bipolar disorder is controversial, but it is consistent that hippocampal mass appears to decrease with age [41]. Therefore, the hippocampus is a critical region to monitor to understand the progression of the disease and the development of other neurodegenerative diseases that do not develop until later in life. Similarly, when looking at changes in the anatomy of the brain in AD patients, the hippocampus appears to be the most affected region of the brain when it comes to physical mass alterations [42]. In a study conducted by Dhikav and Anand in 2011, it was shown that the very first pathophysiological signs of AD are found in the temporal lobe of the hippocampus, suggesting that mass loss occurs early in the onset of the disease [43]. Memory loss therefore is not entirely dependent on the accumulation of amyloid-beta peptide, but rather the decline in hippocampal neurogenesis that leads to neurodegeneration as the result of cell dysfunction and death that is seen in the earliest stages of AD [43]. In both patients with BD-II and AD patients there is a volumetric reduction in the DG region of the hippocampus [44]. Studies have found that depressive states reduce hippocampal volume which is consistent with the mood swings that are associated with BD [44]. The loss of this area in patients with AD is cause for cognitive and memory impairments. The DG is primarily where neurogenesis occurs [45]. Hippocampal

neurogenesis is related to memory, learning and mood including social interactions [45]. When this neurogenesis is impaired by a decrease in mass, normal cognitive function is unable to take place resulting in neuropsychiatric disorders (Fig. 5).

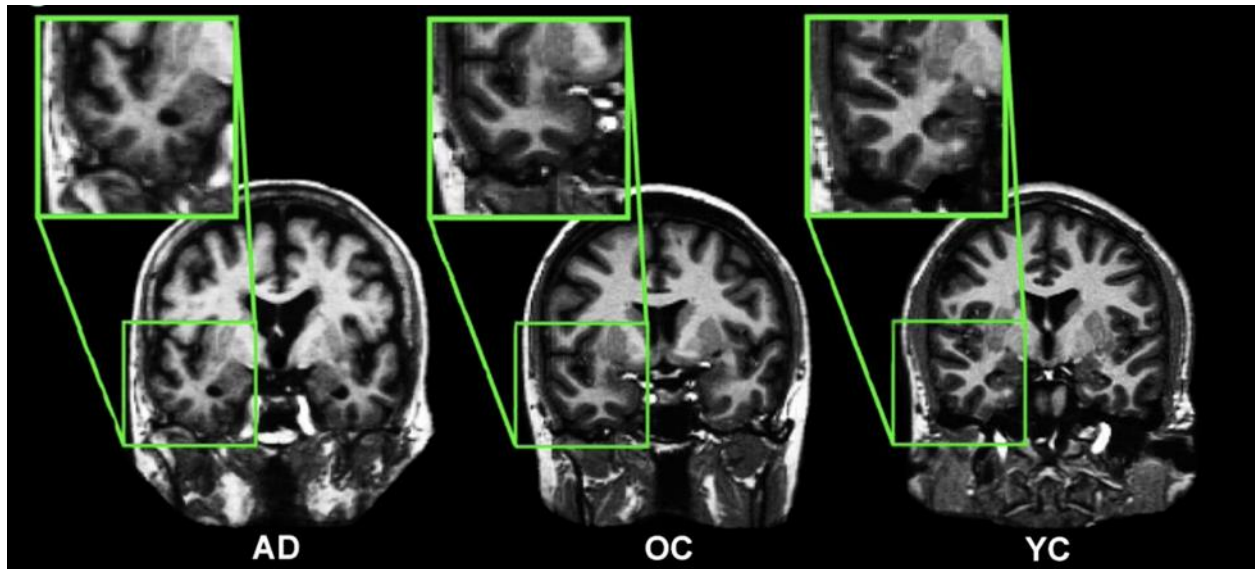


Figure 5: Demonstration of the differential regional gray matter/white matter tissue contrast in an individual with Alzheimer's disease (AD), an older adult (OA), and a Younger Adult (YA) [39].

