"A Comprehensive Review of the Adverse Effects and Complications Associated with Alzheimer's Disease"

[1]Arshad F. Rajkotiya, [2]Shraddha P. Malokar, [3]Vivek R. Chandrashekhar, [4]Prof. Ashwini V. Aswar,

[5]Dr. Harigopal S. Sawarkar

[1,2,3]Student, [4]Assistant Professor, [5]Principal

Department of Pharmacology, Dr. Rajendra Gode College of Pharmacy, Amravati-444601, Maharashtra (India)

Abstract

Alzheimer disease (AD) is a progressive neurodegenerative condition that is marked by accumulation of amyloid-b, tau pathology, and extensive neuronal loss that cause severe cognitive, behavioral and functional deficiency. The present review summarizes the existing literature on the negative outcomes and complications of AD, which are beyond simple core cognitive impairment and neuropsychiatric disturbances, sleep and circadian rhythm disorders, motor and neurological impairments, life-threatening secondary conditions such as aspiration pneumonia and cardiovascular risks. Adverse effects of medications, especially those caused by cholinesterase inhibitors and memantine are discussed with references to their gastrointestinal, cardiovascular, and neuropsychiatric effects. In the review, emerging biomarkers, such as plasma and CSF amyloid, tau, and neurodegeneration biomarkers and imaging-based diagnostic innovations that can be used to identify disease earlier and accurately are described. Moreover, dynamic therapeutic and global policy programs in the early detection, minimization of the risk, caregiver support and managing the long-term dementia are also addressed. This review identifies the most significant gaps in diagnosis, treatment tolerance, and late-stage care, which are based on the application of the molecular, clinical, and public-health perspective, and the necessity of more effective interventions and preparedness, on a system level. Should you prefer it shorter, more technical, or even to fit a particular journal format, then inform me and I will put it still shorter.

Keywords: Alzheimer disease, Dementia, Neurodegenerative disorders, Neurofibrillary tangles, Cognitive decline

Introduction

In 1907, Alois Alzheimer described the case of a 51-year-old woman who presented with a relatively rapidly deteriorating memory along with psychiatric disturbances. She died four years later. While a variety of progressive and fatal neurological conditions were known at that time, including senile dementia, the early age at onset, and a new pathological finding, the neurofibrillary tangle (NFT), made this condition unique. The justification for Alzheimer's disease (AD) as a new nosologic entity, and the motivations of the prominent psychiatrist, Emil Kraepelin, for promoting an evidently new condition, continue to be debated. Nevertheless, AD is today, as it was then, a relentless neurologic deterioration accompanied by hallmark pathology.

Over time, AD was split into two clinical conditions depending on the age of onset. Alzheimer disease, because of its initial description in a relatively young woman, was a term reserved for a type of "presenile" dementia affecting individuals younger than 65 years of age, whereas a similar dementia in the elderly, i.e., in individuals over 65 years of age, was referred to as senile dementia of the Alzheimer-type after the pioneering studies of Tomlinson, Roth and Blessed [[1]][[2]] Of historical note, Alzheimer himself was ambivalent about the

possibility that this entity was distinct from "dementia senilis," [3] and although these age-related classifications are still sometimes used, AD has never been shown to have a bimodal age of onset. AD is now generally recognized as a single entity with a prevalence that increases sharply after age 65. AD must be differentiated from other causes of dementia: Vascular dementia, dementia with Lewy bodies, Parkinson's disease with dementia, frontotemporal dementia and reversible dementias.

As yet, there is no reliable peripheral biochemical marker for AD, and a definitive diagnosis can only be made on histological examination of the brain at autopsy. Positron emission tomography (PET) scanning technology, using the C11-labelled Pittsburgh Compound B (PiB), a derivative of thioflavine T, that binds selectively to amyloid-β (Aβ), has produced conflicting reports[[4], [5], [6], [7], [8]]. It would appear that PiB binding to Aβ may not always differentiate symptomatic AD from asymptomatic controls with amyloid plaques.

Also, the binding of PiB to Aβ depends on the secondary and tertiary structure of the peptide, accounting for the reported false negative result. [9] While PiB has opened the door to visualizing brain function in a manner relevant to amyloid plaque buildup, more longitudinal studies are needed to determine its relative usefulness.

Refinement of the diagnostic criteria has improved the clinical diagnostic accuracy somewhat, although we may be nearing an endpoint, in light of the mild cognitive impairment (MCI) issue, which attempts to diagnose early neurodegenerative disease, but does so in only a subset of patient [10].

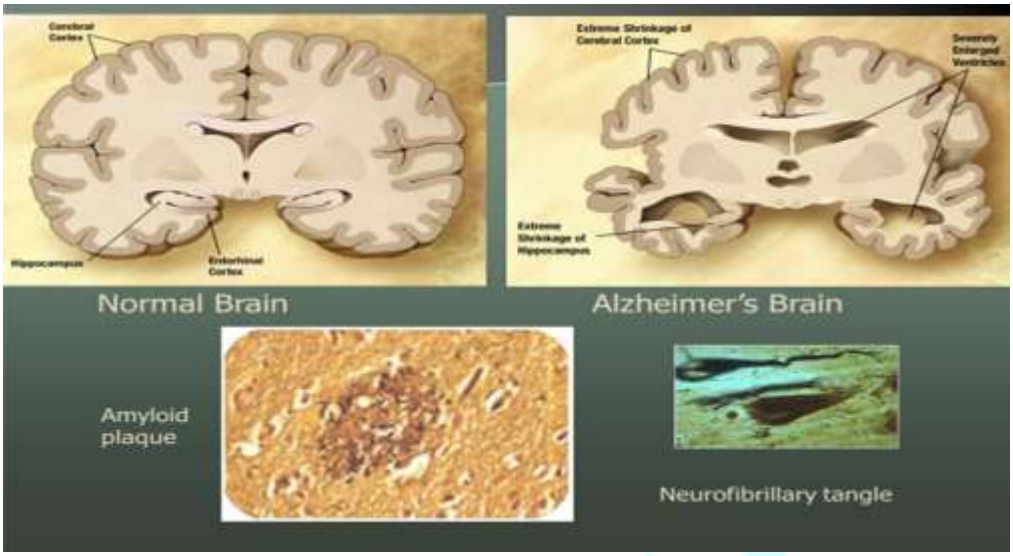
The impact of Alzheimer disease on the patients:

Alzheimer disease (AD) is a type of neurodegenerative disorder, which is progressive and impacts on memory, thinking, behaviour, and performance of daily activities. It mostly attacks the hippocampus and the cerebral cortex of the brain, the parts of the brain that are involved in the formation of memory, and the higher functions. AD is caused by abnormal accumulation of amyloid-b (Ab) plaque and tau protein tangles that impairs nerve cell communication resulting in neuronal death and brain atrophy [11], [12]. This loss of neurons will lead to slow memory loss, a lack of judgment, and poor problem-solving skills.

The disease causes growing communication, orientation, and reasoning impairment, which leads to the inability to carry out the regular everyday functions like cooking, finances, personal hygiene, etc [13]. There are also behavioural and psychological symptoms such as depression, anxiety, irritability, aggression, and hallucinations, which are disturbing to both the patients and the caregivers [14]. Disturbances in sleep, alteration of the sleep-wake cycle are frequent and are likely to cause so-called sundowning, when the confusion and agitation deteriorate during the evening [15]. Later stages of an Alzheimer disease impact physical activities including swallowing and movement leading to immobility, malnutrition and high chances of infection [16].

The reason why it matters to learn about the adverse effect:

Knowledge of the negative outcomes, of drugs, procedures, or illnesses, is critically important in achieving patient safety, enhancing care, and promoting health outcomes. Adverse effects are undesired or adverse responses in the course of using medical interventions or secondary to the condition of the disease. Being aware and knowledgeable about these effects can enable medical practitioners to weigh between the risks and benefits of the treatment, make informed clinical choices as well as personalize the treatment to the patient [17]. Education on possible side effects facilitates early diagnosis and intervention hence minor problems can be avoided to become serious complication [18].Moreover, the knowledge of the negative outcomes improves patient education and communication. Informed patients would also report emerging symptoms earlier, be responsible in taking treatment plans, and trust health care providers [19]. On the one hand, the knowledge of adverse effects contributes to the development of safer drugs, enhancements in pharmacovigilance systems, and the optimization of clinical guidelines, which are considered the goals of understanding adverse effects [20]. It also facilitates the ethical medical practice by promoting the transparency and informed consent in the choice of treatment [21].



