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Ashley Park , Gina Finan , Tae-Wan Kim *

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Review

Emerging Therapeutic Opportunities for Alzheimer's Disease Psychosis

Ashley Ye-won Park [1,2], Gina M. Finan [2], Tae-Wan Kim [2,*]

[1] Hankuk Academy of Foreign Studies, Gyeonggi-do 17035, Korea
[2] Department of Pathology and Cell Biology, Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University Irving Medical Center, New York, NY 10032, USA
* Correspondence: authors: twk16@cumc.columbia.edu

Abstract: Psychosis in Alzheimer's disease (AD) is a prevalent phenomenon, marked by delusions and hallucinations, along with other neuropsychiatric symptoms such as agitation, depression, anxiety, and apathy. These neuropsychiatric symptoms, also known as behavioral and psychological symptoms of dementia (BPSD), affect up to 97% of Alzheimer's patients. The presence of psychosis in AD significantly impacts patients' daily lives and places a considerable burden on caregivers. The development of AD-related psychosis (ADP) is influenced by a range of factors, including genetic predispositions and life-acquired factors. AD affects cognitive function and various brain regions, resulting in widespread brain atrophy. In addition to its neurological impact, AD can induce pathological physiological changes that serve as biomarkers for ADP. Research efforts have focused on developing pharmacological treatments for psychosis in AD, aiming to minimize side effects. Brexpiprazole has emerged as a promising medication for ADP, alongside other antipsychotics. Treatment approaches for ADP extend beyond pharmacology, incorporating methods such as sensory stimulation and digital therapeutics. This review will explore the characteristics of psychosis in Alzheimer's disease, the pathological underpinnings of ADP, and the current therapeutic landscape, highlighting emerging opportunities for managing this challenging condition.

Keywords: Alzheimer's disease; psychosis in Alzheimer's disease; neuropsychiatric symptoms; behavioral and psychological symptoms of dementia; delusions; hallucinations; cognitive decline; pharmacological treatment; quality of Life; neurodegeneration

1. Introduction

Alzheimer's disease is the most common neurodegenerative brain disorder causing dementia, gradually onset over an extended period, impairing cognitive function and leading to memory decline. Although Alzheimer's is often considered solely a memory disorder, it is accompanied by psychotic symptoms as well as behavioral and cognitive symptoms. With increasing average lifespan and a growing elderly population, the prevalence of Alzheimer's disease is rising, rendering it a globally significant public health issue. Currently, 50 million people worldwide are affected by dementia, including Alzheimer's disease, and this number is expected to triple by 2050. While Alzheimer's is most prevalent in the United States and Western Europe, the incidence is predicted to rise sharply in low- and middle-income countries, particularly in African nations and India. Alzheimer's disease induces various neuropsychiatric symptoms as cognitive function deteriorates and brain damage progresses, with delusions and hallucinations being the most common. Psychotic symptoms such as delusions and hallucinations can be compared to functional psychoses like schizophrenia. However, Alzheimer's involves a significantly different mental experience, including psychotic symptoms such as depression, anxiety, agitation and aggression. These symptoms and mental changes in Alzheimer's are associated with emotional communication and emotional experience. Impairments in the understanding and expression of emotions, as well as in prosody comprehension, are related to deficits in emotional communication, while mood disorders such as

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depression and anxiety, and symptoms of agitation and aggression, are linked to disturbances in emotional experience. Psychotic symptoms associated with Alzheimer's disease can worsen as the disease advances, significantly impacting the Quality of Life (QoL) of both patients and caregivers. Hence, continuous research is underway to alleviate Alzheimer's psychosis symptoms and slow down the rate of brain atrophy through pharmacological interventions and therapeutic approaches.

2. AD-Associated Psychosis

2.1. Definition, Types and Diagnostic Criteria

Alzheimer's disease is a cognitive disorder characterized by psychosis and various behavioral and psychological symptoms of dementia (BPSD). The typical mental symptoms include delusions and hallucinations, and once these symptoms appear, two-thirds of patients experience them for at least one year. While patterns of relapse and recovery haven't been precisely identified, longitudinal studies have shown that delusions and hallucinations persist for two years in 43% and 73% of individuals, respectively (Ballard 2020). Delusions and hallucinations are associated with different levels of cognitive impairment. Hallucinations show greater cognitive deficits compared to delusions. Delusions are mainly associated with older age and depression, while hallucinations are more closely related to the duration of the illness and worsening symptoms of dementia.

Delusion:

There are various types of delusions associated with Alzheimer's disease, with common and typical symptoms including delusions of theft, abandonment, and spousal infidelity. These simple delusions occur in about 35% of individuals, and in addition to these, more elaborate and specific delusions may manifest, such as beliefs of being duplicated, someone living in the house, or mistaking individuals in mirrors, photographs, or on television for real people (Mühlbauer 2021) (Ballard 2020). However, it is important to distinguish whether these symptoms are true delusions or mere confabulations. It is crucial to determine whether the information has been encoded into memory, as persistent false beliefs suggest delusions specific to Alzheimer's disease, while transient or inconsistent false statements are indicative of confabulations. Research indicates differences in delusions between individuals with and without agitation. While those with agitation may show a more favorable response to treatment with ongoing symptom improvement, it remains unclear whether this difference stems from agitation itself or if it represents a distinct phenomenological phenomenon. Studies have suggested that individuals with delusions but without agitation are more likely to experience hallucinations compared to those without (Ismail 2022).