History of Treatment of Bipolar Disorder and Psychiatric and Biochemical Capabilities of Lithium in Treatment of Bipolar Disorder

Bipolar disorder consists of three main phases that must be treated: mania, depression, and prophylaxis [46]. Mania is treated using an antipsychotic such as olanzapine or risperidone, which is generally agreed to be both effective and tolerable [46]. Bipolar depression on the other hand is not the same as a generalized depressive disorder. Currently, quetiapine, olanzapine, antidepressants, lamotrigine, and lurasidone have proved to have some efficacy but show varying tolerability [46]. Lithium is the most popular drug used to prevent the relapse of bipolar disorder. In 2014, a meta-analysis of maintenance treatment was published based on 33 trials and 17 treatments and combinations [47]. Lithium and quetiapine prevented the reoccurrence of manic episodes. Lithium was more effective than competing drugs even when the trials were designed to favor the active competitor, making lithium the first go-to treatment for most individuals diagnosed with BD [47]. Though lithium has proven to be effective in preventing psychiatric episodes, the drug is not without its drawbacks. Lithium has many side effects and is potentially toxic [47]. Lithium can be a contributing factor to renal failure as well as a concern for women of childbearing age who are breastfeeding [48]. The side effects of this mood stabilizer are often taken into consideration and outweighed by the fact that this drug has the potential to reduce risk of suicide, mortality, and dementia. This paper will further explore the properties of lithium that allow this drug to be considered for the prevention of dementia and treatment of Alzheimer's disease.

Discussion

Therapeutic and Neuroprotective Effects of Lithium and The Potential Treatment of Neurodegenerative Disease

Patients with the characteristic episodes of mania and depression separated by euthymic episodes of bipolar disorder typically respond well to lithium [47]. It has been found that lithium also may be effective in reducing overall mortality of bipolar disorder by reducing the number of suicide attempts in patients [48]. In a meta-analysis of 28 studies conducted in 1997, the yearly suicide risk was significantly reduced in BD patients that took lithium as opposed to those who did not [49]. In addition to lithium's reported ability to reduce suicide, more recently lithium has been investigated as a neuroprotective agent [50]. Newly discovered properties of this ion provide hope of a new therapeutic treatment for neurodegenerative disorders such as AD [50].

It has recently been found that chronic lithium treatment significantly increases the levels of B-cell lymphoma/leukemia-2 gene (Bcl-2), a neuroprotective protein [51]. Bcl-2 is a viral apoptosis-regulating protein, meaning that it regulates the common pathways for apoptosis [51]. Bcl-2 has a mechanism of action that appears to inhibit the apoptotic and necrotic cell death induced by various stimuli such as oxidant stressors that play an environmental role in the development of AD [51]. In a study conducted

by Manji, et al., in 2000, evidence was found to support that lithium increases Bcl-2 levels in the frontal cortex, hippocampus, and striatum *in-vivo* and in cultured cells of both rodent and human neuronal origin *in-vitro* [51,52]. Lithium increases Bcl-2 levels in human neuroblastoma SH-SY5Y cells and increases Bcl-2 levels in C57BL/6 mice, in rat cerebellar granule cells and in nucleus magnocellularis neurons [51,52].

Various studies have reported that there is a significant decrease in regional Central Nervous System (CNS) volume and cell numbers in patients with mood disorders and neurodegenerative disorders, such as BD and AD [53]. A study conducted in 2006 reveals that patients treated chronically with lithium had greater prefrontal cortex volumes, and it was found that therapeutic doses of lithium also exerted increases in gray matter volume in the brain as well as increases in N-Acetyl-Aspartate (NAA), which is a marker of neuronal viability [54]. The result of increased density in gray matter in patients chronically treated with lithium compared to control patients offers support for the idea that neurogenesis may be encouraged by drug therapy [54]. These results suggest there could be hope for lithium as a potential drug treatment for neurodegenerative disorders such as AD. An additional target of lithium action is Glycogen Synthase Kinase 3 (GSK-3) (Fig. 6) [55]. GSK-3 is a serine-threonine kinase that is typically highly active in cells and inhibited at therapeutic concentrations; the enzyme has two different forms, α and β , and is known for its ability to regulate a variety of cytoskeletal processes by affecting tau proteins and synapsin 1 [55]. At clinical lithium concentrations (1mM), the inhibition of GSK-3 β reduces tau phosphorylation [55]. As previously mentioned, hyperphosphorylation of the protein tau is an early event in the development of AD due to the potential for the microtubule cytoskeleton to be disrupted. These results suggest that GSK-3 β is a potential mechanism for reducing hyperphosphorylated tau in neurofibrillary tangles which could possibly be in the treatment of AD [55].

