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Causes and Therapy of Depression Posing Risk to Alzheimer's: A Comprehensive Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Depression is a complex mental disorder that not only affects mood but also poses a significant risk factor for the development of Alzheimer's disease. Key findings unravel a bilateral relationship where depression not only emerges as a precursor but also as a consequence of Alzheimer's pathology, thereby creating a vicious cycle that exacerbates the cognitive decay. The review article traverses the landscape of both disorders, elucidating the pathological and biochemical links that interlace their neuropathological signatures. It further reviews the current landscape of treatment modalities and management strategies, positioning non-pharmacological interventions like lifestyle modifications and cognitive therapies at the forefront, alongside conventional pharmacotherapy. A novel angle is provided by the exploration of herbal plants used in treatment, gauging their efficacy and potential as alternative or adjunct therapies. Recent advancements in the therapeutic domain, such as personalized medicine and innovative drug targets, are also highlighted, offering a roadmap for translational research and clinical practice.

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1. INTRODUCTION

Depression is increasingly recognized as a common mental illness among those who have Alzheimer's disease (AD). Numerous researches have examined depression in Alzheimer's disease during the last ten years, concentrating on the disease's causes, epidemiology, clinical correlations, and management [1]. Dementia, affecting 24 million people globally, is projected to increase fourfold by 2050 due to aging populations. Alzheimer's disease is the primary cause in older adults, with other types like vascular, Lewy body, and fronto-temporal dementia being less prevalent. A recent meta-analysis found that major depression rates were 15.9% in all-cause dementia and 14.8% in Alzheimer's disease [2].

Dementia and depression have a complex and dynamic interaction. The belief that it was difficult to discern between early dementia and depression-related cognitive symptoms led to the term "pseudodementia" being used in the past to characterize cognitive impairment in depression. The theory of pseudodementia postulated that cognitive impairment might be attributable to depression rather than dementia if treating depression improved cognitive symptoms. Nonetheless, the term pseudodementia is becoming less popular as knowledge about depression and its links to illnesses like dementia has grown, indicating a greater comprehension of the complexity involved. The goal of this study is to investigate the common pathogenesis of Alzheimer's disease (AD) and late-life depression (LLD). To that end, an overview of the epidemiological data connecting the two disorders is provided. Next, the emphasis will be on the three main neurobiological processes neuro dialysis, cerebrovascular accident, and chronic inflammation that are linked to both AD and LLD [3].

We hypothesize that depression and related diseases make the brain more vulnerable to neurofibrillary plaques and tangles, two pathological consequences of Alzheimer's disease (AD). The threshold for the emergence of behavioural symptoms associated with AD, such as dementia and cognitive loss, is lowered by this increased susceptibility. We also investigate variables including social support, physical and mental activities, and cognitive reserve that may improve resistance to the effects of both AD and late-life depression (LLD). Lastly, we make recommendations for future lines of inquiry to examine these connections and their consequences in more detail.

2. RELATION BETWEEN DEPRESSION AND ALZHEIMER'S RISK

Many studies suggest that depression is associated with an increased risk of cognitive decline and dementia, especially Alzheimer's disease (AD). Scholars have investigated whether depression directly increases the likelihood of getting AD, or if it occurs before cognitive deficits in the illness. The duration between an AD diagnosis and a diagnostic of depression appears to positively correlate with an increased chance of developing AD given in Fig 1, according to a meta-analysis by Ownby et al. (2006) [4]. The results suggest that depression might operate as a stand-alone risk factor for AD instead of being a prodromal symptom. Notable is the association between a later start of Alzheimer's disease and depression that occurred earlier in life (more than 25 years prior to dementia diagnosis).

According to study by Kessing and Andersen, the likelihood of getting Alzheimer's disease increases with every new episode of a mood illness [5]. In particular, they found that for every episode that resulted in a hospital stay, the prevalence of dementia rose by 13% in those with depressive illness. Moreover, there is a high correlation between dementia and depression, according to both clinical and epidemiological evidence. Significant cognitive deterioration frequently coexists with late-life depression, which is defined by its beginning beyond age 50. Individuals with multiple cognitive impairments frequently exhibit deficiencies in attention, language, memory, visuospatial skills, and executive function. Numerous lines of evidence indicate that depression in later life raises the possibility of developing dementia.

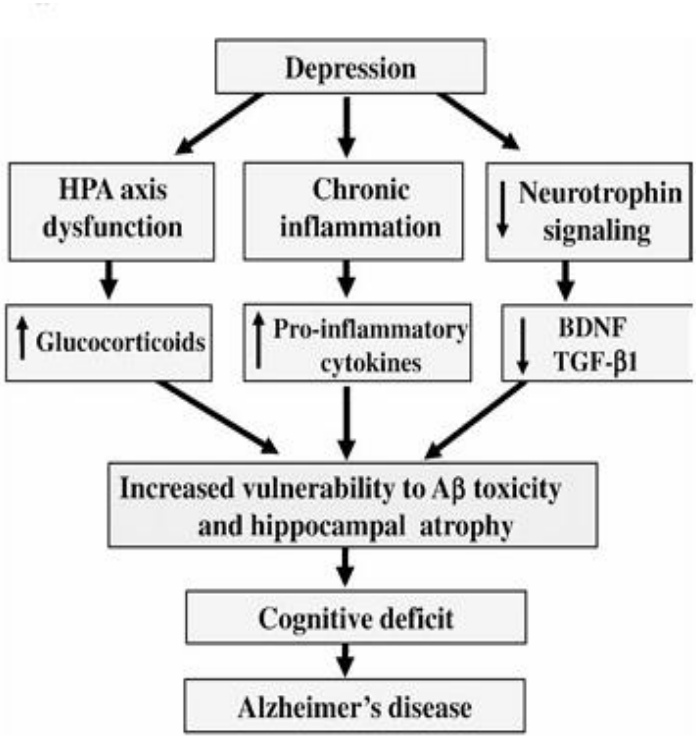


Fig. 1. From depression to Alzheimer's disease: Neurobiological links

Furthermore, neurodegenerative alterations identified in several brain parts of individuals with depression, including the hippocampus, which is frequently among the first regions impacted by Alzheimer's disease. Alzheimer's disease progresses from moderate cognitive impairment to depression symptoms as well. Houde et al. (2008) discovered that in patients with moderate cognitive impairment, prolonged depression lasting two to three years is predictive of cognitive deterioration that results in Alzheimer's disease [6].

Additionally, Modrego and Ferrández (2004) showed that people who suffer from depression and moderate cognitive impairment are greater than twice as apt to acquire Alzheimer's disease than people who is devoid of depression, especially if they do not respond well to antidepressants (7). Interestingly, depression impacts the clinical course of Alzheimer's disease and affects a considerable fraction of people with the condition. Alzheimer's disease patients who also have serious depression show signs of increased neurofibrillary tangles and neuritic plaques, two of the illness's main pathological characteristics that are most prominent in the hippocampus, along with a faster rate of cognitive impairment [8].