Moreover, the detection of adverse effects also helps to improve medical studies and evidence-based practice. A consistent tracking and recording of side effects results in improved drug development, dosage changes, and alternative therapeutic options that are safe [22]. In general, awareness of adverse effects is essential in protecting patients, promoting effectiveness of treatment, and the efficient and ethical provision of healthcare services [23].

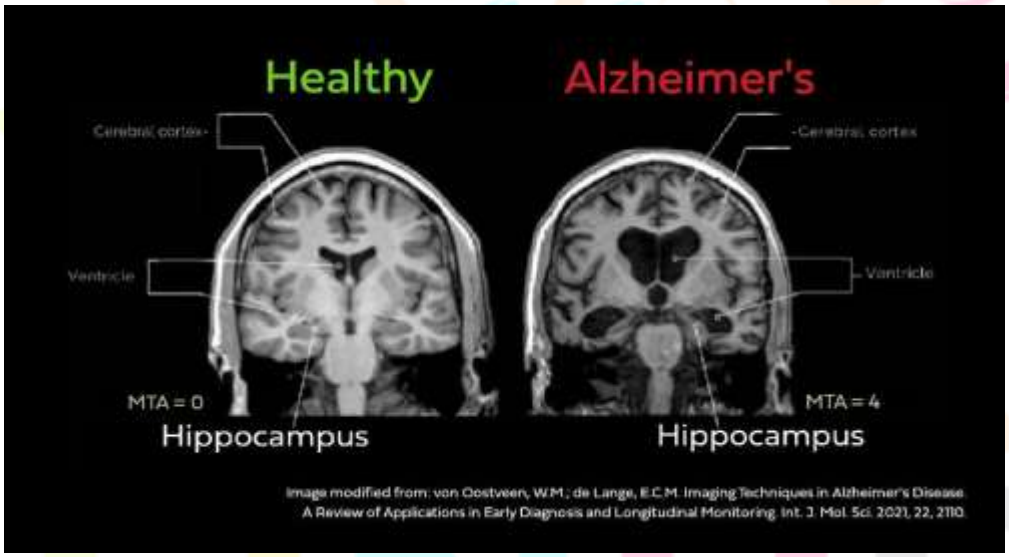


Figure 1: Condition of Hippocampus before and after Alzheimer's [24

Figure 2: Inside the Alzheimer's Brain: Shrinkage, Plaques & Tangles Explained. [25]

Objectives of the Review:

A review aims at overall summarizing, evaluation, and synthesis of existing studies on a specific subject with the aim of giving a reader a summary view of the current body of knowledge. The reviews promote discerning patterns, strengths, weaknesses, and literature gaps and inform the direction of future research and help in making clinical or policy decisions [26]. Reviews eliminate the duplication of research work, emphasize the critical findings, and form the basis of evidence-based practice by critically analysing the work of the previous research published [27].

Review limits are determined by the scope of the review, i.e. research questions, population, interventions, outcomes and time frame taken into consideration. A clear scope helps one to be focused and to be coherent so that the reviewer can be able to meet particular goals. [28]An appropriate scope is also used to establish the criteria to include or exclude literature as this enables the review to be systematic and within the context of its target audience [29].

Reviews in the field of healthcare and biomedical sciences are important in converting scientific evidence to clinical practice. They assist clinicians, policymakers and researchers to make sense of complicated data, analyse the safety and effectiveness of treatments, and work out new hypotheses to be explored [30]. Finally, the aims and extent of a review offer an opportunity to synthesize the preexisting evidence into a coherent, well-balanced, and informing synthesis that can help advance the knowledge and facilitate informed decision-making. [[31], [32]]

Pathophysiology

The preclinical stage of Alzheimer's disease is known as the cellular phase by basic scientists. Before cognitive impairment is noticed, the disease progresses subtly because of changes in neurons, microglia, and astrocytes [33]. Neuroinflammatory disease [34]. changes in the vessels, [[35], [36]] aging, [37], and lymphatic system dysfunction [38] act either concurrently or upstream of the buildup of amyloid β in this picture of cellular illness. Through an unidentified mechanism, amyloid β causes tau pathology [39] to spread, which is linked to the emergence of necroptosis markers in neurons exhibiting granulovacuolar degeneration [40]. The response of microglia has been clarified by single-cell transcriptome research [41] Two key genes that increase the risk of Alzheimer's disease, APOE and TREM2, play a significant role in this reaction. [[42], [43]]. ApoE attaches itself to amyloid β plaques [44] and the genetic variations of TREM2 linked to Alzheimer's disease, Arg 47 His, Arg62His, and Asp87Asn, reduce TREM2's affinity for ApoE (figure 3) [45].

Other proteins such as SHIP1, CD2AP, RIN3, BIN1, PLCG2, CASS4, and PTKB2, which are linked to a genetic predisposition for Alzheimer's disease, are likely to operate downstream of the signalling pathways involving ApoE and TREM2, influencing the endocytosis, motility, and phagocytosis of microglia TREM2 [46] is counteracted by CD33, while MS4A4A modulates the secretion of soluble TREM2 protein [47] The pathways involved in the microglial response are vital to the development of Alzheimer's disease, as demonstrated by the overlap of various risk genes associated with the condition within these pathways. Further research is needed to determine whether the microglial response is exclusively reactive to amyloid β plaques [48], mediates the toxicity caused by tau pathology [49], or acts as a protective factor against tau.

The conflicting impacts of the microglial response partly illustrate the constraints of mice. models that excessively express tau for investigating Alzheimer's disease. It might be that powerful. Transgenic tau overexpression [50] triggers an unnaturally intense neuroinflammatory reaction. which is not observed in less aggressive tau models. [[51], [52]]The utilization of mouse models that do not have overexpression tau, [53]

chimeric mice combining mouse and human traits [[54], [55]], or innovative in vitro models created from human sources, Induced pluripotent stem cells [56] could aid in clarifying the inconsistent findings. It is important to mention, all preclinical models are inherently reductionistic, suggesting that any conclusions drawn regarding Therapeutic advancements must be approached carefully. While cellular pathology has become pivotal in Alzheimer's disease research, substantial. Advancements have also been achieved in comprehending the prior biochemical stage of the illness (in ATN terminology, prior to A positivity [existence of amyloid β]). Thanks to cryogenic electron [57] and tau fibrils are now understood with greater precision [58] Cryo-electron. Microscopy has provided complete understanding of how presenilin's, the catalytic subunits of γ-secretases engage with APP and Notch substrates [59] Enhanced by functional research on isolated γ-secretase complexes, [60]

Figure 3: The genetic landscape of Alzheimer's disease

MAF (x-axis) is the frequency at which a non-reference (variant) allele occurs in the population. Variant carriers with OR=1 and non-carriers have the same odds of developing Alzheimer's disease, variants with OR >1 are associated with an increased risk of Alzheimer's disease, and variants with OR <1 are associated with a protective effect (y-axis). (A) Causative or strong risk increasing variants. A schematic representation of individual rare variants for which ORs cannot be estimated due to extreme variant rareness. Linkage studies in large pedigrees indicate that specific rare variants in PSEN1, PSEN2, and APP cause autosomal dominant Alzheimer's disease, in some cases with age at onsets as early as 40 years old. Note that not all variants in these three genes give rise to autosomal dominant Alzheimer's disease; some might be risk-modifiers or non-pathogenic. Further, evidence is accumulating that certain variants in the SORL1 gene are causative of Alzheimer's disease before the age of 70 years. The Alzheimer's disease-association of variants in the SORL1, ABCA7, and TREM2 genes was found in gene-based tests; carriers may come from small pedigrees with inheritance patterns of Alzheimer's disease suggestive of autosomal dominant inheritance. (B) GWAS hits are common (by convention, MAF >1%) variants that represent risk alleles that occur with significantly different frequency in patients with Alzheimer's disease and controls. Each variant is represented by the gene in which it occurs, or when the variant is non-coding, by the gene that maps closest to the variant (depicted in dark grey). (C) Protective variants are (very) rare variants suggested