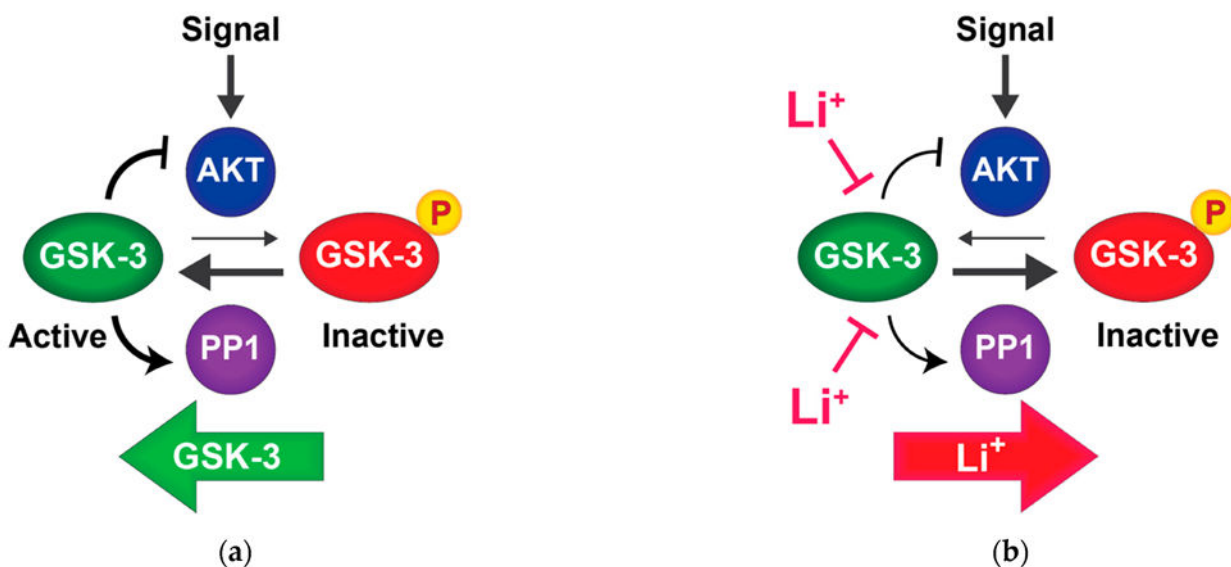


Figure 6: (a) GSK-3 is phosphorylated and inhibited. PP1 dephosphorylates and activates GSK-3; (b) lithium inhibits GSK-3 directly and disrupts both feedback circuits. Disruption of these feedback circuits by lithium may enhance the response to endogenous ligands [55].

Introduction to Stem Cells and Stem Cell Therapy

Stem cells are generally characterized by having the ability to self-renew over time, differentiate, and regenerate tissue following the occurrence of an injury. Studies conducted up to the current date looking at stem cells in the treatment of neurodegenerative diseases have focused on two specific types of stem cells: NSCs as we have mentioned before, and mesenchymal stem cells (MSCs) [56,57]. While the mechanisms of action of MSCs are not fully understood, MSCs have been found to enter sites of injury and inflammation and trigger the body's immune response through microglia activation and anti-inflammatory response [58,59]. As the microglia is altered, it has been found to have an improved ability to degrade A β deposits thanks to the A β -degrading enzyme, neprilysin [58,59]. As a result, memory dysfunction is improved as A β deposition is reduced [58-60]. In a study conducted in 2012, it was shown that a negative correlation exists between MSC-induced microglial activation with high anti-inflammatory cytokines expression and A β deposits decrease and tau phosphorylation reduction in the hippocampus of mice

[61,62]. Direct implantation of MSCs into the hippocampus of mice has been shown to improve cognition and improve neovascularization, causing memory and learning deficits recovery [62,63]. These studies provide hope for early interventional drug therapies for neurodegenerative disorders using stem cells.