Hallucination:

Hallucinations can be considered one of the most common symptoms of psychosis in Alzheimer's disease, and they can be more fleeting compared to delusions (Ismail 2022). Hallucinations can occur in all sensory modalities, including tactile, olfactory, and gustatory, but visual hallucinations, followed by auditory hallucinations, are the most frequent and common. Among them, visual hallucinations are the most prevalent. Visual hallucinations often involve seeing people or animals, but they can also include inanimate objects or unrecognizable images (Ballard 2020). Research suggests that visual hallucinations often occur at more advanced stages of Alzheimer's disease, and they tend to manifest significantly later than in patients with Lewy body dementia. In the case of auditory hallucinations, complete conversations or noises may occur, but phenomena such as hearing multiple voices conversing or interpreting personal actions, unlike in schizophrenia, are extremely rare. Alzheimer's hallucinatory symptoms may overlap with misidentification syndromes, making it difficult to distinguish in every situation. Hallucinatory symptoms can have significant impacts on a behavioral level, leading to functional decline, frequent falls, aggressive behavior, and more. Moreover, hallucinations are associated with mortality rates. Hallucinations dramatically increase the risk of death in patients, and the risk of death further escalates when both visual and auditory hallucinations are present. According to a study by Wilson et al. involving 407 Alzheimer's patients, 146 patients with hallucinatory symptoms out of 41.0% of patients tracked during the follow-up period passed away (El 2017).

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Diagnostic criteria:

Alzheimer's disease is diagnosed when specific cognitive and behavioral symptoms manifest. Diagnostic criteria include psychiatric symptoms not attributable to major mental disorders, objective evaluation from the patient's caregiver, decline in the ability to acquire and retain new information, impairment in insight, visuospatial abilities, and language function (McKhann 2011). The prominent diagnostic criteria for psychosis in Alzheimer's disease, as proposed by Jeste and Finkel in 2000 (Jeste 2000), focus on the presence or absence of delusions and hallucinations once the diagnosis of Alzheimer's disease is established. However, subsequent research has revealed that psychosis can also occur during the mild cognitive impairment (MCI) stage of neurodegenerative diseases. The International Psychogeriatric Association (IPA) has thus incorporated MCI and other dementia etiologies into the criteria for psychosis in neurocognitive disorders. A crucial aspect of diagnosing psychosis in Alzheimer's disease is distinguishing it from psychosis caused by other factors. For instance, while psychosis in Alzheimer's disease may superficially resemble functional psychotic disorders like schizophrenia, there are clear phenomenological differences between the two conditions. Therefore, a comprehensive evaluation of various potential causes such as pain, confusion, unmet needs, etc., is necessary to exclude treatable alternative causes before considering treatment with antipsychotics.

2.2. Clinical Significance of ADP-Impact on Patients and Caregivers

Quality of Life:

The clinical significance of Alzheimer's disease lies in its substantial impact on both patients and caregivers. First and foremost, patients experience a decline in cognitive abilities, impairment in activities of daily living (ADL), as well as psychological, emotional, and social factors that collectively affect their quality of life (QoL). Various factors interact to shape a patient's QoL, with studies often focusing on identifying the most significant contributors. According to meta-analyses, religious and social factors, along with the relationship with caregivers, have been identified as the most crucial factors. Additionally, factors such as residential area, functional abilities, health status, and depression have been measured to influence QoL (Tahmi, 2022). For instance, a French study evaluating QoL-AD found a significant association between patient depression and lower QoL (Barbe, 2018). Neurological and psychiatric symptoms significantly diminish a patient's quality of life, which can lead to anxiety, social withdrawal, and even worsened dementia (Tahmi, 2022).

Alzheimer's disease not only affects the patient but also significantly impacts the QoL of caregivers. The decline in a patient's ADL due to Alzheimer's disease can greatly alter their emotions, mental state, personality, and behavior. These unpredictable changes can lead caregivers to experience burden and stress, consequently decreasing their own quality of life (Yu, 2015). Factors associated with caregiver burden, as revealed through research, include the stage of a patient's dementia, ADL, mental state, psychosis, and cognitive abilities (Kim, 2021). Research from China suggests that caregiver burden increases further as the patient's cognitive function declines (Yu, 2015). Although cognitive function and psychosis in patients are associated with caregiver burden, the exact causality remains undetermined (Kim, 2021). The inherent personality traits of caregivers, their available resources, and social support determine the extent of caregiver burden (Yu, 2015). Thus, symptoms associated with Alzheimer's disease worsen cognitive impairments and health status in patients, while also inducing psychological distress on caregivers. Caregiver burden can strain relationships between patients and caregivers and lead to more significant societal issues, such as elder abuse (Kim 2021).