2.1 Pathological and Biochemical Linkage

Significant neuronal death is a characteristic of Alzheimer's disease (AD), yet depression usually does not show this kind of widespread loss. Nevertheless, studies show that pro-apoptotic markers are upregulated and anti-apoptotic markers are downregulated in animal models of depression. Furthermore, apoptotic dysregulation is further implicated in the etiology of depression since postmortem investigations on depressed patients have shown lower levels of extracellular signal-related kinase 1/2, which is essential for neuroplasticity and cell survival.

Reduced levels of monoamines are caused by neurodegeneration in Alzheimer's disease (AD) in key areas such the hippocampus, locus coeruleus, and brainstem raphe nucleus, all of which are linked to the development of depression. Moreover, signalling for corticotropin releasing hormone (CRH) may be interfered with by neurodegeneration in AD. On the other hand, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis results in greater levels of cortisol and CRH, which are linked to a higher risk of AD.

Reduced levels of neurotrophic factors result in diminished neurogenesis and poor neuroplasticity, which makes them essential for the survival of neurons. Both the onset of depression and the biological mechanisms behind antidepressant medication work revolve around these processes. Changes in the neurotrophic factor BDNF signalling pathway in AD cause apoptosis by promoting the amyloidogenic pathway in hippocampus neurons. In some animal models of AD, BDNF also has neuroprotective properties. BDNF gene transfer can improve cell signalling, reverse synaptic loss, regulate gene expression, and restore cognitive function in amyloid transgenic mice. Moreover, BDNF improves age-related cognitive decline, reverses neuronal atrophy, and stops lesion-induced neuronal death in adult rats and primates.

Pro-inflammatory cytokine levels are elevated in AD and depression, affecting neuronal function in important brain areas such as the hippocampus and prefrontal cortex. Patients with AD and moderate cognitive impairment had higher levels of monocyte-produced cytokines, including IL-1β, IL-6, IL-12, and TNFα. These cytokines affect growth factors and central neurotransmitters, which are important for the severity of depression. Interestingly, in AD models, IL-1β impairs BDNF signalling. Moreover, pro-inflammatory cytokines exacerbate neuronal damage by inducing the generation of reactive radicals and other neurodegenerative factors [9]. Some of the common factors shared are discussed and given in Fig 2.

Decreased levels of anti-inflammatory cytokines, alongside heightened levels of pro-inflammatory cytokines, are correlated with depression and Alzheimer's disease (AD). Reviewed to similar-aged controls, AD patients have increased anti-inflammatory responses, whereas depressed individuals show lower levels of IL-4 and IL-10. Studies indicate that IL-10 gene expression isn't always linked to AD, even if protein levels vary. Lower concentrations of the anti-inflammatory cytokines IL-4 and IL-10 are also seen in animal models of AD. Therefore, it is still unclear exactly what functions anti-inflammatory factors serve.

According to Suranyi-Cadotte et al., platelet 3H-imipramine binding is decreased in sad people but not in AD patients, indicating that it may be a helpful marker to distinguish AD from serious depression. Nonetheless, reduced central nervous system (CNS) or platelet serotonergic activity is seen in both depression and AD, suggesting that the serotonergic system is involved in both disorders [10]. Learning and memory regulation are influenced by serotonin. Patients with AD have demonstrated improved cognitive function after using antidepressants that target monoamines, such as sertraline and fluoxetine.

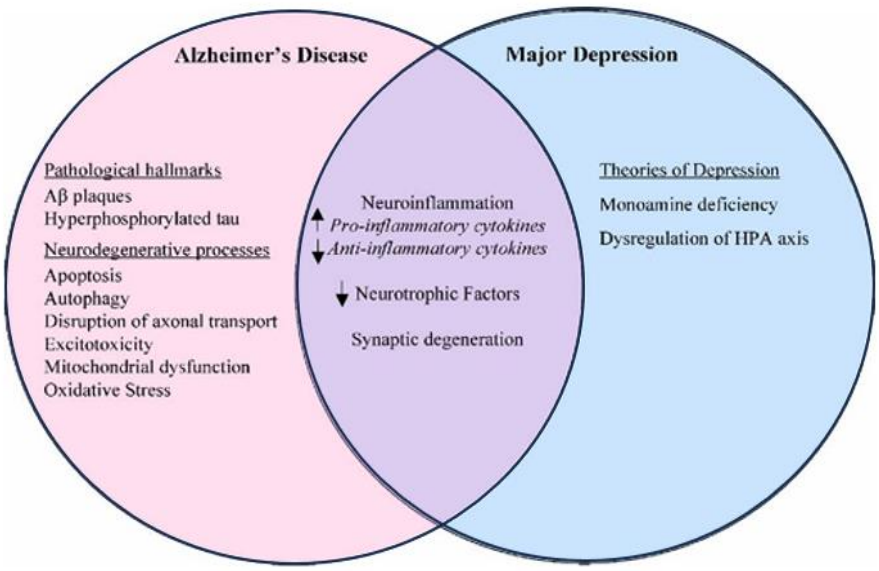


Fig. 2. Common factors shared between depression and AD [9]

Ladostigil and other multifunctional medications show promise in the treatment of dementia and depression. Antidepressants such as paroxetine and fluoxetine have been shown in animal experiments to be effective in reducing symptoms associated with AD and depression. These results point to antidepressant therapy's therapeutic potential in the treatment of both conditions and raise the possibility of a connection between depression and AD.

3. NEUROPATHOLOGY

3.1 Depression and AD's Monoaminergic Systems

Subcortical nuclei alterations are believed to be a major factor in the development of Late-life depression and Alzheimer's disease (AD). One of the main features of AD is the disintegration of subcortical populations, especially the monoaminergic and cholinergic systems. These systems are especially vulnerable to harm in AD because their lengthy, poorly myelinated axons extend far to cortical and hippocampus areas.

Preliminary studies revealed significant reductions in nucleolar volume and total RNA levels in the brainstem of AD patients in both norepinephrinergic and serotonergic neurons. Additionally, decreased inhibitory G-protein-linked 5-HT1A receptors have been observed in the hippocampus tissue of Alzheimer's disease patients with comorbid depression during postmortem examination. Certain brainstem monoaminergic nuclei, especially the rostral raphe, are selectively vulnerable to tangle development; plaque and tangle expression are seen in other brainstem nuclei of AD patients. But research on depression in later life and Alzheimer's disease (AD) has shown less conclusive findings; histological alterations in AD individuals with and without depression frequently do not vary.

Patients with Alzheimer's disease (AD) consistently lose 5-HT neurons. Nevertheless, there was no difference in neuron count between the groups of individuals that were classified as depressed and those that were not. Comparably, lower binding of the 5-HT transporter protein, which is linked to 5-HT function, was seen in AD; no higher decreases were observed in AD groups compared to those without depression. Furthermore, no further neuronal loss was found in individuals with AD and depression, despite the fact that AD patients had a significant reduction in pigmented norepinephrinergic neurons in the locus ceruleus.