In the adult brain, Neural Stem Cells (NSCs) reside in the CNS [64]. Adult NSCs are a major area of interest in the field currently as they have the potential to enhance neurogenesis and compensate for neuronal loss that occurs with neurodegenerative diseases such as AD [64-66]. NSCs in the brain are only found in the Subgranular Zone (SGZ) of hippocampal Dentate Gyrus (DG) and the Subventricular Zone (SVZ) of the lateral ventricle [67]. These cells then can differentiate into more distinct neural cell types and migrate to other regions of the brain [67]. When inserted into the hippocampus, NSCs have been seen to improve cognitive function, synaptic activity, and neuronal survival in animal models (Fig. 7,8) [68]. NSCs express the proteolytic enzyme neprilysin which underlies the endogenous degradation of A β [69]. These neural stem cells were found to increase the number of mitochondria and mitochondrial proteins expressed and as a result, increase cognitive function in the damaged brain [69]. While it should be noted that in cases of brain degradation that have progressed past the early stages NSCs failed to restore cognitive function, the use of stem cells offers hope of a potential treatment for neurodegenerative diseases such as AD [69].

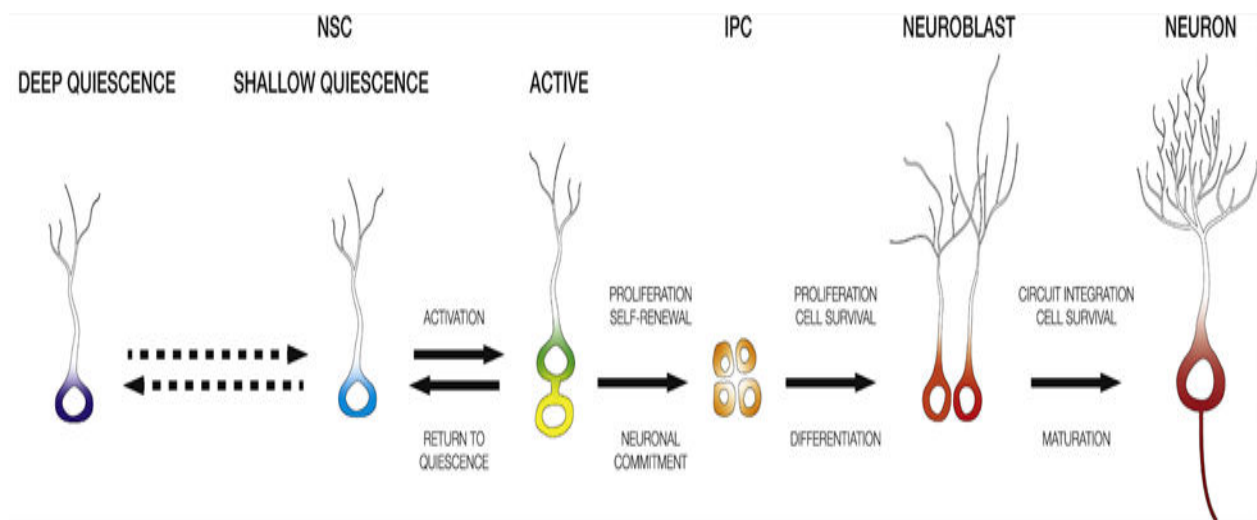


Figure 7: Neural stem cells in the SGZ and ventricular-subventricular zone show alterations in gene expression and cellular physiology as they vary between levels of quiescence and activity states [64].

