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MEMOIRE DE FIN D'ETUDES POUR
L'OBTENTION DU DIPLOME DE DOCTEUR EN PHARMACIE

THÈME:

A Meta-analysis of the evaluation of the effectiveness of available treatments for Alzheimer's Disease

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Soutenu le
30 Juin 2024

Jury

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Thanks to:

I am overcome with thankfulness for Almighty God, who gives us both the health and the motivation to finish our final dissertation.

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I would like to thank the jury members and the President

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To the members of the jury,

Allow us to thank you **Madam President, Dr. ILHEM MOKHTARI**

for this great honour that you do us, by agreeing to chair this jury despite your multiple occupations.

With all respect and consideration, we kindly ask you to accept our most honourable feelings.

Dr. Mohammed Nassim BOUKLI HACENE and Dr. ABDELALLI YOUSSOUF

You do us the honour of kindly accepting to sit among our dissertation jury.

Dedication:

I dedicate this modest work as a statement of my thanks to my parents, *Catherine Munengwa and Willie Trichadt Munengwa* who have been my source of strength and pride and who have showered me with love, kindness, and hope. I owe you respect and success for all the efforts you took to ensure my wellbeing, as well as for your prayers and unwavering support during my academic career.

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Abstract

A meta-analysis of the efficacy of the various treatments for Alzheimer's disease (AD) is presented in this thesis. We examine the general aspects of AD in the first chapter and the pharmaceutical treatments in the second. When we visited the CHU of Tlemcen's neuropsychiatry department, we saw that memantine (10 mg) and donepezil (10 mg) work well with very few side effects. Despite the lack of statistically significant differences between the treatment and placebo groups, other factors indicate that treatments are beneficial in lowering costs and providing advantages to caregivers. This meta-analysis emphasises the significance of memantine and cholinesterase inhibitors, as well as the necessity for more study to create novel therapies.

Keywords: Alzheimer’s Disease, MetaAnalysis, Cognitive Decline

Resume

Une méta-analyse de l'efficacité des traitements disponibles pour la maladie d'Alzheimer (MA) est présentée dans ce mémoire. Dans le chapitre initial, nous examinons les aspects généraux de la MA, tandis que dans le chapitre suivant, nous examinons les traitements pharmacologiques. Au CHU de Tlemcen, nous avons fait une visite au département de neuropsychiatrie et constaté que le donépézil (10 mg) et la mémantine (10 mg) sont efficaces, avec des rares effets indésirables. Malgré l'absence de différences significatives entre les groupes de traitement et de placebo, l'analyse statistique montre que d'autres facteurs mettent en évidence l'efficacité des traitements dans la diminution des dépenses et les avantages pour les aidants. L'importance des inhibiteurs du cholinestérase et de la mémantine est mise en évidence par cette méta-analyse, et il est essentiel de mener des recherches supplémentaires afin de développer de nouveau traitement.

Mots-clés : Maladie D’alzheimer, Meta-analyse, Declin Cognitif

ملخص:

العلاجات المختلفة لمرض الزهايمر. ندرس الجوانب العامة لمرض الزهايمر في الفصل تقدم هذه الرسالة تحليلاً لفعالية الأول والعلاجات الدوائية في الفصل الثاني. عندما زرنا قسم الأمراض العصبية والنفسية في وحدة الأمراض العصبية ملغ) يعملان بشكل جيد مع آثار جانبية قليلة جداً. على الرغم 10) والنفسية في تلمسان، وجدنا أن الميمانتين والدونيبيزيل من عدم وجود فروق ذات دلالة إحصائية بين مجموعتي العلاج والعلاج الوهمي، إلا أن هناك عوامل أخرى تشير إلى أن العلاج مفيد في خفض التكاليف وتوفير مزايا لمقدمي الرعاية. يؤكد هذا التحليل هذا على أهمية الميمانتين ومثبطات الكولينستراز، بالإضافة إلى ضرورة إجراء المزيد من الدراسات لابتكار علاجات ج

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List of abbreviations:

- **Aβ :** Alpha Beta plaques
- **Ab :** Alpha Beta plaques
- **Acetyl-CoA :** Acetyl Coenzyme A
- **ACh :** Acetlycholine
- **AChE :** Acetlycholinesterase
- **ADCS-ADL:** Alzheimer's Disease Cooperative Study - Activities of Daily Living
- **AD :** Alzheimer's Disease
- **ADAS-Cog:** Alzheimer's Disease Assessment Scale-Cognitive
- **ADL:** Activities of Daily Living
- **ALF:** Accelerated Long-Term Forgetting
- **APP :** Amyloid precursor protein
- **APOE4 :** Apolipoprotein E 4
- **BADL:** Basic Activities of Daily living
- **BPSD:** Behavioural and psychological symptoms of Dementia
- **BuChE:** Butyrylcholinesterase
- **CHEI:** Cholinesterase inhibitors
- **CHU:** Central University Hospital
- **CIBIC+:** Clinical Interviewer - Based Impression of Change plus carer interview
- **CJD:** Creutzfeldt-Jakob Dementia
- **CMAI:** Cohen-Mansfield Agitation Inventory
- **CNS:** Central Nervous Sysytem
- **CT:** Computed Tomography
- **CSF:** Cerebrospinal Fluid
- **DAD-K:** Disability Assessment for Dementia
- **DMT:** Dimethtryptamine
- **DS:** Down Syndrome
- **FAD:** Familial Alzheimer's Disease
- **FDA:** Food and Drug Administration
- **FDT:** Frontotemporal Dementia