Cost:

Another issue stemming from Alzheimer's includes the costs associated with Alzheimer's treatment. A study from Japan demonstrated an increase in caregiving costs for caregivers and families as Alzheimer's disease progresses and ADL declines (Ashizawa, 2021). According to research in the United States, the population of Alzheimer's patients is on the rise, and the comprehensive costs associated with caring for and treating those with Alzheimer's disease were approximately $500 billion in 2020, with projections indicating that this figure will steadily increase to $1.6 trillion by

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2050. Furthermore, when the time spent by caregivers in caring for individuals with Alzheimer's is monetized, it constitutes two-thirds of the total costs of Alzheimer's treatment (Aranda 2021).

2.3. Other Neuropsychiatric Symptoms Associated with AD

Neuropsychiatric symptoms are common features observed in the majority of dementia patients (Mühlbauer 2021). These symptoms include agitation, depression, anxiety, apathy, executive dysfunction, and their co-occurrence is frequent (Borsje 2018) (Mühlbauer 2021). Among early Alzheimer's disease patients, depression and apathy are the most frequently observed neuropsychiatric symptoms, although agitation also exhibits a high incidence. While aggression tends to gradually manifest as the disease progresses, apathy stands out as the most persistent and prevalent symptom among all neuropsychiatric symptoms (Lyketsos 2011).

Agitation:

Defining agitation simply is difficult, but agitation in the context of dementia can be described as exhibiting verbal, physical aggression, or excessive and unstable behavior, with significant impact of mental or emotional distress. Additionally, agitation can be considered synonymous with aggression and is a common symptom in Alzheimer's disease. The degree of agitation can lead to severe disability, often surpassing that caused by cognitive impairment (Heilman 2022) (Mühlbauer 2021). Agitation in Alzheimer's disease arises from an exaggerated perception of threat magnitude, accompanied by heightened attention and vigilance towards threats, as well as uncertainty regarding the threat target. This results in maintaining a state of mental and emotional hypersensitivity due to misinterpreting threats as a consequence of cognitive deficits. When individuals with impaired agitation circuits forget routine activities in daily life, sudden and unexpected situations may occur, triggering a heightened reaction due to damaged agitation circuits mistaking the situation as a threat. Consequently, patients with impaired agitation circuits may perceive caregivers as strangers and exhibit significant agitation (Rosenberg 2015). Agitation not only burdens patients themselves but also their caregivers and surrounding individuals, significantly impacting treatment costs as agitation symptoms worsen (Livingston 2020). Therefore, removing the triggers causing agitation as much as possible can help alleviate symptoms, and methods such as music therapy, massage therapy, or psychological treatments, as well as medication in severe cases, are used to alleviate agitation (Lyketsos 2011). Agitation often co-occurs with other neuropsychiatric symptoms. Although it is associated with anxiety, apathy, and hallucinations, it is not strongly correlated with depression. Agitation influences the worsening and rapid progression of dementia, potentially leading to early mortality (Heilman 2022).

Depression:

Depression is a symptom that often accompanies Alzheimer’s disease, and depressive moods tend to be persistent rather than transient (Heilman 2022). In Alzheimer's disease, the diagnostic criteria for depression encompass enduring feelings of melancholy, diminished enjoyment in social engagements, recurrent sentiments of despair, instances of suicidal ideation or behavior, social seclusion, and diminished self-esteem. Owing to the cognitive regression associated with Alzheimer's, individuals frequently underreport their depressive manifestations, underscoring the imperative reliance on caregiver observations to evaluate such symptoms in patients (Heilman, 2022). Although depression may precipitate cognitive decline, its impact on cognitive function remains relatively insignificant during the incipient and advanced phases of Alzheimer's (Botto, 2022). Depression emerges as a prevalent manifestation in Alzheimer's pathology, consequently warranting significant attention in the therapeutic approach to Alzheimer's disease (Rosenberg, 2015). The intricacies inherent in diagnosing and treating depression in Alzheimer's stem from the commonalities shared with late-life depression unrelated to Alzheimer's and symptoms of apathy, necessitating careful differentiation (Lyketsos, 2011). Furthermore, depression in Alzheimer's can exacerbate the occurrence of additional cognitive impairments or impinge upon frontal lobe functionality, yet remedying depression may concurrently ameliorate these deficits (Botto, 2022).

Anxiety:

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Anxiety symptoms are observed in as many as 70% of Alzheimer's patients and are often associated with other psychiatric manifestations. Significant manifestations are particularly likely to show up in patients who develop Alzheimer's before the age of 65 (Heilman 2022). Anxiety manifestations in Alzheimer's disease typically emerge during the intermediate to advanced stages of the condition and may serve as a harbinger for subsequent agitation or depressive indications. Anxiety may also be accompanied by overt behaviors and vocalizations (Mendez 2021). In a study involving individuals with preserved cognitive function, anxiety is posited as a contributory factor to the onset of Alzheimer's, either autonomously or in conjunction with depression or sleep disturbances. These anxiety-related symptoms tend to be more prevalent among individuals with early-onset Alzheimer's, potentially attributable to abrupt shifts in lifestyle, social disorientation, and cognitive deterioration (Botto 2022). There is an indication that anxiety in Alzheimer's could expedite the transition from mild cognitive impairment (MCI) to full-fledged dementia (Mendez 2021).