LONG-TERM FATE OF NSCs

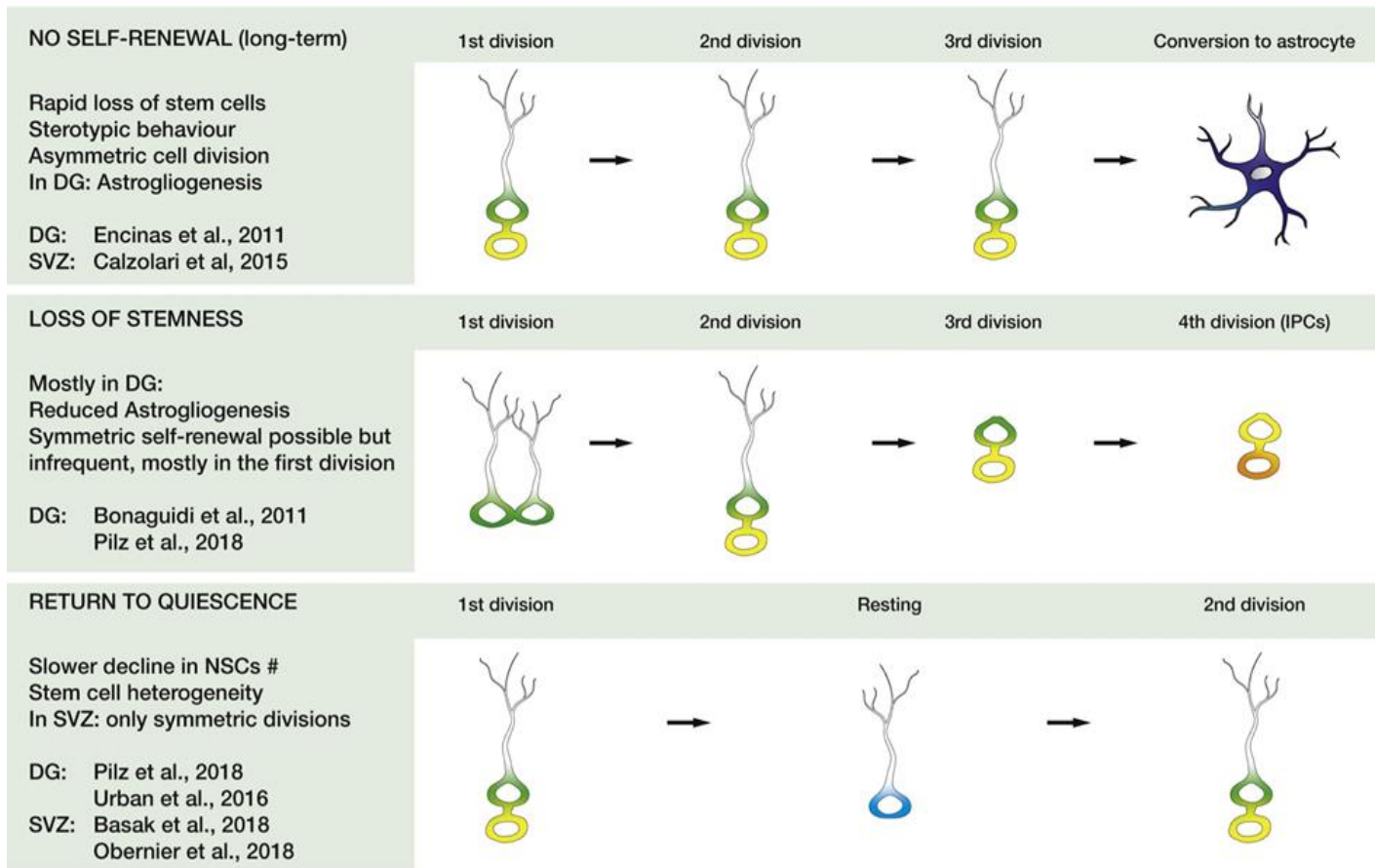


Figure 8: Neural stem cells in different zones have been reported to adopt different modes of division and serve different long-term functions [64].

Lithium and Stem Cell Proliferation

According to a study conducted in 2015, lithium was found to possess the ability to increase proliferation of GFP-MSCs in a dose dependent manner [70]. MSCs can differentiate into neural cells that can replace damaged neural tissue in the brain and spinal cord [71]. The cell survival rate when differentiated into neural cells is relatively low, limiting the ability of MSCs to rectify any damage done to neural cells in the brain or central nervous system [71]. However, in more recent years lithium has been reported to have the capability of inhibiting the apoptosis of neural progenitor cells thus enhancing proliferation and differentiation of neural stem cells [72]. In a study testing the influence of lithium on GFP-MSCs proliferation and neural differentiation potential, it was found that lithium in a 0.1 mM dose promotes proliferation and neural differentiation of GFP-MSCs in vitro and promotes cell survival after transplantation into the CNS in rats [70]. This stimulation of neural stem cells explains how lithium can increase brain density and volume in patients with BD and why it has been used as a reliable therapeutic treatment for BD for so long [73]. Lithium also can inhibit the enzyme GSK3 β , which controls many cellular programs that control the growth and differentiation of stem cells [74].