According to a new study, there is no connection between depression symptoms and brainstem tangles. On the other hand, increased levels of depressed symptoms were linked to a decreased number of immunoreactive neurons expressing tyrosine hydroxylase in the ventral tegmental area, suggesting that the mesolimbic dopamine pathway is involved in late-life depression. There are links between the components of this route and mood control, and it is essential to reward processing. Nonetheless, there have been limited and inconsistent postmortem examinations of the dopaminergic system linked to depression.

The high prevalence of depression in neurodegenerative disorders, particularly in those that affect dopaminergic transmission (e.g., dementia with Lewy bodies and Parkinson's disease, where depression affects 50–60% of patients), and the fact that depression is more persistent than Alzheimer's disease (AD) make it imperative to investigate the role of dopamine in affective dysregulation in these conditions.

Despite the lack of conclusive evidence linking pathological alterations in monoaminergic nuclei to late-life depression, particularly within dementia, treatment strategies for depression in Alzheimer's disease (AD) are based on the "catecholamine hypothesis of depression," as put forth by Schildkraut in 1965. Currently, the cornerstone of treatment for depression in dementia patients is still sertraline and other selective serotonin reuptake inhibitors (SSRIs). Until recently, there was uncertainty about the extent to which standard monoaminergic drugs may effectively alleviate depressed symptoms in individuals suffering from dementia. Two recent, significant investigations, however, have shown the opposite.

Sertraline, a popular SSRI antidepressant, was compared with a placebo in the DIADS-2 research to treat depression in AD patients. However, after 12 or 24 weeks, there was no discernible difference in symptoms, response, or remission rates. Additionally, they saw a rise in side effects with sertraline, which led them to conclude that it is not appropriate for depression in AD patients. In a similar vein, the UK-based SADD research discovered that two other antidepressant classes, sertraline and

mirtazapine, were equally ineffective when compared to a placebo and more likely to cause unwanted consequences.

3.2 Involvement of Glutamatergic Signalling in the Pathogenesis of Depression

Reassessing treatment and research approaches for depression in dementia seems necessary given the insufficient efficacy of monoaminergic agents and the absence of clear proof of pathological alterations in monoaminergic circuitry in brain tissue of late-life depressed individuals, especially in the contextual framework of AD. There has been an increasing amount of interest lately in investigating the possible use of substances that influence glutamate, the principal excitatory neurotransmitter in the brain. Ionotropic receptors are important for rapid excitatory neurotransmission in the central nervous system, whereas metabotropic receptors also involved in glutamate signalling at pre- and post-synaptic locations.

N-methyl-D-aspartate (NMDA), Alpha-amino-3-hydroxy-5-methylisxazole-4-propionic acid (AMPA), and kainite receptors are three subfamilies of ionotropic receptors that have been found. Novel models of depression and antidepressant treatments have been developed by manipulation of NMDA receptor complex and the related molecular pathways connected with neural and synaptic plasticity. Glutamatergic abnormalities are found in individuals with significant depression in a number of imaging and postmortem investigations. Magnetic resonance spectroscopy has shown elevated cortical glutamate levels. Studies carried out following death have demonstrated elevated glutamate content in frontal cortex along with a significant downregulation of mRNA transcripts for vesicular glutamate transporters and excitatory amino acid transporters, which are critical for the rapid release of glutamate from synapses. These modifications are correlated with modifications in NMDA, AMPA, and kainate receptor expression and post-synaptic receptor binding in severe depression.

Preclinical models suggest that NMDA-mediated processes are crucial to the etiology and management of depression. Unavoidable stress interferes with the NMDA receptor-regulated long-term potentiation of hippocampus neurons. Additionally, data point to role of glycine recognition sites on NMDA receptors in modulating anxiety-related behaviours. In animal models, functional antagonists that target different locations on NMDA receptors, including ionophore recognition sites, polyamine, glutamate, glycine, and divalent cation (Zn^{2+}), show fast anxiolytic and antidepressant effects. Furthermore, in preclinical models, chronic administration of conventional monoamine-acting antidepressants, as opposed to acute administration, modulates NMDA receptor activity, suggesting rather than having a direct impact on the extracellular synaptic monoamine levels, therapeutic effects are the result of processes of neuronal adaptation.

A growing body of research indicates that the changes in morphological alterations and synaptic function deficiencies, which can start years before cell death, are what lead to the clinical symptoms linked to Alzheimer's disease (AD). There is a clear correlation between synaptic degeneration indicators and cognitive impairment. It has been demonstrated that vesicular proteins—such as synaptotagmin, Rab3a and synaptobrevin, and pre- and post-synaptic proteins—such as drebrin synaptophysin, synaptopodin and neurogranin—have anomalies in a number of brain regions affected by AD patients. Preliminary research on glutamate levels in AD was followed by biochemical tests that reveal decreased glutamatergic transmission. Additionally, it has been shown that AD is associated with decreases in the exhibition of AMPA and NMDA receptors, while kainate markers remain unaffected. This data implies that glutamatergic dysfunction, both pre- and post-synaptic, influences neurite outgrowth, neurogenesis, neuronal cell survival, and synaptogenesis in addition to playing a role in the pathogenesis of AD.

During the early stages of Alzheimer's disease (AD), populations of hippocampal glutamatergic cells in the entorhinal cortex and subiculum disappear, while GABAergic system is mostly spared. The alterations linked to astroglial atrophy cause disruptions in synaptic connection and neurotransmitter balance, which in turn intensifies glutamate-mediated neurotoxicity and ultimately results in neuronal death. Increased Ca2+ levels brought on by excessive NMDA receptor activation injure cells by generating free radicals and initiating proteolytic processes that might lead to cell death or injury. Ionic homeostasis is changed by decreased glutamate

clearance and release resulting from disrupted energy metabolism in AD.

As a result of the displacement of the Mg2+ block from the NMDA receptor, damaged neurons become depolarized, which permits excessive activation of glutamate receptors. The cognitive impairment associated with AD is mostly caused by this aberrant state, which disrupts NMDA receptor signalling and the receptor's ability to produce long-term potentiation (LTP).

Excitotoxic events can cause neuronal death and injury as a result of synaptic glutamate buildup and sustained receptor activation. Several lines of evidence point to the critical role glutamate-mediated excitotoxic damage plays in AD. Glutamate-mediated neurotoxicity in vitro has been demonstrated to be enhanced by elevated intracellular Ca2+ levels and oxidative stress induced by Aβ. Moreover, Aβ has a major effect on glutamatergic signaling associated with NMDA receptors, which leads to cognitive deterioration, more specifically in the entorhinal and frontal cortical areas of patients with Alzheimer's Disease (AD). As a result of downregulated glutamate transporters and Aβ's ability to either promote or reduce glutamate reuptake, AD pathogenesis may be exacerbated by increased tau hyperphosphorylation and excessive glutamatergic activity.