Apathy:

Apathy in Alzheimer's is characterized by diminished emotional responsiveness, loss of motivation, and loss of initiative. Such symptoms of apathy typically begin before cognitive decline and tend to worsen as cognitive impairment progresses (Heilman 2022). Apathy emerges as a prevalent and enduring neuropsychiatric manifestation within Alzheimer's disease, marked by a prolonged decline in motivation lasting a minimum of four weeks, coupled with diminished goal-oriented behaviors, cognitive activities, and emotional responsiveness (Lyketsos 2011) (Rosenberg 2015). Conceptually, apathy can be construed as the polar opposite of engagement, signifying a diminished propensity for initiative and involvement. Despite individuals with Alzheimer's participating in activities of preference akin to those without dementia, apathy demands heightened energy expenditure even for tasks traditionally enjoyed (Livingston 2020).

3. Pathophysiological Alterations of the Brain Underlying ADP

3.1. Genetics and Other Risk Factors that Contribute to ADP

Genetics:

Approximately 70% of the factors contributing to the onset of Alzheimer's disease can be attributed to genetic factors (Ballard 2011). Early-onset Alzheimer's disease mostly arises from mutations in APP, PSEN1, and PSEN2, while late-onset Alzheimer's disease is strongly associated with the APOE gene (Silva 2019). APP is one type of transmembrane protein encoded by the APP gene on chromosome 21. Subsequently, it is sequentially cleaved by α-, β-, and γ-secretases to generate Aβ. The primary components of γ-secretase are PSEN1 and PSEN2 (Breijyeh 2020) (Karch 2014). Most mutations found in the APP gene are related to Alzheimer's disease. More than 30 dominant mutations already identified are associated with autosomal dominant Alzheimer's disease, and mutations in the PSEN1 and PSEN2 genes are also associated with Alzheimer's disease (Silva 2019). While mutations in other genes may also be related to the onset of Alzheimer's disease, APP, PSEN1, and PSEN2 primarily act as causative factors. APOE, a major risk factor for late-onset Alzheimer's disease, is a protein encoded by the APOE gene on chromosome 19. APOE is involved in lipid metabolism and is essential for normal brain function. It can induce Alzheimer's disease due to its association with brain vascular damage. APOE alleles include ε2, ε3, and ε4, with the ε4 allele being a decisive risk factor for late-onset Alzheimer's disease, whereas the ε2 allele reduces the incidence of Alzheimer's disease (Silva 2019) (Breijyeh 2020).

Alzheimer's disease is divided into early-onset Alzheimer's disease (EOAD) and late-onset Alzheimer's disease (LOAD), based on the age of onset (Breijyeh 2020). Late-onset psychoses generally have distinct clinical characteristics. In cases such as late-onset schizophrenia, delusional disorder, and psychotic depression, it is important to investigate the underlying causes of secondary psychosis, which include neurodegenerative, infectious, nutritional, toxic, endocrine, and inflammatory etiologies (Devanand 2024). Older adults are more susceptible to the adverse effects of psychotropic medications, particularly antipsychotics. Therefore, it is essential to accurately diagnose, estimate the prognosis, and manage late-onset psychosis cautiously considering the

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possible etiologies (Devanand 2024). Cases occurring after the age of 65 are more common and frequent, while the disease is rarely observed in younger individuals. The prevalence of Alzheimer's increases with age, reaching 30-35% in individuals over 85 years old, and it may even reach 50% (Armstrong 2019). This prevalence is higher in individuals with a positive family history of Alzheimer's disease. The increasing incidence with aging is attributed to factors such as decreased brain volume and synaptic loss. Alzheimer's disease is sometimes considered merely an accelerated form of normal aging, as many phenomena observed in Alzheimer's are commonly seen in normal aging as well. Symptoms such as cholesterol abnormalities, mitochondrial dysfunction, and cognitive decline are common in normal aging, making it difficult to accurately distinguish Alzheimer's disease (Breijyeh 2020).

Acquired Factors:

In addition to genetic factors, there are also factors that can be acquired throughout life. In early life, education can be considered a risk factor, and lifelong education reduces the incidence of Alzheimer's disease. According to research, education before adolescence plays a role in enhancing overall cognitive abilities. Risk factors for Alzheimer's disease in midlife include obesity, alcohol misuse, and hypertension; while risk factors in later life include diabetes and lack of physical activity due to social isolation. In particular, persistent hypertension in midlife increases the incidence of Alzheimer's disease; and if hypertension persists into later life, the incidence increases even more (Livingston 2020) (Silva 2019).

The reason diabetes is strongly associated with Alzheimer's disease is because insulin plays a central role as a neuromodulator (Armstrong 2019). According to research, there is a clear association between type 2 diabetes and the onset of Alzheimer's disease. The associated mechanisms include impaired insulin receptors, insulin deficiency, and damage to brain blood vessels (Silva 2019). Obesity, which can lead to type 2 diabetes and other conditions such as cancer, is therefore also considered a risk factor for Alzheimer's disease. Metabolic changes associated with obesity can damage the nervous system, weakening cells and leading to cell death (Breijyeh 2020) (Armstrong 2019). Additionally, factors such as smoking, pesticides, and heavy metal pollution can also impact human mental health (Maciejewska 2021).