In a study conducted in 2004, short-term lithium was found to induce neurogenesis in rodent striatal injury sites [75]. Neural stem cells were tagged with BrdU labeling and injected into rats. The tagged stem cells were found in a large concentration in the subventricular zone of the rodents [76]. Chronic lithium treatment was also tested. Chronic lithium use was shown to enhance hippocampal neurogenesis in rats, as the number of cells tagged with BrdU dramatically increased in the hippocampus after 28 days of being treated with lithium [76]. Lithium selectively increases neuronal differentiation of hippocampal neural progenitor cells, implying that lithium may also affect the way neural cells interact with each other [76]. It was also found that in aged mice,

chronic lithium treatment is not as effective [76]; this finding highlights the importance of early diagnosis when treating neuropsychiatric disorders such as BD and AD.

In 2004, gray matter volumes were measured in patients with BD that were treated with lithium, patients with BD who were not treated with lithium, and healthy individuals [77]. Cingulate cortices were measured in all participants of the study [77]. It was found that untreated bipolar subjects had smaller left anterior cingulate volumes compared to healthy subjects and lithium treated subjects [77]. In 2007, it was found that lithium increases gray matter density in people with BD [78]. 28 patients with BD and 28 healthy control patients were studied [78]. Greater cortical gray matter density was found in the patients with BD that were treated with lithium when compared to the 28 healthy control subjects [78]. This data suggests that lithium increases stem cell proliferation and could potentially be used as a drug to enhance the therapeutic efficacy of MSCs transplantation therapy in CNS disorders, such as AD [78,79].

Clinical Studies - Chronic Lithium Use and the Development of Dementia

The high mortality rate of dementia and all its types including AD has had a tremendous public health impact. There is not currently a disease-modifying treatment available for dementia, however, chronic use of lithium has shown potential as a treatment option in recent studies. In a study published in 2022, 548 patients who were exposed to lithium and 29,070 patients who were not exposed to lithium between January 1, 2005, and December 31, 2019, using data from electronic clinical records of secondary care Mental Health (MH) services in Cambridgeshire and Peterborough NHS Foundation Trust were analyzed [80]. Over the course of the study, it was found that there was an association between lithium use and a decreased risk of developing dementia [80]. While there were limitations to this study including the fact that 73% of the patients in the lithium-exposed group had BD, a significant risk factor for dementia, other studies investigating the relationship between chronic lithium use and dementia have had similar results [80].

Gerhard, et al., conducted a study in 2018 that examined a cohort of individuals over 50 years of age that have been diagnosed with bipolar disorder and who did not receive dementia-related services during the prior year [80]. Each follow-up day was classified by past-year cumulative duration of lithium use and anticonvulsants, which are commonly used as mood stabilizers, served as the negative control [80]. The purpose of this study was to investigate the association between lithium and dementia risk in a cohort of older individuals with bipolar disorder who were at higher risk of developing a form of dementia [80]. The findings of this study are consistent with the belief that chronic lithium usage will decrease the incidence of dementia in patients with BD [80].

To further test the idea that chronic lithium usage in treatment of bipolar disorders may have benefits in neurodegenerative disorders, Nunes, et al., in 2015 conducted a study on lithium microdose potential in preventing disease development; the aim of this work was to verify the effects of chronic treatment with microdose lithium given before and after the appearance of symptoms in a mouse model of a disease like AD [80]. It was found that transgenic mice treated with lithium for two months showed decreased number of senile plaques, and no neuronal loss in cortex and hippocampus when compared to non-treated transgenic mice [80]. From these results, it can be concluded that this data offers support for the use of lithium in the treatment of neurodegenerative disorders such as Alzheimer's disease.

On the other hand, the proportions of infection, necrotizing enterocolitis, cyanosis, feeding difficulties and hypoglycaemia reduced after KMC was started. These reductions are similar to the results of the others authors; Kalhor M, et al., Lawn E, et al., Adarsh, et al., Hoque, et al., Ellen Bounty, et al., and Conde, et al., who all found that KMC significantly reduces morbidity [11,14-16,19,20].