Adverse effects of Alzheimer's disease

1. Cognitive Adverse Effects:

When asked about the disease which cause memory loss, majority of doctors would likely select Alzheimer's disease (AD). The most frequent cause of dementia is AD. The World Health Organization estimates that during the next 20 years, the 30 million people who currently suffer from Alzheimer's disease will triple in number [61]. Alzheimer's dementia is quite common, with projections suggesting that its cumulative incidence will rise from approximately 5% at age 70 to 50% by age 90. Until a cure for Alzheimer's disease is found, or at least a treatment that postpones the onset of dementia by five to ten years, healthcare systems in many societies will face pressure due to increasing longevity and changes in demographics. First identified by Alois Alzheimer in 1907, AD is a polygenetic neurodegenerative brain disease marked by neocortical atrophy that develops over decades and exhibits an increasing loss of synapses and neurons [62] Alzheimer's disease can be directly brought on by changes in the genes that encode the amyloid precursor proteins, presenilin-1 and presenilin-2. Trisomy 21 individuals and entire families are impacted by these deterministic genes, and the patients frequently exhibit an early onset of dementia in their forties. Nonetheless, they represent just 1% of all cases of Alzheimer's disease. The bulk of the remaining 99% of sporadic Alzheimer's cases involves patients aged over 65; [63] While not associated with the previously mentioned genes, these individuals also inherit approximately 60% to 80% of their risk for late-onset Alzheimer's disease, with the rest attributed to environmental factors[[63], [64]]. Late-onset AD may be an example of antagonistic pleiotropy because it involves a large number of genes, some of which are still unknown, and each of which contributes just a small portion of the person's total risk [65].

Executive functions encompass a broad array of cognitive processes that enable appropriate responses to environmental triggers. This collective term includes skills such as verbal reasoning, problem-solving, planning, sustained attention, resistance to distractions, multitasking, cognitive flexibility, and the capacity to handle new situations [66]. In order to support research on Executive Functions, numerous writers [67].

We have established a three-part classification that encompasses:

- Inhibition, which involves inhibitory control, self-regulation (behavioural inhibition), and interference control (selective attention and cognitive inhibition). This category includes the intentional suppression of prevailing or instinctive responses [68]. and would enable the regulation of behaviour, thoughts, and emotions, along with attention-related factors, in order to appropriately address the requirements of the task and specific goals [69]. Revising, which enables the retention and handling of information. It encompasses the refreshment and oversight of the representations gathered in the working memory (engagement of the Dorsolateral Prefrontal Cortex) [70] which enable suitable reactions to outside tasks or stimuli by processing pertinent information [71]. Cognitive flexibility (set-shifting) enables individuals to adjust their behavioural reactions to external stimuli [72]

2. Behavioural and Psychological Effects: -

The behavioural and psychological symptoms that are the most prevalent among patients with Alzheimer's disease (AD) include depression. Research studies indicate an average depressive symptom in approximately 38 to 50 percent of individuals with AD in the course of the disease [73]. Depression can be noted during the early AD phase and it is usually a mental response to the loss of memory and deteriorating functioning [74]. In others, it can even be considered a precursor of dementia implying the presence of common neurobiological processes like low levels of serotonin and noradrenaline and atrophy of the hippocampal and cortices [[75], [76]]. AD has been linked to the presence of depression which has been linked to accelerated cognitive decline, poor quality of life and high burden on the caregivers [73]. Depressive symptoms in AD are usually not similar to those of primary depression, and they are less guilty, less sad, and have fewer suicidal ideations [77]. The management normally involves selective serotonin reuptake inhibitors (SSRI) and psychological interventions

like cognitive behavioural therapy, which have relatively helped in the symptoms [78] . Nonetheless, the differing response rates in treatment indicate the necessity to work with individuals using a specific approach.

Agitation and Aggression in Alzheimer's Disease:

Agitation and aggression are common, uncomfortable behavioural-psychological complications in the patients with Alzheimer disease (AD). Agitation occurs in about 30-50% of AD patients and aggressive behaviours are much more prevalent in AD than in mild cognitive impairment or healthy ageing (odds ratio 4.9) [[79], [80]]. These behaviours can be in the form of restlessness, pacing, verbal outbursts, physical aggression or resistance to care and they lead to accelerated institutionalisation, burdened caregivers and higher cost of healthcare [[81], [82]]. Neurobiological processes that have been involved are the decline in cholinergic and dopaminergic transmission, cortical and limbic atrophy, and the inflammatory changes that may underlie agitation and aggression in AD [83]. Due to the safety issues and the complexity of the care, it will focus on non-pharmacological methods (environmental changes, behavioural interventions) prior to pharmacotherapy because of the lack of solid evidence of any particular drug treatment and adverse effects [[80], [84]]. Early identification and management of agitation/aggression is crucial to enhancing patient and carer outcomes.

A. Hallucination

One of the neuropsychiatric symptoms in the late stage of Alzheimer disease (AD) is hallucinations, especially visual hallucinations. They are found in about 10-25 per cent patients and have been linked with increased severity of the disease and worsening of the mind [[85], [86]]. A visual hallucination is more prevalent than auditory or tactile and can be in the form of seeing people, animals, or objects that do not exist [87].

B. Delusions:

Delusions are misconceptions which are inflexible convictions that are unreasonable and are also found in approximately 30-40 percent of patients with Alzheimer disease [88]. The delusional triggers are typical and encompassed paranoia, theft, infidelity, or misidentification of the well-known individuals [89]. It has a pathophysiology of dysfunction of the frontal and temporal cortical circuits and dopaminergic imbalance, which impairs reality testing [90]. Delusions also add to the agitation, aggression, and distress among caregivers and usually signal faster progression of the disease [91].

C. Sleep Disturbances:

A significant number of AD patients (up to 45% of patients) have sleep disturbances that can be in the form of insomnia, frequent night awakenings, and sleepiness [[92], [93]]. The disturbances exacerbate cognitive decline and burden of care. Physiologically, they are caused by the damage of suprachiasmatic nucleus (the circadian pacemaker of the brain) and deficiency of melatonin [94]. Disruption of sleep is also associated with higher deposition of b-amyloid, which indicates a two-way interaction between poor sleep and the development of AD [95]. The management involves regular sleep schedules, light therapy and melatonin and the use of sedative medications is done carefully [96].

D. Circadian Rhythm Disorder:

Another non-cognitive symptom of Alzheimer disease is circadian rhythm disorder, which is manifested by reversed sleep-wake, sundowning behaviour, and activity patterns [97]. The causes of these symptoms are the degeneration of the hypothalamic suprachiasmatic nucleus (SCN), and changes in the expression of the circadian genes [98]. As the illness advances, the patient will tend to exhibit sleepiness in the day and alertness in the nights hence resulting in caregiver fatigue and institutionalization [99]. Bright-light therapy, routines, morning exercise, and so forth have been documented to ameliorate sleep quality and effect the reestablishment of the circadian rhythm [100].

Medication-Related Adverse Effects:

Adverse Effects of Cholinesterase Inhibitors: - Cholinesterase (ChEls) - donepezil, rivastigmine and galantamine are a popular and common therapeutic option used to promote cognitive performance and slow-down functional impairment in Alzheimer disease (AD). Nevertheless, the cholinergic activity of them is generally not afraid to have adverse effects, the majority of which are related to the gastrointestinal, cardiovascular, and central nervous systems [101]. These are nausea, vomiting, diarrhoea, loss of appetite, and loss of weight which are dose-dependent and most common side effects seen in approximately 20-30% of patients who are treated [[102], [103]]. The symptoms are caused by the excessive stimulation of the parasympathetic because of the elevation of acetylcholine in the gut [104]. As cardiovascular adverse events, bradycardia, syncope and dizziness are particularly relevant among the elderly patients, or those taking Ss-blockers, or having existed conduction abnormalities [105]. Effects related to central nervous system (such as insomnia, vivid dreams, muscle cramps, fatigue, etc.) are also reported, especially with donepezil [106].Transdermal preparations are less likely to cause side effects related to gastrointestinal tract, however, whereas acetyl- and butyryl-cholinesterase inhibitor, rivastigmine, is more prone to do so [107]. In general, ChEIs have limited cognitive advantage but are tolerated and may cause severe cardiac complications that should be monitored carefully and individually dosed [108].