3.2. Neuroimaging and Brain Regions Affected in ADP

The entorhinal cortex and the hippocampus are predominantly affected by Alzheimer's disease (AD). In the early stages of AD, the entorhinal cortex is impacted, followed by subsequent effects on the hippocampus and cerebral cortex. Notably, the hippocampus undergoes transformation due to ischemia, affecting key AD-related genes such as APP, PSEN1, and PSEN2 in the CA1 and CA3 regions. It is noted that the pattern and timing of gene alterations differ between CA1 and CA3 regions. Apart from genetic alterations, a significant factor influencing the brain due to AD is atrophy. Atrophy in AD follows a specific pattern, initially affecting the hippocampus and entorhinal cortex, then spreading to the temporal and frontal lobes, eventually leading to cortical atrophy. Moreover, atrophy is observed even in the Mild Cognitive Impairment (MCI) stage, and its progression accelerates with the onset of full AD diagnosis. Age-related dementia typically exhibits a slow onset over several years. Although it progresses gradually, signs of atrophy appear before clinical dementia symptoms. Thus, distinguishing between normal aging and dementia onset can be challenging, potentially leading to erroneous inferences about normal brain aging, especially concerning vulnerable areas like the entorhinal cortex and hippocampus. Experimental studies aimed at differentiating between normal aging and AD have shown evidence of atrophy in both AD patients and normal elderly controls. The debate arises regarding whether brain shrinkage in healthy elderly individuals signifies early AD symptoms or is considered a part of normal aging. To address this, investigations have explored whether factors contributing to AD-related atrophy are also associated with normal aging. The experimental findings indicate distinct effects of Aβ1-42, a factor inducing atrophy, on the brains of AD patients and normal elderly individuals, revealing no association with the hippocampus even when a correlation between Aβ1-42 and atrophy is observed in normal brains (Fjell 2014).

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3.3. Molecular and Pathophysiological Changes Associated with ADP

The pathological features of Alzheimer's disease (AD) include neuronal damage, excessive accumulation of amyloid-beta peptide (Aβ) and tau aggregates (p-Tau), cell loss, mitochondrial distortion, and synaptic dysfunction. As mentioned earlier, these pathological changes accumulate in the brain over a long period and eventually lead to clinical dementia. In dementia with clinical symptoms, the neuropathological features have significantly impaired many brain regions responsible for cognitive function (Schilling, 2016). One of the most prominent pathological features is related to Aβ, which arises due to neuro-metabolic dysfunctions. A significant portion of the body's glucose is utilized to maintain the basal metabolic rate of the brain. Alzheimer's disease induces hypometabolism of glucose, leading to a sharp decline in ATP production due to neuro-metabolic dysfunctions, which in turn leads to mitochondrial distortion and subsequent accumulation of Aβ. In Alzheimer's pathology, the amyloid cascade hypothesis has long dominated, suggesting that eliminating or inhibiting the formation of Aβ could prevent Alzheimer's. However, research results have shown little efficacy in preventing Alzheimer's by solely targeting Aβ accumulation. Consequently, other factors associated with AD, such as mitochondrial dysfunction and neuroinflammation, have been proposed as factors to be addressed (Verma, 2022). Mitochondrial dysfunction manifests early in Alzheimer's pathology (Armstrong, 2019). Pathological factors associated with mitochondrial dysfunction in Alzheimer's include decreased mitochondrial DNA, altered mitochondrial morphology, reduced mitochondrial axonal transport, increased reactive oxygen species (ROS) production, leading to a decrease in brain metabolic rate, brain inflammation, and neuronal damage (Verma, 2022). The manifestation of mitochondrial dysfunction in Alzheimer's disease has led to the formulation of the 'mitochondrial cascade hypothesis,' which assumes that mitochondrial dysfunction is the initial event leading to Alzheimer's pathology (Armstrong 2019).

3.4. Biomarkers

Typical Alzheimer's disease is further classified into typical and atypical forms, differing in the extent and regional deposition of neuropathological hallmarks. Contemporary diagnostic criteria for both typical and atypical Alzheimer's disease dementia rely on biomarkers to delineate the pathology (Graff-Radford 2021). Biomarkers are also utilized to diagnose Alzheimer's disease and assess its progression. As previously mentioned, prominent neuropathological features in Alzheimer's disease include the accumulation of Aβ and tau proteins. To assess the levels of tau and Aβ, as well as other neuropathological features such as synaptic degeneration and glial activation, fluid and blood biomarkers are commonly employed (Khan 2020). Tau and amyloid PET imaging provide information on the distribution of tau and Aβ in the brain, while CSF and plasma biomarkers indirectly detect these pathological phenomena. Tau levels correlate with the severity of neurodegeneration in both typical and atypical Alzheimer's disease, whereas CSF Aβ42 levels are inversely associated with Aβ plaque burden (Graff-Radford 2021). In addition to fluid and blood biomarkers, plasma proteins and brain lipids can also serve as biomarkers. Plasma proteins such as vascular cell adhesion protein 1 and α2-macroglobulin, pancreatic polypeptide Y, and immunoglobulin M are associated with Aβ burden (Lashley 2018). Brain lipids, being essential for cellular signaling in the central nervous system, can also be utilized as biomarkers. The most abundant brain lipids include cholesterol, ceramides, and phosphatidylcholine. Such biomarkers may serve as safer alternatives for diagnosing dementia progression (Khan 2020). Furthermore, biomarkers of neurological injury exist. As mentioned earlier, dementia induces atrophy in regions like the hippocampus and temporal lobe, making the degree of atrophy a potential Alzheimer's biomarker (Mantzavinos 2017). The need for more practical biomarkers is consistently emphasized, as many existing biomarkers are limited in accessibility due to high costs. Thus, there is a growing demand for the development of more economical and widely accessible biomarkers.