3.3 Disrupted NMDA Receptor Signaling: Linking Depression and Alzheimer's

Given that pivotal role glutamatergic transmission plays in both Late-life severe depression and Alzheimer's disease (AD), there may be certain signal transduction processes shared by the two conditions. The antidepressant and antidementia characteristics exhibited by NMDA receptor antagonists suggest that they may have similar therapeutic applications. But NMDA receptor inhibition is probably not the only factor contributing to the therapeutic effect. Thus, it is important to study how these neuroadaptive mechanisms impact cellular signaling networks. Studies examining the molecular mechanisms underlying neuroplasticity, particularly synaptic plasticity, and the subsequent molecular processes of antidepressant action have repeatedly demonstrated similarities.

Glutamate levels have been discovered to be directly impacted by modifications in the HPA axis' function, and in animal stress models that mimic depressive states, alterations in the proteins associated with glutamatergic signalling have been observed. Under depressed scenarios, glutamate is changed into the non-toxic amino acid glycine by the enzyme L-glutamate-ammonia, and important glutamate transporters (SLC1A2 and SLC1A3) have been shown by microarray analysis to be significantly downregulated cortically. These changes may increase the amount of extracellular glutamate, which might lead to excitotoxic reactions and affect the effectiveness of glutamate transmission.

Glutamatergic signaling abnormalities may cause excitotoxic damage as well as hinder vital restorative or compensating mechanisms that are required for brain healing. Higher intracellular calcium levels, mitochondrial damage, generation of free radicals, immunological changes, and faster cell aging are some examples of this. For example, glutamate/GABA transmission controls the production of brain-derived neurotrophic factor (BDNF), a key regulator of synaptic plasticity, neuronal survival, and differentiation. Besides its known function in cell survival, BDNF also plays a critical function in higher order cognitive phenomena such as behaviour, memory, and learning.

Electroconvulsive treatment and antidepressant medications target brain-derived neurotrophic factor (BDNF) because alterations in its production and activity are frequently seen in AD and depression. Amyloidosis (AD) and late-life depression are linked to genetic differences in BDNF. Neuroplasticity, growth, and survival are among the cellular processes that are influenced by growth factor signaling pathways, which include those involving BDNF. The signaling pathways that result in the production of BDNF are initiated by the activation of NMDA receptors. It is therefore probable that disease in glutamatergic pyramidal projection cells is caused by abnormalities within the NMDA receptor complex in depression, which impacts resilience and neuronal plasticity in particular. In affective circuitry regions like the dorsolateral prefrontal cortex (DLPFC) and orbitofrontal cortex (OFC) given in Fig 3.

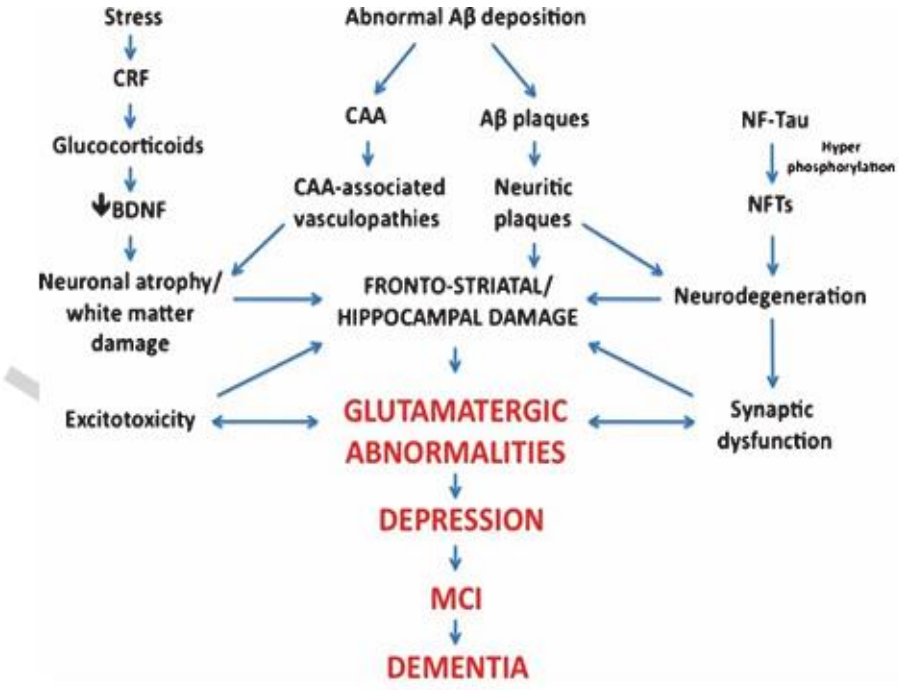


Fig. 3. Schematic diagram showing pathological cascade involved in depression in dementia [11]

The NMDA antagonist ketamine's rapid antidepressant impact is attributed to biological processes that have identified prospective therapeutic targets related to the management of Alzheimer's disease (AD). One such target is the mammalian target of rapamycin (mTOR) signaling pathway, which is crucial for maintaining synaptic connections and is a major regulator of protein production. Two signaling pathways, phosphoinositide-3-kinase (PI3K) and Akt/protein kinase (Akt/PKB), lead to mTOR signaling, which integrates inputs from NMDA, metabotropic glutamate, and dopaminergic receptors in addition to BDNF. Remarkably, depressed suicide victims exhibit a significant decrease in Akt activity in the prefrontal cortex.

Neural diseases, memory loss, and alterations in synapses are all associated with mTOR signalling. As per recent study, ketamine and another NMDA antagonist, Ro-25-6981, boost the activation of the mTOR-regulated pathway, which promotes the development of fresh synapses in rat prefrontal cortex and enhances synaptic signalling proteins. The mTOR inhibitor rapamycin inhibited this action and kept ketamine-induced synaptogenesis from happening. Similarly, MK-801, another NMDA receptor antagonist, was shown to activate mTOR and related proteins, suggesting that NMDA antagonism has a common mechanism. After-death AD brains have been shown to have altered mTOR-regulated pathways, including Akt and mTOR itself., supporting the theory that mTOR dysregulation is linked to Alzheimer's disease.

To summarize, investigation of treatment-resistant depression, as shown in Alzheimer's disease (AD), has sparked creative research that goes beyond the monoaminergic theory and has potential for discovering new biomarkers and treatments. Evidence points to a convergence of the neurobiology of depression and AD through common participation in NMDA-regulated signalling pathways. With the prevalence of AD increasing worldwide, these novel treatments may provide a substantial therapy challenge.