Adverse Effects of Memantine: - The N-methyl-D-aspartate (NMDA) receptor antagonist, memantine, is taken to treat moderate-to-severe cases of Alzheimer disease to prevent excitotoxic neuronal damage. It is usually well tolerated although there are reported adverse effects that occur as a result of the dose [109]. The most common ones are dizziness, headache, confusion, constipation, and hypertension, which are as a result of glutamatergic neurotransmission modulation, which transiently changes neuronal signalling [110]. Neuropsychiatric effects have also been described with agitation, hallucinations, anxiety, and somnolence especially with old patients or in the severely ill [[111], [112]]. Uncommon though significant side effects would be fatigue, vomiting, and balance issues, which would predispose older adults to the risk of falls [113]. Memantine also has fewer side effects (gastrointestinal and cardiovascular) than cholinesterase inhibitors, so it is appropriate to patients who are unable to tolerate these drugs [114]. However, patients with dysfunction in the kidney should be cautioned on the use because memantine is mainly released in its entirety and can build up in these patients.

Physical and Neurological Complications:

Balance problems and motor impairment are typical non-cognitive signs of Alzheimer-disease (AD), particularly during the later stages. There is a tendency to gait slowing, shorter stride length, and postural instability among patients that drastically elevate the risk of falls and other associated injuries [[115], [116]]. The motor impairments are caused by neurodegeneration outside the hippocampus, including the basal ganglia, cerebellum, and motor cortex, in addition to the fact that the sensorimotor integration is disrupted through the white matter degeneration [117]. Research indicates that AD patients are at two to three times more risk of falls than normal-minded older adults [118]. Visual-spatial disorientation, orthostatic hypotension, and the side effects of drugs like cholinesterase inhibitors or sedatives only worsen the balance problems [[119], [120]]. There is also a relationship between gait abnormalities, such as shuffling or freezing, and the progressive functional decline and higher rates of institutionalization [121]. The non-pharmacological measures that can be involved in the prevention of falls, as well as mitigating mobility in AD patients are physiotherapy, strength and balance training and environmental modification [[122], [123]].

Seizures have been identified as a severe neurological complication of advanced Alzheimer disease (AD), which affects 10-22% of the patients [[124], [125]]. These seizures are non-convulsive or focal often becoming short-term unresponsiveness, automatisms or myoclonic jerks which are easily confused with behavioural symptoms [126]. Neurodegeneration, Ss-amyloid deposition, and tau pathology increase seizure vulnerability in AD by disrupting neuronal networks and propensity of excitatory glutamatergic activity [[127], [128]]. The early-onset

patients or familial AD patients are more susceptible to seizures with mutations in the APP and PSEN1 genes resulting in an increase of neuronal hyperexcitability [129]. The occurrence of seizures is linked to increased cognitive deterioration and worse prognosis in general [130]. Electroencephalographic (EEG) recordings tend to demonstrate epileptiform discharges or subclinical seizure activity, and thus indicating the necessity of careful neurological assessment at the advanced stages [131]. These are usually treated with low doses of antiepileptic drugs (AEDs) including levetiracetam or lamotrigine that are favoured because of their cognitive safety profiles; benzodiazepines and older AEDs (e.g., phenytoin) are not preferred due to their sedative and cognitive adverse effects [[132], [133]].

Comorbidities and Secondary Complications:

Cardiovascular, Metabolic, and Infectious Complications Due to Immobility and Age

In more severe forms of the Alzheimer disease (AD), cardiovascular, metabolic, and infectious complications develop due to progressive cognitive impairment and immobility of the patients. Long-term immobility causes venous stasis, orthostatic hypotension, and decreased cardiac output, which exposes one to the risks of deep vein thrombosis (DVT), pulmonary embolism, and pressure-induced changes in ischemia [[134], [135]]. Furthermore, sedentary living leads to sarcopenia, insulin resistance, and dyslipidaemia thus exacerbating metabolic syndrome and cardiovascular morbidity [[136], [137]]. Age-associated vascular hardening and endothelial dysfunction complicate these complications and increase the risk of stroke and myocardial incidents in old AD patients [138].

Metabolically, poor nutrition, dehydration and catabolic stress lead to weight loss, hypoalbuminemia, and poor glucose tolerance all of which dull immune defences [139]. As a result, there is a high risk of respiratory tract and urinary tract infection, especially aspiration pneumonia and catheter-associated infections in the case of immobility and impaired swallowing mechanisms [[140], [141]]. The pneumonia is ranked as one of the major causes of mortality among patients with super-advanced AD and is frequently complicated by dysphagia and decreased cough reflex [142]. The early mobilization, physiotherapy, proper hydration, and careful infection prevention are the preventive measures that are necessary to curb these age- and immobility-related complications [[143], [144]].

Risk of Aspiration Pneumonia and Increased Mortality:

Aspiration pneumonia is one of the most common morbidity and mortality causes of patients with an advanced Alzheimer disease (AD). With the disease, patients also develop dysphagia, loss of cough reflex, and loss of consciousness, which predisposes them to food, liquid, or saliva spillage into the lower respiratory tract [[145], [146]]. Poor oral hygiene and immobility also contributes to the underlying neurodegeneration of cortical and brain stem swallowing canters, which predispose patients to micro aspiration and bacterial colonization [[147], [148]]. Research indicates that between 50-70 percent of severe AD patients develop swallowing dysfunction and aspiration pneumonia is the leading cause of hospitalization and even death among this group [[149], [150]].

Malnutrition, dehydration and weakened immunity increases the risk because it reduces the capacity to combat infection [151]. Moreover, airway protection reflexes and swallowing dysfunction may be worsened by the use of sedatives, antipsychotics and muscle relaxants [152]. As soon as aspiration pneumonia evolves, the prognosis is negative, and the mortality rates are reported to be over 40 percent six months after the initial attack [[153], [154]]. Prevention is possible by early detection of dysphagia, feeding support, sitting up during the taking of food and oral hygiene programs [155]. Although these interventions have been implemented, aspiration pneumonia continues to be a fatal outcome in most patients, as it adds to the prevalence of higher mortality and less quality of life in the end-of-life AD [156]

Emerging Biomarkers, Therapeutic Strategies, and Policy Initiatives in Alzheimer's Disease

It is mandatory to effectively interfere with Alzheimer disease (AD) at an early stage to be able to intervene with the disease in time and detect it properly. Some of the promising biological indicators that could be used to identify AD at an early stage even prior to the onset of the symptoms that signify a major clinical problem have been identified due to the recent developments in biomarker studies. Cerebrospinal fluid (CSF) biomarkers, including a decrease in amyloid-b42 (Ab42) and an increase in total tau (t-tau) and phosphorylated tau (p-tau) are traditionally regarded as important contributors to the pathology of Alzheimer ([157], [158]). More recent technologies have however made these proteins detectable in the blood, and provide less invasive and more accessible screening options. Ab42/Ab40 ratios and plasma p-tau isoforms (p-tau181, p-tau217, p-tau231) have been demonstrated to have a strong correlation with amyloid and tau pathology in the brain, and may therefore be useful in population-level screening ([159], [160]).

Neurofilament light chain (NfL), an axonal injury marker, has also become a sensitive neurodegeneration measure, which can be both measured in the CSF and blood, and that can distinguish among AD and other neurodegenerative conditions [161]. Besides fluid biomarkers, amyloid and tau deposition positron emission tomography (PET) and advanced MRI measures of brain atrophy are also used to assist the early and accurate diagnosis of AD [162]. New biomarkers, such as microRNAs, inflammatory cytokines, and synaptic proteins (e.g., neurogranin), which indicate disease processes at both molecular and cellular scales, are also identified as a potential in recent studies [163]. Combined, these new biomarkers have immense potential to diagnose Alzheimer disease in its preclinical stage giving an opportunity to intervene earlier and to create precision medicine strategies that could slow down or prevent cognitive impairment [164]