4. Currently Available Therapeutics

4.1. Antipsychotics

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Antipsychotics are one of the primary treatment options for Alzheimer's disease, targeting psychiatric symptoms such as delusions and hallucinations, as well as resulting behavioral disturbances. Besides Alzheimer's, they are also utilized in treating conditions like schizophrenia, depression, and bipolar disorder. Antipsychotics can be categorized into traditional, first-generation typical drugs and second-generation atypical ones. Haloperidol stands out as the most commonly used typical antipsychotic, along with others like thiothixene and chlorpromazine. Among atypical antipsychotics, risperidone is frequently prescribed, while others include olanzapine, aripiprazole, and quetiapine (Mühlbauer 2021).

Explaining the efficacy of these atypical antipsychotics, risperidone acts as an antagonist on dopamine, serotonin, and noradrenaline receptors. Olanzapine is approved for treating schizophrenia and bipolar disorder in adults, while aripiprazole is used for schizophrenia in adults and adolescents, mania in bipolar disease across various age groups, autism, and major depression in adults. Quetiapine is indicated for schizophrenia and bipolar disorder in adults and off-label for conditions like post-traumatic stress disorder, anxiety, insomnia, and behavioral symptoms in dementia (Calsolaro 2019).

Some argue that antipsychotics simply induce chemical restraint, providing sedative effects rather than treating psychosis specifically. Antipsychotics' widespread use in psychiatric disorders also brings notable adverse effects to the forefront. They are not entirely devoid of risks. Side effects may include sedation, motor disturbances, and cognitive decline, with more severe ones such as stroke and malignant neuroleptic syndrome. These effects arise from the potent and prolonged binding of D2 receptors across various brain regions, particularly those associated with neurological symptoms, leading to adverse psychiatric outcomes. Moreover, antipsychotics are linked to an increased risk of venous thromboembolism and mortality, especially in elderly dementia patients. Studies have shown a dose-dependent increase in adverse effects like motor disturbances and peripheral edema with risperidone. Additionally, concerns exist regarding the cardiovascular system, with known associations between antipsychotics and QT interval prolongation, torsades de pointes, and sudden cardiac death (Calsolaro 2019, Mühlbauer 2021). Thus, the safety of antipsychotics in dementia treatment remains uncertain. Nevertheless, they continue to be widely used as the drug of choice for managing psychiatric symptoms in dementia patients (Podsiedlik 2022).

Aripiprazole:

Aripiprazole is defined as a third-generation antipsychotic drug (APD), used to treat schizophrenia, major depression, and bipolar disorder. Aripiprazole is an atypical antipsychotic that acts on dopamine D2 and 5-HT1A receptors. It exhibits potent partial agonistic activity at 5-HT1A receptors but antagonistic on 5-HT2A receptors. Thus, aripiprazole can prevent dopamine supersensitivity associated with psychosis (Guido 2015) (Heo 2020). Additionally, its partial agonism at dopamine D2 receptors not only prevents hyperdopaminergic states related to psychotic symptoms but also reduces prefrontal cortex activity, which is relevant for cognitive function. However, excessive blockade of dopamine D2 receptors may lead to worsened clinical outcomes and cognitive impairment (Guido 2015). Aripiprazole may induce sedation, hypertension, weight gain, headache, agitation, and anxiety as common side effects. Due to these potential side effects, aripiprazole is prescribed selectively for patients experiencing severe psychotic symptoms or refusing non-pharmacological treatments, where symptoms significantly impact daily life and pose risks of self-harm (Yuka 2019) (De 2013).

Pimavanserin:

Pimavanserin is an atypical antipsychotic medication, still under clinical investigation for its use in treating mental disorders such as Alzheimer's disease and schizophrenia. Pimavanserin gained FDA approval in 2016 as a treatment for psychosis, including hallucinations and delusions, associated with Parkinson's disease, based on the results of a placebo-controlled clinical trial conducted in that year. In addition to Parkinson's disease, there is a prospect that pimavanserin may also be used as a treatment for Alzheimer's disease, which is characterized by hallucinations and delusions (Srinivasan 2020) (Gründer 2021). Pimavanserin acts selectively as a 5-HT2A inverse agonist, with low affinity

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for 5-HT2C receptors. Unlike other antipsychotics, pimavanserin does not demonstrate clinically significant activity in blocking dopamine receptors, adrenergic receptors, histaminergic receptors, or muscarinic receptors. Due to these characteristics, pimavanserin avoids side effects such as tremor and akathisia associated with dopamine-blocking antipsychotics, and does not adversely affect motor or cognitive function (Jimenez 2022) (Ballard 2019).