3.4 Hypothalamic-pituitary-adrenal (HPA)-axis Dysfunction, Inflammatory Pathway, and Neurotrophin Deficiency

Both chronic depression and Alzheimer's disease (AD) patients exhibit dysfunction of the HPA axis, which results in neurodegeneration through excessive glucocorticoid release. There is ample evidence linking depression and AD to elevated glucocorticoid levels in plasma and cerebrospinal fluid (CSF). On the other hand, AD and major

depression have different patterns of hyper cortisolemia: whereas depression exhibits chronic elevation, AD exhibits phasic increase. Both idiopathic depression and depression in AD have different pathogenic pathways, according to direct data. Cortisol levels in AD patients are more than twice as high as in controls, however studies comparing the CSF cortisol levels of depressed and non-depressed patients did not find any statistically significant differences. Investigations looking at plasma cortisol levels in AD patients with and without depressive symptoms revealed similar results.

The pathogenesis of depression and Alzheimer's disease (AD) is significantly influenced by the activation of inflammatory pathways. Proinflammatory cytokines such as TNF-, IL-1, IL-6, and IFN- may stimulate amyloid-β formation in astrocytes and microglia and also raise the expression of the precursor protein for amyloid-β. These cytokines are frequently elevated in depressed people. On the other hand, changes in AD-related amyloid-β and phosphorylated tau may cause astrocytes and microglia to generate more proinflammatory mediator molecules and cytokines. But more research is needed to fully understand the precise function that the inflammatory system plays in depression, especially in AD patients. Furthermore, an increasing amount of data points to the impairment of neurotrophins in AD and depression, namely brain-derived neurotrophic factor (BDNF), which is broadly distributed in the CNS.

Hippocampal BDNF levels consistently decline in both postmortem investigations of depressed persons and animal models of depression. Nevertheless, electroconvulsive therapy and antidepressant medication can successfully stop this decrease. On the other hand, BDNF mRNA expression and protein levels in different postmortem brain areas are lower in AD patients. In rodent and primate models of AD, the administration of BDNF has been demonstrated to restore neurodegenerative alterations caused by exogenous Aβ42.

Multiple factors are involved in the complex mechanism of depression in Alzheimer's disease (AD). Inflammatory processes, neurotrophin insufficiency, and dysfunction of the HPA axis can all lead to neuropathological alterations that may be important to understand and target for future therapy. However, direct data supporting this relationship is few.

3.5 Aβ accumulation and Tau Pathology

Animal models of depression have provided ample evidence of stress-induced tau pathology and Aβ buildup, which are essential for cognitive impairment. Furthermore, rats administered with soluble Aβ may exhibit behaviours resembling depression, along with regional variations in neurotrophin expression and serotonin neurotransmission. Studies on the connection between AD pathology and depression symptoms have been conducted. In comparison to AD patients without concomitant depression, one research found that the former had higher levels of neuritic plaques and neurofibrillary tangles. The hippocampal plaque and tangle development was also higher in AD patients with a history of depression, especially in those who were also depressed at the time of diagnosis. Nevertheless, a different research with senior Catholic clergy members discovered no connection between clinical AD patients' sad symptoms and neuritic plaques or neurofibrillary tangles in the brain.

These prospective cohort studies look mainly at the connection between depression and the neuropathological alterations that follow in AD. Cross-sectional studies could not, however, provide conclusive evidence linking neurofibrillary tangles or amyloid plaques in CSF to depression symptoms in AD patients. Thus, while depression may play a role in the pathological alterations of AD, further research is needed to determine whether the neuropathology of AD or other processes underlie depressed symptoms in clinical AD.

3.6 Vascular-related Risks

Depression and Alzheimer's disease (AD) are associated with vascular risk factors, such as dyslipidemia, diabetes, hypertension, cardiovascular disease, and stroke. Numerous AD patients also have mixed forms of vascular dementia, pointing to a possible link between depression and cerebrovascular illness that is known as "Vascular Depression". There are several theories as to how this happens, including disruption of the brain's circuitry, inflammation, and decreased blood flow. Studies have shown that individuals with Alzheimer's disease (AD) who have had a stroke are more likely to experience despair and apathy, maybe as a result of damaged brain circuitry. This is further supported by recent studies that demonstrate how asymptomatic stroke and hypertension exacerbate depression symptoms in AD patients.

In individuals with both Alzheimer's disease (AD) and vascular dementia, spontaneous brain emboli are a major source of vascular damage to fronto-striatal pathways and are substantially correlated with clinically meaningful depressed symptoms. Depression in AD is thought to be caused by a similar process to vascular depression, in which white matter lesions and ischemia damage brain connections that are important in mood regulation. Nonetheless, contradictory findings from other longitudinal and cross-sectional research cast doubt on the contribution of vascular risk factors to the modification of depression in AD. However, these results may have therapy ramifications since vascular risk factors may be efficiently addressed, which may reduce depression in AD patients.

3.7 Genetic Factors

Depression and Alzheimer's disease (AD) have intricate genetic pathways. Current research has looked into the possibility of a genetic risk factor for depression or AD being correlated with depression that occurs concurrently in AD patients. Across several investigations, depression in AD has been consistently associated with a greater frequency of the APOE4 allele, regardless of the severity or duration of AD. This implies that depression in AD may be specifically predicted by the APOE4 genotype. Furthermore, depression symptoms in AD have been linked to genetic differences in BDNF, an essential neurotrophin.

Numerous investigations have revealed a noteworthy correlation amidst depression in individuals with AD and A allele of the BDNF G196A polymorphism, which affects depressive symptoms and antidepressant responsiveness. The BDNF gene's C270T polymorphism, however, does not seem to have an impact on depression linked to AD. Few studies have looked at BDNF levels in the setting of AD-related depression, despite the gene's potential significance. Of those that have, only one found no difference in BDNF levels between depressive AD patients and their non-depressed siblings in the cerebrospinal fluid. Additionally, a higher incidence of depression in AD has been associated relating transforming growth factor-1 (TGF-1) gene's CC 569 genotype. Further studies have investigated the relationship between depression susceptibility in AD and genetic differences in neurotransmitters, receptors, or transporters.

There have been contradictory results with respect to serotonin-related pathway in depression in AD patients. When 5-HT2A and 5-HT2C receptor gene polymorphisms were examined, one research indicated a substantial increase in depression among AD patients; however, other studies that looked at 5-HTTLPR, 5-HT2A, and 5-HT6 receptors found no connection. Other neurotransmitters, such choline and dopamine, have been the subject of comparatively few research, and hence have not gotten as much attention as serotonin. The polymorphism of the choline O-acetyl transferase (CHAT) gene was shown to be substantially correlated with comorbid depression in AD in a longitudinal cohort investigation. That same study, however, did not discover a connection between depression and the exon III polymorphism of the dopamine D4 receptor (D4DR).

Depression and the dopamine receptor 3BalI polymorphism were shown to be directly correlated in a large cohort research that included over 1,000 probable AD patients and examined 11 variants from 10 genes. Using the Neuropsychiatric Inventory as a screening tool, this study concentrated a great deal on complicated psychosocial symptoms in AD patients. The dopamine transporter (DAT1) gene was not linked to concomitant depression in AD patients, notably, according to a previous study that used the same methodology. Furthermore, rs10410544 TT carriers exhibit protection against depressive symptoms, providing further evidence of a link between depression in AD and the Sirtuin2 (SIRT2) gene polymorphism. Depression is a prevalent and crippling symptom of AD, and these genetic connections shed important light on the molecular basis of the condition [12].