Modern medicine has a wide range of therapeutic strategies, starting with pharmacological therapy, which involves the use of medications to control biochemical pathways, decrease symptoms or alter disease progression; examples include antihypertensives, antibiotics, immunosuppressants, and targeted biologics [165]. Lifestyle modification, physical therapy, cognitive-behavioural therapy (CBT), and nutritional intervention are some of the non-pharmacological treatments that are significant in the treatment of chronic diseases and enhancement of quality of life [166]. Surgical surgery is still needed in case of structural or life-threatening conditions, including the simplest laparoscopic operations and the most sophisticated robotic surgeries [167]. The past few decades have seen the emergence of regenerative medicine, such as stem-cell therapy, tissue engineering, and gene therapy as the areas of study that might be able to repair or replace damaged tissues on a cellular level [168]. Moreover, the area of immunotherapy, especially in cancer treatment, has become a radically different approach using the immune system of the patient to kill cancerous cells with the use of checkpoint blockers, CAR-T cells, and cancer immunization [169]. Precision medicine is a genomics-based, biomarker profiling-driven approach that is based on personalized treatment to enhance the effectiveness of therapy and decrease adverse events [170]. The proactive measures such as vaccination, early screening and management of the risk factors also contribute to the long-term health and disease-reduction [171]. Alzheimer disease policy efforts have beginning to shift to early diagnosis, better care systems, and giving more resources to research. The Global Action Plan on the Public Health Response to Dementia (2017-2025) prepared by the World Health Organization encourages the member states to prepare national dementia plans that focus on raising awareness, risk-reduction, support to the caregiver, and surveillance [172]. Other national frameworks that have been put in place by many countries such as the United States to prevent and effectively treat Alzheimer and other related diseases include the National Plan to Address Alzheimer Disease that seeks to eliminate Alzheimer and effectively treat it by 2025 through increased research and better clinical care and family and caregiver support [173]. European Union Joint Action on Dementia facilitates the cross-nation cooperation to make care standards similar, enhance workforce training, and establish integrated care models within Europe [174]. Other initiatives worldwide are more focused on dementia-friendly communities, reform

in long-term care, and more funding toward biomarker discovery, research in precision-medicine, and programs focused on early-intervention [175]. Collectively, the policies are meant to minimize the burden of Alzheimer disease in the world through coordination of health-system, acceleration of research and social support systems.

Conclusion:

Alzheimer disease is a very complicated and devastating neurodegenerative condition characterized by progressive cognitive impairment, severe neuropsychiatric symptoms and various physical and medical complications that greatly aggravate both the results and the caregiver burden among the patients. The effect of the condition goes further than memory impairment, and affects behaviour, sleep pattern, mobility, neurological stability and predisposition to potentially fatal secondary complications of the condition, including aspiration pneumonia, infections, cardiovascular and metabolic decline. The available pharmacological interventions like the cholinesterase inhibitors and memantine have their modest symptomatic benefits but expose the patient to other adverse effects, which complicate the long-term treatment, which underscores the limitation of the existing treatment modalities.

The recent developments in biomarker discoveries, such as plasma and CSF tau/amyloid measures, neurofilament light chain, and imaging-based diagnostics are transforming the diagnosis of the disease at an early stage and could provide more tailored intervention approaches in the future. The new treatment options and international policy measures represent the increasing awareness of the importance of early diagnosis, caregiver involvement, and integrated care networks to alleviate the general load of AD. Nonetheless, there are still significant gaps in the disease-modifying treatments, long-term care planning, and practical application of precision-medicine strategies.

Taken together, the evidence points to the necessity of long-term research, better diagnostic quality, safer drugs, and overall public-health systems. These issues are important in reducing morbidity and mortality as well as enhancing the quality of life of patients, families and caregivers impacted by the Alzheimer disease.

Reference:

[1] T. B. G. Roth M, “Correlation between scores for dementia and counts of "senile plaque" in cerebrul grey matter of elderly subjects.,” *Nature ,* pp. 109-110, 1966.

[2] B. G. R. M. Romlinson BE, “Observarion on the brain of demented old people.”.

[3] B. G, “Alzheimers disease: A conceptual history.,” *International Journal of Geriatric Psychiatry.,* vol. 5, pp. 355-365, 1912.

[4] L. B. V. S. P. J. k. W. D. S. e. a. Wiley CA, “Carbon 11-labeled Pittsburgh Compound B and Carbon 11-labeled (R)-PK1119 position emission tomographic imaging in Alzheimer disease.,” *Arch Neurol,* vol. 66, pp. 60-67, 2009.

[5] M. M. D. G. X. C. G. E. M. J. Roe CM, “ Alzheimer disease and cognitive reserve: variation of education effect with carbon 11-labeled Pittsburgh Compound B uptake.,” *Arch Neurol,* pp. 1467-1471, 2008.

[6] K. WE., “Biopsy support for the validity of Pittsburgh compound B positron emission tomography with a twist.,” *Arch Neurol,* pp. 1281-1283, 2008.

[7] I. M. B. T. S. M. F. A. S. A. e. a. Cairns NJ, "Absence of Pittsburgh compound B detection of cerebral amyloid beta in a patient with clinical, cognitive, and cerebrospinal fluid markers of Alzheimer disease: a case report.," *Arch Neurol,* vol. 66, pp. 1557-1562, 2009.

[8] N. R. S. J. P. J. M. C. T. N. e. a. Aizenstein HJ, "Frequent amyloid deposition without significant cognitive impairment among the elderly.," *Arch Neurol ,* vol. 65, pp. 1509-1517, 2008.

[9] A. I. A. S. S. T. S. S. N. K. e. a. Leinonen V, "Assessment of beta- amyloid in a frontal cortical brain biopsy specimen and by positron emission tomography with carbon 11-labeled Pittsburgh Compound B.," *Arch Neurol,* vol. 65, pp. 1304-1309, 2008.

[10] P. RC, " Mild cognitive impairment as a diagnostic entity.," *J Intern Med ,* vol. 256, pp. 183-194, 2004.

[11] N. I. o. Aging., "What Happens to the Brain in Alzheimer's Disease?," 2024.

[12] H. J. Selkoe DJ, " The amyloid hypothesis of Alzheimer's disease at 25 years.," *EMBO Molecular Medicine. ,* vol. 8(6), pp. 595-608, 2016.

[13] A. Association., "2024 Alzheimer's Disease Facts and Figures. Alzheimer's & Dementia.," Alzheimer's Association. , 2024.

[14] L. L. M.-L. E. Cerejeira J, "Behavioral and psychological symptoms of dementia.," *Frontiers in Neurology. ,* 2012.

[15] H. D. Musiek ES, "Mechanisms linking circadian clocks, sleep, and neurodegeneration.," *Science. ,* vol. 354(6315), pp. 1004-1008, 2016.

[16] B. A., "Alzheimer's disease.," *BMJ,* 2009.

[17] WHO, "Pharmacovigilance: Ensuring the Safe Use of Medicines.," WHO, 2023.

[18] P. B. C. P. Lazarou J, " Incidence of adverse drug reactions in hospitalized patients: a meta-analysis.," *JAMA,* vol. 279(15), pp. 1200-1205, 1998.

[19] G. K. S. J. Q. C. J. Schmittdiel JA, "Effect of physician and patient communication on adherence to treatment.," *Medical care,* vol. 38(3), pp. 300-309, 2000.

[20] A. J. Edwards IR, "Adverse drug reactions: definitions, diagnosis, and management.," *The Lancet.,* vol. 365(9237), pp. 1255-1259, 2000.

[21] C. J. Beauchamp TL, "Principles of Biomedical Ethics.," Oxford University Press, 2019.

[22] E. S. Waller PC, "A model for the future conduct of pharmacovigilance.," *Pharmacoepidemiology and Drug Safety. ,* vol. 12(1), pp. 17-29, 2003.

[23] A. MJ., "Factors affecting the development of adverse drug reactions (Review article).," *Saudi Pharmaceutical Journal. ,* vol. 22(2), pp. 83-94, 2014.

[24] w. Von Oostveen and E. de Lange, "Image Techniques in Alzheimers disease.," *Int.J.Mol.Sci,* 2021.

[25]

[26] B. A. Grant MJ, " A typology of reviews: an analysis of 14 review types and associated methodologies.," *Health Information & Libraries Journal.,* vol. 26(2), pp. 91-108, 2009.

[27] J. C. A. A. Green BN, "Writing narrative literature reviews for peer-reviewed journals: secrets of the trade.," *Journal of Chiropractic Medicine.,* vol. 5(3), pp. 101-117, 2006.

[28] R. H. Petticrew M, "Systematic Reviews in the Social Sciences: A Practical Guide," *Blackwell Publishing,* 2006.

[29] T. J. C. J. e. a. (. Higgins JPT, "Cochrane Handbook for Systematic Reviews of Interventions," *Version 6.3. Cochrane,* 2022.