Brexpiprazole (RexultiTM):

Brexpiprazole is a medication that regulates serotonin and dopamine activity and is used as a treatment for schizophrenia and depression. Brexpiprazole acts as a partial agonist at serotonin 5-HT1A and dopamine D2 receptors, and as an antagonist at serotonin 5-HT2A receptors. Thus, brexpiprazole is associated with dopamine, serotonin, and noradrenaline neurotransmitters, which are directly or indirectly related to various symptoms of dementia (Grossberg 2019). Therefore, brexpiprazole effectively treats symptoms such as psychosis and behavioral disturbances in Alzheimer's disease. Agitation is a prominent symptom of Alzheimer's psychosis, and brexpiprazole effectively alleviates agitation while maintaining safety. Unlike other medications, the reduction in agitation is not due to sedation, and brexpiprazole has significantly fewer side effects such as sedation and somnolence. Headache is the only common side effect associated with brexpiprazole use. Moreover, brexpiprazole has a very low mortality rate and is virtually free of such risk (Lee 2023).

4.2. Non-Pharmacological Approaches

Music therapy:

Recent studies suggest that music therapy has a positive impact on the mental state and life motivation of Alzheimer's patients and their caregivers (García-Navarro 2022). The use of music therapy aims to stimulate patients' memories and prompt specific verbal responses (Bleibel 2023). By playing familiar music, the therapy leverages the connection between past memories and music to alleviate psychotic symptoms like anxiety and depression often seen in Alzheimer's patients, helping them enhance their awareness of reality. Beyond this, music therapy offers various benefits, including boosting positive emotions in patients and reducing the perceived burden on their caregivers. It also aids patients in managing their emotions, providing motivation for a longer life. Since music therapy involves interacting with others and sharing experiences, it helps patients maintain contact with reality, potentially preventing complications. Consequently, music therapy not only amplifies the effects of pharmacological treatments but also addresses their limitations.

Music therapy can be divided into two forms: active and passive. In active music therapy, patients engage in playing instruments, singing, or even creating music. In passive music therapy, patients listen to music. Of these two forms, active music therapy has been shown to provide greater benefits in terms of improving both short-term and long-term memory. It also plays a more significant role in alleviating emotional, cognitive, and psychological symptoms (García-Navarro 2022). Since each patient presents different symptoms and behaviors, therapists often create personalized playlists or adjust the therapy process for each individual, which is a core part of the therapist's discretion (Bleibel 2023).

The primary brain region activated by music therapy is the anterior hippocampus. This area, known for its involvement in autobiographical memory, also plays a role in emotional processing, making it a key target of music therapy. However, the hippocampus is not the only brain structure affected, as other regions are also associated with emotion-induced by music. Despite these findings, the precise mechanisms through which music therapy impacts the brain remain not fully understood (Matziorinis 2022). Studies have used functional magnetic resonance imaging (fMRI) to investigate brain regions associated with the encoding of long-term musical memories and to examine how these regions respond to and process music. These areas were assessed using Alzheimer's biomarkers, such as amyloid accumulation, cortical atrophy, and hypometabolism. The results indicated that while cortical atrophy and metabolic dysfunction were present, amyloid accumulation was not significantly reduced. This suggests that brain regions related to music processing remain relatively preserved even in Alzheimer's patients. Such findings provide insights into why music therapy may be effective in recovering musical memories in Alzheimer's patients (Bleibel 2023).

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While the effects of music therapy are most pronounced when familiar music is played, it is also effective with unfamiliar music. Listening to unfamiliar music can improve a patient's ability to recall specific episodic memories. For example, patients who listened to unfamiliar, soft music as background during autobiographical memory recall showed greater improvement in memory recall and a more significant reduction in emotional distress compared to patients who attempted memory recall without music (Matziorinis 2022).

One of the greatest advantages of music therapy is that it has no side effects and involves no invasive procedures. Additionally, it can address multiple Alzheimer's psychoses simultaneously, is easy to administer, and is cost-effective. However, music therapy does have limitations, particularly in patients with severe dementia. These individuals may have significant cognitive and physical impairments, preventing them from actively participating in the therapy (Bleibel 2023).

Aromatherapy:

Aromatherapy can assist in overcoming behavioral disturbances in Alzheimer's disease patients by providing relief and enhancing their ability to cope with external influences (Jimbo 2009). These extracts can enhance cognitive function in Alzheimer's patients and also significantly improve sleep quality and reduce agitation. The active components of aromatic plants are essential oils, which are found in the leaves, seeds, roots, and flowers. These mixtures are secondary metabolites of plants and are volatile and complex. Aromatic products contain various chemical compounds, and essential oils can be absorbed through the skin, respiratory tract, or orally. Regardless of the method of administration, they can cross the blood-brain barrier (BBB) and reach the central nervous system (CNS) (Ma 2023). A prominent example is lavender essential oil, which, when used in aromatherapy, reduced depression, anxiety, and stress in Alzheimer's patients (Bavarsad 2023). In addition, lavender oil and orange oil mixtures, commonly used for Alzheimer's patients, activate the parasympathetic nervous system; while mixtures of rosemary and lemon oils have shown effects in alleviating depression and improving patients' concentration (Jimbo 2009).