4.THERAPEUTIC APPROACHES

4.1 Anti Depressants

Antidepressant trials have evaluated a variety of medications targeting different neurotransmitter systems. These include selective serotonin reuptake inhibitors (SSRIs) like citalopram, fluoxetine, and sertraline; the noradrenergic and specific serotonergic antidepressant mirtazapine; and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine. Additionally, classic antidepressants such as tricyclic antidepressants (TCAs) like imipramine and clomipramine, as well as the reversible selective monoamine oxidase inhibitor moclobemide, have been studied. Detailed characteristics of these antidepressant studies can be found in Table 1 [13].

Table 1. Features of Anti-depressant studies

Design	Depression diagnosis/ measures	Duration of outcome	Negative result	Positive result
Open-label study of ecsitalopram	NIMH consensus criteria	8 weeks	_	Efficacious and safe
Open-labelled study with milnacipran	HRSD-17	12 weeks	_	There was a notable improvement observed in depressive suicidal tendencies, loss of interest, psychomotor retardation, psychic anxiety, gastrointestinal symptoms, general somatic symptoms, and hypochondriasis.
Open-labelled study with milnacipran	HRSD	12 weeks	Mild hypomanic state in two patients and daytime somnolence in one patient	Ten out of eleven patients showed a response, with a decrease in scores of over 50%, and eight out of eleven achieved remissions, indicated by a HAM-D score of 7 or lower.
Moclobemide (400mg daily) or placebo assigned to dAD (DSM-III for AD) versus major depressive disorder patients with cognitive decline, no dementia	HRSD-24, 17	42 days, large sample, no significant differences in side-effects	_	Both the dAD and major depression groups exhibited significantly greater improvement (p=0.001).
AD patients meeting DSM-III criteria for depression or not, received imipramine (83mg/d) or placebo	HRSD DSM-III	8 weeks	_	Significant improvement in both groups
Clomipramine (100mg/d) or placebo	HRSD	6 weeks	_	While both groups experienced a significant improvement in mood over the 6-week period, the clomipramine group showed a notably greater enhancement compared to the other group.
Venlafaxine (75mg/d) or placebo	DSM and CSDD	6 weeks	There were no significant variations in response between the groups, as assessed by MADRS	_
Fluoxetine (40mg/d) or placebo	HRSD, DSM-IV,	6 weeks, minor or major depression	There were no notable distinctions between the drug and placebo groups.	_
Citalopram (max 30mg/d) or placebo	MADRS	44 weeks, moderate AD/SDAT or VaD	There were no significant improvements in patients with VaD	Significant improvement in depressed mood, emotional bluntness, confusion, irritability, anxiety, fear/panic, and restlessness
Sertraline (target dose 150mg per day), mirtazapine (45mg), or placebo	CSDD (>8)	39 weeks, elaborating design	The treatment demonstrated lower efficacy than the placebo, with a higher occurrence of adverse events.	_

Design	Depression diagnosis/ measures	Duration of outcome	Negative result	Positive result
Sertraline (95 mg/d), or placebo	HRSD, CSDD, NPI	12 weeks	_	Sertraline was preeminent to placebo
Sertraline (mean 81 mg/d), or placebo	CSDD, HRSD	12 weeks	_	The sertraline group exhibited a more significant decrease in CSDD from baseline compared to the placebo group.
Sertraline (mean 92 mg/d), or placebo	CSDD, CGIC, ADCS	12 weeks	There were no discernible differences between the groups in depression rates. However, adverse events were more prevalent.	_
Sertraline, venlafaxine and desipramine (all, at 150mg/d max doses)	HRSD	12 weeks	_	All significantly effective. Sertraline overall superiority.
Sertraline, or placebo	CSDD	24 weeks	The treatment demonstrated inefficacy compared to the placebo, with a higher incidence of adverse events.	_
Sertraline (max 100mg/d) or placebo	CSDD	8 weeks, nursing home patients	Sertraline showed no significant benefits over placebo	_

Table 2. Features of acetyl-cholinesterase inhibitors studies

Approach	Diagnosis of depression/ measures	Duration of Outcome and comments	Negative Effect	Positive Effect
Research with rivastigmine	RMBPC	Thirty months, out patients	Worsening depressive behaviour	_
Administration of donepezil in an open-label format, followed by a random assignment.	NPI	The 20-week study showed a 0.39 improvement effect for the mood-encoding factor, with psychosis, agitation, frontal lobe function, and appetite and eating disorders being the other four factors.	The majority of patients experienced full or partial relief from depression symptoms.	_
Rivastigmin study in an open-label format	CERAD and DSM-Ⅳ Modified DSM-IV criteria and Dysphoria scale for MDE in AD	Six months	_	Significant decrease in the progression of depression.
Galantamine naturalistic study.	CIBIC-plus	Six months, modest effects on behavioural deterioration	_	Intermediate stability on mood/behavioural
Study utilizing donepezil in a cross-sectional design.	NPI	Prior to treatment, subjects who reacted positively after 12 weeks showed a significant increase in cerebral blood flow in the premotor and parieto-temporal cortices.	_	Thirty percent of patients exhibited a behavioural response

Approach	Diagnosis of depression/ measures	Duration of Outcome and comments	Negative Effect	Positive Effect
The study examines the comparison of cases and controls related to the administration of donepezil.	CERAD (CBRSD)	Twelve months	_	Moderate positive result
Placebo or Donepezil	NPI	Twenty four weeks	_	Notable variances in the efficacy of depression treatments.
Comparison of combined donepezil (10mg daily) plus cognitive treatment versus drug treatment.	GDS	Twelve months	_	Both groups saw improved effective symptoms.

The effectiveness of antidepressants has been studied using a variety of assessment instruments, including the MADRS (Montgomery-Asberg Depression Rating Scale), NPI (Neuropsychiatric Inventory), ADCS-CGIC (Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change), CSDD (Cornell Scale for Depression in Dementia), HRSD (Hamilton Rating Scale for Depression), DSM (Diagnostic and Statistical Manual of Mental Disorders), VaD (Vascular Dementia), NIMH (National Institutes of Health), HRSD-17 (Hamilton Rating Scale for Depression-17 item), dAD (depression in Alzheimer's disease), and HAM-D (Hamilton Depression Rating Scale). Antidepressant effects on depression sufferers, especially those with depression associated with dementia, are the focus of these trials.

4.2 Acetylcholinesterase Inhibitors

Various randomized controlled trials (RCTs) investigating the response of depression in Alzheimer's disease (AD) patients have focused on acetylcholinesterase inhibitors (AChEIs). For details regarding the characteristics of these studies, please refer to Table-2 [13].