[30] P. M. S. C. e. a. Munn Z, "Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach.," *BMC Medical Research Methodology.,* vol. 18(1), p. 143, 2018.

[31] S. A. P. D. Booth A, "Systematic Approaches to a Successful Literature Review," *3rd ed. Sage Publications,* 2021.

[32] H. C., "Doing a Literature Review: Releasing the Research Imagination," *2nd ed. Sage Publications,* vol. 2, 2018.

[33] K. E. De Strooper B, " The cellular phase of Alzheimer's disease.," *CELL,* 2016.

[34] K. S. F. B. e. a. Venegas C, "59. Microglia-derived ASC specks cross-seed amyloid-beta in Alzheimers disease.," *Nature,* 2017.

[35] S. A. Z. B. Sweeney MD, "Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders.," *Nat Rev Neurol,* 2028.

[36] L. A. V. A. e. a. Da Mesquita S, "61. .Functional aspects of meningeal lymphatics in ageing and Alzheimer's disease.," *Nature ,* 2018.

[37] A. L. Z. J. e. a. Lu T, "REST and stress resistance in ageing and Alzheimer's disease.," *Nature ,* 2014.

[38] N. M. Plog BA, "The glymphatic system in central nervous system health and disease:past, present, and future.," *Annu Rev Pathol.,* 2018.

[39] H. D. Long JM, "Alzheimer disease: an update on pathobiology and treatment strategies.," *Cell,* 2019.

[40] V. S. E. O. S. e. a. Koper MJ, "Necrosome complex detected in granulovacuolar degeneration is associated with neuronal loss in Alzheimer's disease.," *Acta Neuropathol.,* 2020.

[41] S. A. W. A. e. a. Keren-Shaul H, "A unique microglia type associated with restricting development of Alzheimer's disease.," *Cell,* 2017.

[42] A. T. B. M. e. a. Parhizkar S, "Loss of TREM2 function increases amyloid seeding but reduces plaque-associated ApoE.," *Nat Neurosci,* 2019.

[43] W. L. F. N. e. a. Sala Frigerio C, "The major risk factors for Alzheimer's disease: age, sex, and genes modulate the microglia response to Aβ plaques.," *Cell Rep,* 2019.

[44] H. J. S. M. Hansen DV, "Microglia in Alzheimer's disease.," *J cell Biol ,* 2017.

[45] W. Y. T. I. G. L. S. M. Yeh FL, "TREM2 binds to apolipoproteins, including APOE and CLU/APOJ, and thereby facilitates uptake of amyloid-beta by microglia.," *Neuron ,* 2016.

[46] P. S. F. A. e. a. Griciuc A, "TREM2 acts downstream of CD33 in modulating microglial pathology in Alzheimer's disease.," *Neuron.,* 2019.

[47] F. F. C. F. e. a. Deming Y, "The MS4A gene cluster is a key modulator of soluble TREM2 and Alzheimer's disease risk.," *Sci Transl Med ,* 2019.

[48] L. A. M. R. e. a. Sierksma A, "Novel Alzheimer risk genes determine the microglia response to amyloid-beta but not to TAU pathology.," *EMBO Mol Med,* 2020.

[49] U. J. F. M. e. a. Leyns CEG, "TREM2 deficiency attenuates neuroinflammation and protects against neurodegeneration in a mouse model of tauopathy.," *Proc Natl Acad Sci USA,* 2017.

[50] U. J. F. M. e. a. Leyns CEG, "TREM2 deficiency attenuates neuroinflammation and protects against neurodegeneration in a mouse model of tauopathy.," *Proc Natl Acad Sci USA,* 2017.

[51] L. A. M. R. e. a. Sierksma A, "Novel Alzheimer risk genes determine the microglia response to amyloid-beta but not to TAU pathology.," *EMBO Mol Med,* 2020.

[52] G. M. N. S. e. a. Leyns CEG, "TREM2 function impedes tau seeding in neuritic plaques," *Nat Neurosci,* 2019.

[53] L. A. M. R. e. a. Sierksma A, "Novel Alzheimer risk genes determine the microglia response to amyloid-beta but not to TAU pathology.," *EMBO Mol Med,* 2020.

[54] V. D. D. J. F. N. e. a. Mancuso R, "Stem-cell-derived human microglia transplanted in mouse brain to study human disease.," *Nat Neurosci,* 2019.

[55] C. M. E. W. e. a. Hasselmann J, "Development of a chimeric model to study and manipulate human microglia in vivo.," *Neuron,* 2019.

[56] W. I. M. I. e. a. Park J, "A 3D human triculture system modeling neurodegeneration and neuroinflammation in Alzheimer's disease.," *Nat Neurosci ,* 2018.

[57] S. D. S. C. e. a. Gremer L, "Fibril structure of amyloid-beta (1–42) by cryo-electron microscopy.," *science ,* 2017.

[58] F. B. H. S. e. a. Fitzpatrick AWP, "Cryo-EM structures of tau filaments from Alzheimer's disease.," *Nature ,* 2017.

[59] Z. R. Z. Q. e. a. Yang G, "Structural basis of Notch recognition by human γ-secretase.," *Nature ,* 2019.

[60] M. B. L. S. e. a. Szaruga M, "Alzheimer's-causing mutations shift Aβ length by destabilizing γ-secretase-Aβn interactions.," *Cell,* 2017.

[61] A. J. L. &. W. B. Wimo, "An estimate of the worldwide prevalence and direct costs of dementia in 2003.," *Dementia and Geriatric Cognitive Disorders,* vol. 21(3), pp. 175-181, 2006.

[62] A. Alzheimer, "eine eigenartige Erkrankung der Hirnrinde.," *llgemeine Zeitschrift für Psychiatrie und Psychisch-Gerichtliche Medizin,* pp. 146-148, 1907.

[63] K. d. L. M. J. &. Z. H. Blennow, "Alzheimer's disease.," *The Lancet,,* pp. 387-403, 2006.

[64] A. R. G. R. A. M. V. I. D. H. D. A. R. S. R. C. J. H. G. H. P. J. L. L. S. P. J. P. P. L. M. K. B. C. R. D. C. G. M. .. W. Gerrish, "The role of variation at AβPP, PSEN1, PSEN2, and MAPT in late-onset Alzheimer's disease.," *Journal of Alzheimer's Disease,,* pp. 377-387, 2012.

[65] WilliamsGC., "Pleiotropy, natural selection, and the evolution of senescence.," *evolution.*

[66] 1. S. 1. D. 1. S. e. a. 1. G. a. L. 1. e. a. Stuss and Benson, 2000.

[67] L. e. a. D. Miyake et al, "2000, 2003, 2013".

[68] M. e. al., 2000.

[69] Diamond, *2013.*

[70] M. e. al., 2000.

[71] M. e. al., 2000.

[72] S. a. J. D. Baddely and Hitch, 1994, 1999, 2013.

[73] C. e. al., "Depression in Alzheimer's: Prevalence, Mechanism and Management.," *Frontiers in Aging Neuroscience.,* 2023.

[74] Z. Q. e. al., "Behavioral and psychological symptoms in Alzheimer's disease.," *Frontiers in Aging Neuroscience.,* 2023.

[75] L. Y. e. al., "Neurochemical basis of depression in Alzheimer's disease.," *Journal of Alzheimer's Disease.,* 2022.

[76] E. D. e. al., "Depression in dementia: epidemiology, mechanisms, and treatment.," *Psychiatry & Psychopharmacology.,* 2011.

[77] E. D. e. al., "Depression in dementia: epidemiology, mechanisms, and treatment," *4. Psychiatry & Psychopharmacology.,* 2011.

[78] K. D. I. e. a. t. f. d. i. d. a. s. r. a. meta-analysis., "Psychological treatments for depression in dementia: a systematic review and meta-analysis.," *5. The British Journal of Psychiatry.,* 2023.

[79] T. J. e. a. Ryu H, "Aggressive Behaviors in Alzheimer Disease and Mild Cognitive Impairment: A Meta-Analysis.," *PMC,* 2019.

[80] O. J. e. a. Ballard C, "Agitation and Dementia: Prevention and Treatment Strategies in Alzheimer's Disease.," *Frontiers in Neurology.,* 2021.

[81] e. a. Conde-Sala JL, "Agitation and Irritability in Alzheimer's Disease: Evidence-based Review.," *PMC,* 2019.