In addition, there was rather an increase in the duration of hospitalization after the institution of KMC which was not statistically significant. This could be explained by the fact that there were outliers in duration of hospitalization. This is similar to the finding of Boundy, et al., who found that duration of hospitalization did not significantly change between those cared for through KMC and those cared for conventionally. This is however different from the results of Jafari, et al., Kondapali, et al., Shanti, et al., and Kalhor, et al., who found that KMC reduced the length of hospital stay [17,19,21,22]. These studies had either half or double our sample size, which could account for the differences.

We realized a drop in mortality rate by 2.1%. This could be explained by the fact that there was a decrease in infection rate and other complications like necrotizing enterocolitis and hypoglycaemia that are significantly associated with death. This is similar to the findings of Lawn E, et al., Conde, et al., and Boundy, et al., who found that KMC substantially reduces neonatal mortality associated with prematurity and its complications [11,15,16].

We also found that mortality was significantly associated with gestational age; the smaller the gestational age, the more likely the patient was to die. Furthermore, post discharge follow up markedly improved after KMC was started. This could be explained by the fact that mothers were more implicated in the care of their babies, and they understood the need to come back for regular checks.

We also found that exclusive breastfeeding significantly improved after the institution of KMC, both in hospital and at home. This is explained by the fact that in kangaroo position, the babies are close to their mothers' breast and can thus feed at will and as many times as possible. This is similar to the results of Adarsh, et al., Kalhor, et al., Heidarzadeh, et al., Conde, et al., Mahmoud, et al., Hoque, et al., Almeida, et al., Ellen Bounty, et al., Tharashree CD, et al., and Kondapali CS, et al., who found that KMC promoted exclusive breastfeeding in preterm newborns [12-16,19,20,22-24].

Finally, our study revealed that anthropometric measurements (length and head circumference) at discharge were better after the institution of KMC compared to before. This could be due to the fact that babies fed better and developed fewer complications after starting KMC. This finding is similar to those of Rekha, et al., Adarsh, et al., Kondapali, et al., Sarparast, et al., Kalhor, et al., Conde, et al., Hoque, et al., Shanti, et al., and Jafari, et al., who found that KMC improved anthropometric measures (length and head circumference) [14,15,17,19-22,25,26].

Weight was rather found to reduce after KMC was started. This could be explained by the fact that the mean duration of hospitalization in both cohorts was between 12 and 14 days and during this period, babies are still in the physiological period of weight gain (they are gaining the weight they lost in the first week of life). So with KMC, smaller babies can be discharged from the hospital. This finding was contrary to those of Rekha, et al., Adarsh, et al., Kondapali, et al., Sarparast, et al., Kalhor, et al., Conde, et al., Hoque, et al., Shanti, et al., Kanodia P, et al., and Jafari, et al., who found that KMC improved weight at discharge [14,15,18-20,22,25,26]. This difference could be due to the fact that in some of these studies, sample size was higher and KMC was initiated earlier.

Conclusion

The increasing prevalence and extreme public health impact of Alzheimer's disease continues to be a developing problem in Western civilization as no true means of treatment have been implemented to slow or correct the symptoms of this neurodegenerative disease. Individuals with bipolar disorder are at higher risk of developing dementia and its subsets such as Alzheimer's disease. Individuals with Alzheimer's experience pathophysiological effects such as decreased hippocampal volume and neurofibrillary tangles that cause cell dysfunction and cell death leading to loss in cognitive function and physical ability. The comorbidity of bipolar disorder and Alzheimer's disease has led to the investigation of lithium, a drug primarily used to treat psychiatric conditions such as BD, as a potential treatment option for neurodegenerative diseases. The ability of lithium to improve neurogenesis and encourage stem cell proliferation as well as increase gray matter density in damaged regions of the brain has laid the foundation for studies conducted on the association of chronic lithium use and the development of dementia in high-risk individuals. Researchers have found that long-term lithium usage can reduce the incidence of dementia in individuals with bipolar disorder in both animal and human trials. Overall, lithium offers promise as an effective therapeutic approach to treating Alzheimer's disease. Additional research trials are needed to further test the effectiveness of lithium usage in preventing Alzheimer's disease in the general public rather than just individuals with bipolar disorder.

Conflict of Interest

The authors have no conflict of interest to declare.

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