Research has examined the effectiveness of acetylcholinesterase inhibitors using a range of assessment tools, such as the Geriatric Depression Scale, Neuropsychiatric Inventory, CERAD (Consortium to Establish a Registry for Alzheimer's disease), CBRSD (Behaviour Rating Scale for Dementia), CIBIC-plus (Clinician's Interview-Based Impression of Change plus Caregiver Input), MDE (Major Depressive Episode), AD (Alzheimer's disease), RMBPC (Revised Memory and Behaviour Problems Checklist), and DSM (Diagnostic and Statistical Manual of Mental Disorders). These trials are intended to assess how acetylcholinesterase inhibitors affect depressed people, especially those with Alzheimer's disease.

4.3 Other Compounds

Table 3. Summary of the characteristics of studies within other compounds group

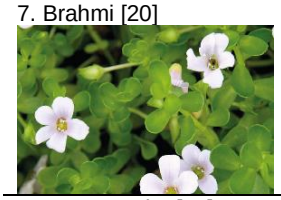
Method	Diagnosis of depression/ measures	Duration of outcome and comments	Positive effects	Negative effects
Open-label study on tandospirone (5-HT1A partial agonist)	NPI	Eight weeks	Prominent progressive sub score in depression.	_
Methylphenidate open-label single-arm study.	AES	Twelve weeks	Remarkable progress in depression	_
Tacrine (160mg/day) or hormone replacement therapy (estrogen+progesterone)	GDS, HRSD	6 months, Improvement impact of the APOE 4 negative genotype on tacrine was observed.	Similar between groups efficacy in mood	_
Pilot RCT- 1-year atorvastatin calcium (80mg o.d.) or placebo	NPI, GDS	Twelve months for GDS and trending (p =0.07) for NPI	Remarkable variation	_
Placebo or Tideglusib	GDS	20 weeks	_	No statistically significant increase in GDS scores was seen.
High-dose supplements of B6, B12, and folate or placebo.	NPI	_	_	Depression
Cerebrolysin (30 mL in 100 mL saline solution IV) or placebo administered five days a week for four weeks.	GDS	Four weeks	_	No remarkable progress.
30 mL intravenous cerebrolysin or a placebo given five days a week for	CSDD	Twenty-four weeks	_	No improvement was seen.

Method	Diagnosis of depression/ measures	Duration of outcome and comments	Positive effects	Negative effects
four weeks.				
EGb 761 (240mg/day) or placebo	NPI	22 weeks	_	Large depression/dysphoria improvements
Nimodipine (90mg/d) or placebo	HRSD	12 weeks	Significantly superior to placebo	_
Ginkgo biloba extract EGb 761(R), donepezil, or their combination.	NPI	22 weeks	_	Insignificant variation between groups
RCT with Rifampin and Doxycycline	CSDD, GDS	Twelve months	_	Ineffective
RCT on decreasing homocysteine levels.	CSDD	Mild to moderate AD or VaD	_	Ineffective
RCT with Rifampin and Doxycycline	Therapeutic ratings	12 months	_	Not effective
Low dose Estradiol and norethisterone, or placebo	HRSD	12 months	A significant main effect on mood, particularly in women who lack the APOE 4 genotype.	_
Placebo or 180 mcg/d DDAVP	HRSD	One patient manifested confusing hyponatremia	_	No substantial improvement observed
Conjugated estrogen (Premarin) 1.25mg/day or placebo	HRSD, HARS	Twelve weeks, No changes in cerebral perfusion rates were identified after 12 weeks.	_	Insignificant progress
Daily intake of 1.7g DHA and 0.6 g EPA (omega-3 group) or placebo	MADRS	6 months	A significant influence on depressed symptoms was reported among non-APOE 4 carriers (72% of the population).	_
Placebo, or Aripiprazole	BPRS, NPI, CSDD	10 weeks, AD with psychosis	Marked progress in depression	_
Placebo, or Lithium	NPI	Ten weeks Single-blind, mild AD	-	Depressive symptoms remained unchanged.
Dimebon (60mg/day), or placebo	11-item behaviour assessment Scale, NPI	26 weeks	Notable enhancement in the NPI- depression subdomain	Depression or depresses mood

Studies involving other substances (that is, not antidepressants or AChEIs). Apathy evaluation scale (AES); Cornell Scale for Depression in Dementia (CSDD); Alzheimer's disease (AD); randomized controlled trials (RCTs); brief psychiatric rating scale (BPRS); Montgomery-Asberg Depression Rating Scale (MADRS); Hamilton Rating Scale for Depression (HRSD); Hamilton Raring Scale for Anxiety (HARS); Geriatric Depression Scale (GDS); Neuropsychiatric Inventory (NPI).

Table 4. Herbal medicines in the management of depression and Alzheimer's

Name of the Plant	Scientific name	Phytochemicals	Mode of action
1.Ashwagandha [14] 	*Withania somnifera*	withanamides A and withanamides C	Effective Inhibition of Acetylcholinesterase and β-Site Amyloid Precursor Protein Cleaving Enzyme (BACE1) (AChE).

2. Ginseng [15] 	*Panax ginseng*	Ginsenoside	Treatment for AD involves cholinergic activation of Rb1, Rg 1-3, Re, and Rh2.
3. Ginger [16] 	*Zingiber officinale*	Shogaol and gingerol	Greatly increases learning and memory rates.
4. Saffron [17] 	*Crocus sativus*	Crocin	In Alzheimer's patients, it lessens cognitive decline. reduces Aβ and enhances Alzheimer's sufferers' cognitive abilities.
5. Ginkgo [18] 	*Ginkgo biloba*	Bilobalideginkgolide	It promotes cell division and neuroblast differentiation in mice. efficient in both treating and preventing AD.
6. Turmeric [19] 	*Curcuma longa*	Curcumin	It prevents Tg2576 mice's brains from developing Aβ oligomer and fibril. lowers the plaque load, Aβ, and the astrocytic marker GFAP in Alzheimer transgenic mice
7. Brahmi [20] 	*Bacopa monnieri*	nicotinine, brahmine, bacosides A and B, herpestine	Nootropic, rejuvenation, Antioxidant, blocks acetyl cholinesterase
8. Lemon Balm [21] 	*Melissa officinalis*	Citronellol, caryophyllene, geraniol, neral, citronella and geranyl acetate	Antidepressant, Nootropic, anxiolytic, anti-amyloid, anti-stress
9. kava [22] 	*Piper methysticum*	It contains 8,11 octadecadienoic acid-methyl ester, 2, 5, 8-trimethyl-1 naphthol and 7 dimethoxyflavanone-5 hydroxy-4' 102.	One of the six primary kavalactones, desmethoxyyangonin, is a reversible MAO-B inhibitor that can raise dopamine levels in the nucleus accumbens. .