[82] A. Society., "Aggressive behaviour and dementia.," Alzheimer's Society., 2021.

[83] e. a. Rossi M, "Neurobiological Alteration in Agitation in Alzheimer's Disease and Related Dementia.," *Frontiers in Psychiatry.,* 2024.

[84] e. a. Zahodne LB, "Prevalence and Correlates of Aggressive Behavior in Alzheimer's Disease.," *J Neuropsychiatry.,* 2011.

[85] e. a. Ballard C, "Neuropsychiatric Symptoms in Alzheimer's Disease: Hallucinations and Delusions.," *Lancet Neurology. ,* 2021.

[86] e. a. Ismail Z, "Prevalence of Hallucinations in Alzheimer's Disease and Other Dementias: A Systematic Review.," *International Journal of Geriatric Psychiatry.,* 2020.

[87] A. Society., "Hallucinations and Dementia.," Alzheimer's Society, 2022.

[88] e. a. Ropacki SA, "Delusions and Hallucinations in Alzheimer's Disease: Prevalence and Clinical Correlates.," *Journal of Alzheimer's Disease.,* 2020.

[89] e. a. Ballard C, "Neuropsychiatric Symptoms in Dementia: Focus on Delusions and Hallucinations.," *Lancet Neurology.,* 2021.

[90] e. a. Sweet RA, "Neural Basis of Delusions in Alzheimer's Disease.," *Biological Psychiatry.,* 2019.

[91] e. a. Zahodne LB, "Association of Psychotic Symptoms with Disease Progression in AD.," *J Neuropsychiatry.,* 2011.

[92] e. a. Lim AS, " Sleep Fragmentation and Alzheimer's Disease Pathology in Older Adults.," *Sleep,* 2020.

[93] e. a. Moran M, "Sleep Disturbances in Alzheimer's Disease: Epidemiology and Management.," *Frontiers in Aging Neuroscience.,* 2022.

[94] e. a. Wang JL, "Circadian Dysfunction and Neurodegeneration in Alzheimer's Disease.," *Nature Reviews Neurology. ,* 2021.

[95] e. a. Ju YE, "Sleep Quality and β-Amyloid Accumulation in Alzheimer's Disease.," *JAMA Neurology.,* 2020.

[96] e. a. McCurry SM, "Nonpharmacologic Management of Sleep Disturbances in Dementia.," *Clinical Geriatrics. ,* 2019.

[97] e. a. Harper DG, "Disturbance of Circadian Rhythms in Alzheimer's Disease.," *American Journal of Geriatric Psychiatry.,* 2020.

[98] e. a. Leng Y, "Circadian Rhythm Disruption and Risk of Alzheimer's Disease.," *Nature Reviews Neurology.,* 2021.

[99] e. a. Musiek ES, "Sleep and Circadian Rhythms in Alzheimer's Disease: Mechanisms and Therapies.," *Nature Reviews Neuroscience.,* 2022.

[100] e. a. Riemersma-van der Lek RF, " Effect of Bright Light and Melatonin on Sleep and Circadian Rhythms in Dementia.," *Journal of the American Medical Association (JAMA).,* 2019.

[101] B. J., "Cholinesterase inhibitors for Alzheimer's disease.," *Cochrane Database of Systematic Reviews.,* 2021.

[102] e. a. Farlow MR, "Safety and tolerability of donepezil in Alzheimer's disease.," *Clinical Therapeutics.,* 2020.

[103] e. a. Rogers SL, "Adverse event profile of cholinesterase inhibitors in Alzheimer's disease trials.," *Neurology,* 2019.

[104] P. S. Lane RM, "Effects of cholinesterase inhibition on the gastrointestinal system.," *Journal of Clinical Psychiatry.,* 2021.

[105] e. a. Gill SS, "Syncope and its consequences in patients with dementia treated with cholinesterase inhibitors.," *Archives of Internal Medicine.,* 2009.

[106] A. P. Information., "Donepezil hydrochloride: Adverse reactions.," Eisai/Pfizer Pharmaceuticals., 2024.

[107] B. R., "Rivastigmine transdermal patch in the management of Alzheimer's disease: efficacy and tolerability.," *CNS Drugs,* 2022.

[108] e. a. Hernández-Ramos FJ, "Cardiovascular adverse events associated with cholinesterase inhibitors: a pharmacovigilance review.," *Frontiers in Pharmacology.,* 2023.

[109] e. a. Reisberg B, "Memantine in moderate-to-severe Alzheimer's disease.," *New England Journal of Medicine.,* 1333-1341.

[110] e. a. Parsons CG, "Memantine: Mechanism of action and clinical update.," *CNS Drugs,* 2020.

[111] e. a. Periclou A, "Pharmacokinetics and safety of memantine in elderly subjects.," *5. Clinical Pharmacokinetics.,* 2006.

[112] M. K., "Memantine: A review of its use in Alzheimer's disease.," *CNS Drugs.,* 2020.

[113] e. a. Burns A, "Tolerability of memantine compared with cholinesterase inhibitors in Alzheimer's disease.," *International Journal of Neuropsychopharmacology.,* 2019.

[114] N. X. P. Information., "Memantine hydrochloride: Adverse reactions and precautions.," *Allergan/AbbVie Pharmaceuticals.,* 2024.

[115] e. a. Sheridan PL, "Influence of executive function on locomotor function: Divided attention increases gait variability in Alzheimer's disease.," *Journal of the American Geriatrics Society.,* vol. 51(11), pp. 1633-1637, 2003.

[116] e. a. Allan LM, "Falls in dementia: frequency, characteristics, and risk factors.," *Age and Ageing,,* vol. 38(6), pp. 620-626, 2009.

[117] e. a. Srikanth V, "White matter lesions and gait decline in Alzheimer's disease.," *Neurology.,* pp. 212-218, 2010.

[118] e. a. Camicioli R, " Gait and balance impairment in Alzheimer's disease: a prospective study.," *Journal of Neurology.,* pp. 59-60, 2006.

[119] e. a. Montero-Odasso M, "Cognitive impairment, gait performance, and fall risk in older adults with dementia.," *Cognitive impairment, gait performance, and fall risk in older adults with dementia.,* pp. 896-903, 2012.

[120] e. a. Gill SS, "Syncope and falls in patients with dementia receiving cholinesterase inhibitors.," *Archives of Internal Medicine,,* 2009.

[121] e. a. Buchman AS, "Alzheimer's disease pathology and parkinsonian signs in older persons.," *Brain,* pp. 504-512, 2011.

[122] e. a. Gillespie LD, "Interventions for preventing falls in older people living in the community.," *Cochrane Database of Systematic Reviews.,* 2012.

[123] e. a. Mirelman A, "Exercise and motor training in Alzheimer's disease: effects on gait and balance.," *Frontiers in Aging Neuroscience,* 2019.

[124] e. a. Vossel KA, "Seizures and epileptiform activity in the early stages of Alzheimer disease.," *JAMA Neurology.,* pp. 1158-1166, 2013.

[125] S. N. Pandis D, "Seizures in Alzheimer's disease: clinical and epidemiological data.," *Epilepsy Currents.,* vol. 12(5), pp. 184-187, 2012.

[126] e. a. Amatniek JC, "Incidence and predictors of seizures in patients with Alzheimer's disease.," *Epilepsia,* vol. 47(5), pp. 867-872, 2006.

[127] K. A. Busche MA, " Neuronal hyperactivity a key defect in Alzheimer's disease?," *BioEssay,* pp. 624-632, 2015.

[128] e. a. Lam AD, "Silent hippocampal seizures and spikes identified by foramen ovale electrodes in Alzheimer's disease.," *Nature Medicine.,* pp. 678-680, 2017.

[129] M. L. Palop JJ, "Epilepsy and cognitive impairments in Alzheimer's disease: causes and therapeutic implications.Lancet Neurology," *Lancet Neurology,* pp. 894-906, 2016.

[130] e. a. Vossel KA, "Impact of epileptiform activity on cognitive decline in Alzheimer's disease.," *Annals of Neurology.,* vol. 80(6), pp. 858-870, 2017.

[131] e. a. Horvath A, "EEG and epilepsy in Alzheimer's disease: A systematic review.," *Neurobiology of Aging.,* pp. 241-255, 2018.