Aromatherapy research conducted by Lin et al. in 2007 revealed that essential oils extracted from *L. angustifolia* have a calming effect on the agitation experienced by Alzheimer's patients. Subsequent studies demonstrated that essential oils from *L. angustifolia Mill.* could also have long-term effects in improving attention. Additionally, *Rosmarinus officinalis L.* has been reported to possess powerful antioxidant compounds that reduce oxidative stress, one of the causes of Alzheimer's, making it beneficial for treatment. *M. officinalis L.*, another strong antioxidant, has been shown to protect the brain from oxidative damage and contribute to reducing oxidative stress (Bavarsad 2023).

Reminiscence therapy:

Reminiscence Therapy (RT) is a non-pharmacological intervention that helps alleviate psychological and emotional distress in Alzheimer's patients by evoking autobiographical memories and improving quality of life (QoL). RT primarily stimulates autobiographical episodic memories by prompting patients to recall past experiences through conversations with caregivers, thereby assisting patients in maintaining a stable psychological state (Morales, 2021). RT can be applied in various settings and is widely recognized as a cognitive rehabilitation intervention that can be utilized in nursing homes and assisted living facilities. Notably, RT plays a significant role in alleviating neuropsychiatric symptoms (NPS) in dementia patients and enhancing their quality of life through social interactions (Cammisuli, 2022).

Originally developed by Butler in 1963, this therapy is based on the "life review approach," which uses various stimuli such as everyday items, past photographs, and music to help patients recall their past memories and autobiographical events. Through this process of recollecting memories, patients can reflect on their life experiences and engage in meaningful social interactions with others (Cammisuli, 2022). While Alzheimer's patients may struggle with new learning, memories from the past that have been frequently revisited remain accessible. In this respect, RT is effective for dementia patients. The experience of recalling past memories offers patients an opportunity to review their lives, potentially enhancing new social interactions. These recollections play a vital role in communication with others and assist in maintaining emotional stability and a consistent emotional state (Cammisuli, 2022).

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RT can also be facilitated through technological devices. For instance, therapy can be provided via personalized digital memory books, mobile applications, and computer-based programs, making it adaptable to various environments such as emergency rooms, daycare centers, long-term care facilities, and private homes. RT is considered a practical and safe treatment method as a simple psychological intervention, with a low risk of side effects for Alzheimer's patients (Cammisuli, 2022). Thus, RT possesses flexibility for application in diverse settings and allows for personalized interventions utilizing technology. RT can be particularly beneficial for Alzheimer's patients, as depression is commonly observed in dementia, and these patients tend to remember past experiences better than recent ones. The experience of reviving past memories offers psychological comfort and provides them with the opportunity to reclaim a meaningful life (Cammisuli, 2022).

The specific procedure of RT emphasizes stimulating Alzheimer's patients' memories through various types of stimuli, including patient albums, letters, cherished items, family artifacts, music, and historical events. These stimuli are often obtained from the patients' families or acquaintances before the therapy begins. They serve to elicit memories focused on the patients' long-term recollections, which is a crucial step in the process of reviving past memories. RT encompasses a total of 12 reminiscence themes, including meals and cooking, family relationships and early memories, weddings, personal collections, work environments, songs and music, old films, first experiences, change and loss, celebrations, and wishes (Li, 2017).

During RT, Alzheimer's patients may exhibit various narrative styles. Some patients may repetitively tell the same story, while others may discuss a wide range of topics or briefly describe their experiences. Therefore, healthcare professionals assist patients in expressing their memories to the fullest extent and integrate these into a coherent narrative. This integration is one of the most critical steps in reminiscence therapy, playing a vital role in helping patients reflect on their lives and find emotional stability through their memories (Li, 2017).

Occupational therapy:

Reminiscence-based occupational therapy programs serve as a valuable non-pharmacological intervention for patients with Alzheimer's disease, aiding in the stimulation of memory and enhancement of cognitive function. This program comprises five categories of activities: physical activities, gardening activities, music activities, art activities, and instrumental activities of daily living (IADL), primarily applied to individuals with mild Alzheimer's disease (Kim, 2020). This therapy encourages patients to engage in more frequent verbal and non-verbal expressions, extending beyond mere memory stimulation, which helps alleviate unstable psychological states, reduce problematic behaviors, enhance emotional stability, and increase social interactions. Consequently, these changes can contribute to an overall improvement in the quality of life for individuals with Alzheimer's disease (Kim, 2020).

Occupational therapy adopts a unique approach by simultaneously considering individual patient characteristics and environmental factors. Occupational therapists focus not only on adults experiencing Alzheimer's disease and neurocognitive disorders (NCD) but also on addressing the complex needs of both paid and unpaid caregivers (Smallfield, 2024). Particularly, they play a crucial role in providing the necessary education and training to caregivers to help them avoid burnout and consistently deliver the care required by patients. Occupational therapists make clinical judgments based on each patient's circumstances and their responses to interventions, often collaborating with occupational therapy assistants in this process (Smallfield, 2024).

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