5. NON-PHARMACOLOGICAL TREATMENTS IN AD

5.1 Psychotherapy

According to a comprehensive study, behaviour management therapy and focused caregiver education are useful strategies for controlling neuropsychiatric symptoms in dementia [23]. A collaborative care paradigm for Alzheimer's disease has been highlighted by recent research. This model includes caregiver support, early detection and treatment of behavioural disorders, psychoses, and depression, as well as cognitive impairment screening [24].

5.2 Electroconvulsive Therapy (ECT)

According to anecdotal evidence, demented individuals who are seriously depressed and resistant to treatment may benefit from electroconvulsive therapy (ECT). On the other hand, post-ECT confusion is frequently observed in depressed dementia patients receiving ECT, and its intensity is associated with the degree of cognitive dysfunction before to the therapy [25].

6. RECENT ADVANCEMENTS IN THE TREATMENT FOR DEPRESSION IN ALZHEIMER'S

Let's explore some recent advancements in the treatment of depression in Alzheimer's disease (AD):

6.1 Vortioxetine Treatment for Depression in Patients with Prodromal vs Mild Alzheimer's Disease: A Six-Month, Open-Label, Observational Study

The effects of vortioxetine on depressed symptoms, behavioural abnormalities, cognitive function, and activities of daily living in prodromal and mild-to-moderate AD patients with depression are presented in this retrospective observational research. This is the only study that we are aware of that contrasts the effects of vortioxetine on depression and cognition across different AD severity stages. At six months, prodromal and mild to moderate biomarker verified AD patients demonstrated a statistically significant reduction in depressed symptoms, according to the study's main analysis. About two- thirds of the patients showed the response rate, which could be predicted by the baseline severity of depression after accounting for clinical and demographic variables such frailty and multimorbidity.

The mood outcomes data demonstrated a substantial decline from baseline to endpoint in the depression subitems of the Geriatric Depression Scale and the Neuropsychiatric Inventory (NPI), as well as in the NPI total scores. These results were consistent in prodromal and intermediate AD. The MMSE (mini mental state examination) revealed a noteworthy improvement in both groups. The drop in the NPI total score from baseline to endpoint was substantially higher in mild-to-moderate AD as compared to prodromal AD. On the other hand, cognitive function showed a group difference that favoured prodromal AD. Baseline MMSE scores were linked to the improvement in cognitive function, which was not influenced by the antidepressant effect [26].

6.2 Multifaceted Music Therapy for Depression in Dementia: A Network Meta-Analysis of Randomized Controlled Trials

The findings presented in this study offer significant insights into the efficacy of different music therapy interventions for depression in dementia patients. Here's a breakdown and discussion of the main findings and their clinical implications:

Main Findings and Clinical Implications:

1. **Novel Perspective through NMA:** The study offers a unique perspective by utilizing Network Meta-Analysis (NMA) to evaluate multiple music therapy approaches simultaneously. This allows for a comparison of the relative effectiveness of various interventions, which is not feasible with traditional meta-analyses.
2. **Effectiveness of AMT + Sing:** The most effective approach identified is AMT + Sing, indicating that the combination of singing and active engagement in music therapy offers superior benefits for depressive symptoms in dementia compared to other interventions.
3. **Moderate Efficacy Across Music Therapy Methods:** While the effect sizes vary, all assessed forms of music therapy, including RMT and AMT, exhibit a positive effect on depressive symptoms in dementia patients.

4. **Tailored Music Therapy Prescriptions:** The comprehensive assessment provided by NMA is invaluable for clinicians and caregivers in formulating tailored music therapy prescriptions, enhancing the quality of life for patients with dementia-related depression [27].

6.3 The Effects of Light Therapy for Depression in Dementia: A Systematic Review and Meta-Analysis

The systematic review and meta-analysis demonstrate that light therapy yields beneficial effects on sleep disturbances in Persons with Dementia (PwD) by reducing the number of awakenings. However, it does not significantly improve wake after sleep onset or reduce agitation and depression. The long-term impact of light therapy remains unclear due to insufficient evidence. Moving forward, there is a pressing need for more multicenter, well-designed Randomized Controlled Trials (RCTs) with substantial sample sizes to further elucidate the efficacy of light therapy in managing sleep disturbances among PwD. These studies will provide invaluable insights into the sustained effects of light therapy and guide the development of more effective therapeutic interventions for this vulnerable population [28].

6.4 Omega-3 Fatty Acids for Depression in the Elderly and Patients with Dementia: A Systematic Review and Meta-Analysis

The meta-analysis lends support to the targeted utilization of omega-3 fatty acids, particularly DHA, for alleviating depressive symptoms among older adults with MCI. It underscores the necessity for tailored treatment approaches that consider the distinct metabolic and health profiles of elderly individuals. However, the preliminary nature of our findings underscores the need for further investigation, including long-term randomized controlled trials encompassing various dosage regimens. These endeavors are crucial for solidifying our conclusions and optimizing omega-3 supplementation strategies tailored to this vulnerable demographic. Furthermore, the findings suggest broader implications, advocating for a re-evaluation of how omega-3 supplements are conceptualized and administered within the framework of personalized medicine for aging populations [29].

6.5 Neurotechnological Approaches to the Diagnosis and Treatment of Alzheimer's Disease

Neurotechnological Approaches: Researchers have been investigating both invasive and non-invasive neuro technologies to ameliorate AD pathology. These approaches include:

- **Neurostimulation via Optogenetics:** Using light to stimulate specific brain regions.
- **Photo biomodulation:** Applying light to brain tissue to enhance cellular function.
- **Electrical Stimulation:** Delivering electrical currents to modulate neural activity.
- **Ultrasound Stimulation:** Using focused ultrasound waves to target brain areas.
- **Magnetic Neurostimulation:** Applying magnetic fields to influence neural circuits.
- **Nanotechnologies:** Employing nano vectors, magnetic nanoparticles, and quantum dots to deliver therapeutic agents [30].

7. CONCLUSION

The article reviewed shed light on the intricate relationship between depression and Alzheimer's disease (AD), highlighting depression as a potential risk factor for cognitive decline and AD. The systematic review of longitudinal meta-analyses revealed a significant association between depression and AD, emphasizing the importance of clinical measures of depression in assessing this risk. Similarly, a study using post-mortem human brain tissue suggested that depression is a risk factor for dementia rather than an early manifestation of AD. Furthermore, a study tracking individuals over 50 found that depression diagnosis increased the risk of developing dementia, with the risk persisting even 20 years later. Additionally, a cohort study highlighted chronic stress and depression as potential risk factors for mild cognitive impairment and dementia, including AD. In conclusion the review underscores the significance of addressing depression as a potential risk factor for Alzheimer's disease. Understanding the complex interplay between depression and AD is crucial for early detection, intervention, and potentially modifying risk factors to mitigate the progression of cognitive decline. Further research and emphasis on effective therapies for depression not only improve mental

health but also have the potential to reduce the risk of developing Alzheimer's disease and other forms of dementia.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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