[132] L. L. Cumbo E, "Levetiracetam, lamotrigine, and phenobarbital in patients with epileptic seizures and Alzheimer's disease.," *Epilepsy & Behavior.,* pp. 461-466, 2010.

[133] L. A. Lozsadi DA, "Prevalence and causes of seizures at the time of diagnosis of Alzheimer's disease.," *Dementia and Geriatric Cognitive Disorders.,* vol. 22(2), pp. 121-124, 2006.

[134] e. a. Mitsumoto H, "ystemic complications of immobility in neurodegenerative diseases.," *Journal of Neurology.,* vol. 254(Suupl 2), pp. 1165-1172, 2007.

[135] K. R. Bridenbaugh SA, "Motor function and falls in Alzheimer's disease: Implications for cardiovascular health.," *Aging Clinical and Experimental Research.2011,* 333-338.

[136] e. a. Kelaiditi E, "Sarcopenia and metabolic impairment in Alzheimer's disease.," *Ageing Research Reviews.,* vol. 15, pp. 58-67, 2014.

[137] e. a. Panza F, "Metabolic syndrome and cognitive impairment: evidence from epidemiological studies.," *Ageing Research Reviews,* vol. 9(4), pp. 355-373, 2010.

[138] I. C., "The pathobiology of vascular dementia and Alzheimer's disease: vascular contributions to cognitive impairment and dementia.," *Neuron, ,* vol. 80(4), pp. 844-866, 2013.

[139] e. a. Faxén-Irving G, "Nutritional and metabolic status of Alzheimer's patients: relation to disease progression.," *Clinical Nutrition,,* vol. 24(6), pp. 982-989, 2005.

[140] e. a. van der Maarel-Wierink CD, "Oral health care and aspiration pneumonia in frail older people: a systematic review.," *Journal of the American Geriatrics Society,,* vol. 59(2), pp. 223-229, 2011.

[141] J.-M. M. Rowe TA, " Urinary tract infection in older adults. Aging Health,," *Urinary tract infection in older adults. Aging Health, ,* pp. 519-528, 2014.

[142] e. a. Kuo CL, "Causes of death in Alzheimer's disease: pneumonia as a frequent terminal event.," *Journal of the American Geriatrics Society,,* vol. 63(4), pp. 740-745, 2015.

[143] e. a. Langmore SE, "Preventing aspiration and pneumonia in elderly patients with dementia.," *Dysphagia,,* vol. 17(4), pp. 298-307, 2002.

[144] e. a. Rolland Y, "Physical activity and functional recovery in nursing home residents with dementia.," *Journal of the American Medical Directors Association, ,* vol. 9(5), pp. 337-344, 2008.

[145] e. a. Langmore SE, "Predictors of aspiration pneumonia: how important is dysphagia?," *Dysphagia,,* p. 298–307., 2002.

[146] e. a. Wada H, "Relationship between swallowing function and cognitive decline in Alzheimer's disease.," *Geriatrics & Gerontology International, ,* vol. 17(12), pp. 2449-2455, 2017.

[147] e. a. Humbert IA, "Cortical and brainstem control of swallowing: implications for neurodegenerative disease. Dysphagia,," *Cortical and brainstem control of swallowing: implications for neurodegenerative disease. Dysphagia, ,* pp. 218-226, 2010.

[148] e. a. van der Maarel-Wierink CD, "Oral health care and aspiration pneumonia in frail older people: a systematic review.," *Journal of the American Geriatrics Society,,* pp. 223-229, 2011.

[149] e. a. Affoo RH, "Prevalence of dysphagia in Alzheimer's disease: a systematic review and meta-analysis.," *Age and Ageing, ,* pp. 372-377, 2013.

[150] e. a. Kuo CL, "Causes of death in Alzheimer's disease: pneumonia as a frequent terminal event.," *Journal of the American Geriatrics Society,,* pp. 740-745, 2015.

[151] e. a. Faxén-Irving G, "Nutritional and metabolic status of Alzheimer's patients and relation to disease progression.," *Clinical Nutrition, ,* p. 982–989., 2005.

[152] e. a. Steele CM, "Medication-induced dysphagia: mechanisms and management.," *Dysphagia,,* pp. 114-120, 2015.

[153] e. a. Mitchell SL, "The clinical course of advanced dementia.," *New England Journal of Medicine,,* pp. 1529-1538, 2009.

[154] K. D. Marik PE, " Aspiration pneumonia and dysphagia in the elderly.," *Chest,,* pp. 328-336, 2003.

[155] S. R. Clavé P, "Dysphagia: current reality and scope of the problem.," *Nature Reviews Gastroenterology & Hepatology, ,* pp. 259-270, 2015.

[156] C. C. T. K. Finucane TE, "Tube feeding in patients with advanced dementia: impact on survival and aspiration pneumonia.," *JAMA,* pp. 1365-1370, 1999.

[157] B. D. B. K. e. a. Jack CR Jr, " NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease.," *Alzheimer's & Dementia. ,* pp. 535-562, 2018.

[158] Z. H. Blennow K, "Biomarkers for Alzheimer's disease: current status and prospects for the future.," *Journal of Internal Medicine. ,* pp. 643-663, 2018.

[159] J. S. Q. Y. e. a. Palmqvist S, " Discriminative accuracy of plasma phosphorylated tau181 and 217 for Alzheimer's disease versus other neurodegenerative disorders.," *Nature Medicine. ,* pp. 387-397, 2020.

[160] L. J. R. W. A. e. a. Thijssen EH, "Diagnostic value of plasma phosphorylated tau181 in Alzheimer's disease and frontotemporal lobar degeneration.," *Nature Medicine,,* pp. 387-397, 2020.

[161] L. A. L. Y. e. a. Ashton NJ, "Increased plasma neurofilament light chain concentration correlates with severity of Alzheimer's disease.," *Nature Communications. ,* 2021.

[162] B. S. B. P. e. a. Villemagne VL, " Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study.," *The Lancet Neurology. ,* 2013357-367.

[163] W. N. G. S. S. A. Swarbrick S, "Systematic review of miRNA as biomarkers in Alzheimer's disease.," *Molecular Neurobiology. ,* pp. 6156-6167, 2019.

[164] B. B. Zetterberg H, "Biomarkers for Alzheimer's disease—preparing for a new era of disease-modifying therapies.," *Molecular Psychiatry. ,* pp. 296-308, 2021.

[165] e. a. Katzung BG, "Basic & Clinical Pharmacology.".

[166] A. C. o. L. Medicine., "Lifestyle Medicine Guidelines.," American College of Lifestyle Medicine..

[167] e. a. Townsend CM, Sabiston Textbook of Surgery..

[168] M. C. &. D. P., ""A brief definition of regenerative medicine."," Regenerative Medicine..

[169] C. D. &. M. I., "Elements of cancer immunity and the cancer–immune set point."," *Nature* .

[170] C. F. &. V. H., " "A new initiative on precision medicine."," *NEJM.*

[171] C. f. D. C. a. P. (CDC)., "Prevention Guidelines.," Centers for Disease Control and Prevention (CDC). .

[172] W. H. Organization., "Global Action Plan on the Public Health Response to Dementia.," WHO, 2017-2025.

[173] U. D. o. H. a. H. Services., "National Plan to Address Alzheimer's Disease.," U.S. Department of Health and Human Services. .

[174] E. Commission., "EU Joint Action on Dementia: Aims and Outcomes.," UC.

[175] e. a. Prince M., "World Alzheimer Report: Improving Healthcare Systems to Address Dementia.," Alzheimer's Disease International..

[176] d. rathod, "abs," *tyhe,* p. 12, 2025.

[177] WHO, " Pharmacovigilance: Ensuring the Safe Use of Medicines.," WHO, 2023.

[178] L. A. M. R. e. a. Sierksma A, "Novel Alzheimer risk genes determine the microglia responseto amyloid-beta but not to TAU pathology.," *EMBO Med Mol ,* 2020.

[179] e. a. McShane R, "Memantine for dementia. Cochrane Database of Systematic Reviews.".

[180] e. a. Amatniek JC, "Incidence and predictors of seizures in patients with Alzheimer's disease.," *Epilepsia,* pp. 867-872, 2006.

[181] K. A. Busche MA, " Neuronal hyperactivity a key defect in Alzheimer's disease?," *BioEssay,* pp. 624-632, 2015.