- **IADL:** Instrumental Activities of Daily Living
- **iGluRs:** Ionotropic Glutamate Receptors
- **LBD:** Lewy Body Dementia
- **LOCF:** Last Observation Carried Forward
- **LTD:** Long Term Depression
- **LTP:** Long Term Potentiation
- **MCI:** Mild Cognitive Impairement
- **Mg2+:** Magnesium cation
- **MMSE :** Mini Mental State Examination
- **MRI:** Magnetic Resonance Imaging
- **MTA:** Medial Temporal lobe atrophy
- **NFT:** Neurofibrillary Tangles
- **NMDA:** N Methyl D-Aspartate
- **NMDAR:** N Methyl D-Aspartate Receptor
- **PET:** Positron Emission Tomography
- **PSA:** Posterior Cortical Atrophy
- **PSEN1:** Presenilin 1
- **PSEN2:** Presenilin 2
- **PSMS:** Physical Self Maintenance Scale
- **PTSD:** Post Traumatic Stress Disorder
- **SIB:** Severe Impairment Battery Language
- **SPSS:** Statistical Package for the Social Sciences
- **Sd:** Sementic Dementia
- **SAPP:** Soluble Amyloid Precursor Proteins

General Introduction

Alzheimer's disease (AD) is a progressive neurological illness characterised by behavioural abnormalities, functional impairments, and cognitive loss. In this thesis, AD, its pharmaceutical therapies, and a meta-analysis assessing their efficacy are all thoroughly examined. The risk factors, epidemiology, and aetiology of AD are covered in the introduction, along with the effects of age and genetic factors including APOE4, trisomy 21, and familial AD. It delves deeper into the pathophysiological alterations in the brain, the amyloid theory, and the development of neurofibrillary tangles and senile plaques. Cognitive, behavioural, psychological, and functional symptoms are the different types of clinical signs and symptoms.

A multimodal method is used to diagnose AD, which includes neurological and physical examinations, behavioural and cognitive testing, brain imaging, blood tests, and the evaluation of biomarkers in cerebrospinal fluid (CSF).

Memantine, an NMDA receptor antagonist, and cholinesterase inhibitors (donepezil, rivastigmine, galantamine) are among the pharmacological therapies for AD that are now available. The modes of action, therapeutic advantages, and side effects of these medicines are discussed. In order to maximise therapeutic outcomes, customised treatment programs are crucial.

A meta-analysis was carried out to assess these treatments' efficacy. Fifteen studies totaling 4,580 patients with a diagnosis of mild to moderate or moderate to severe AD were included in the analysis. Despite modest improvements, the meta-analysis—likely as a result of limited sample sizes—did not uncover a statistically significant difference between the treatment and placebo groups. The evaluated articles did, however, show little side effects, which is consistent with clinical observations made at the Tlemcen hospital.

The results highlight the intricacy of AD and the little but significant advantages of the available pharmaceutical therapies. The meta-analysis emphasises the continuous need for novel therapeutic approaches that address the underlying pathophysiology of Alzheimer's disease as well as the urgent need for larger-scale investigations to reach more conclusive findings. In order to enhance the quality of life for those suffering from Alzheimer's disease, this thesis highlights the significance of early diagnosis, individualised treatment strategies, and the investigation of novel therapeutic targets

1 CHAPTER I:

Alzheimer’s Disease

1.1 Introduction

In terms of dementia, Alzheimer's disease is the most prevalent. This is a sickness that progresses, starting with modest memory loss and perhaps ending with loss of capacity to respond to surroundings and carry on a conversation. The areas of the brain responsible for thought, memory, and language are affected by Alzheimer's disease. It may significantly impair a person's capacity to do everyday tasks(1).

At a convention in Tübingen, Germany, in 1906, Alois Alzheimer presented the first instance of the disease that would come to bear his name. He mentioned the "dense bundles of fibrils" (neurofibrillary tangles) and "military bodies" (amyloid plaques) that are today known to be the neuropathological markers of Alzheimer's disease (AD). Due to the buildup of amyloid-beta peptide (Aβ) in the brain's most impacted region, the neocortical structures and medial temporal lobe(2). The medial temporal lobe is the first area of the brain to show shrinkage during Alzheimer's disease (AD) and is consistent with early involvement of the neurofibrillary tangle (NFT)(3).

More than a century after Alois Alzheimer originally described the neurodegenerative illness that would bear his name, the pathological diagnosis of the condition still depends on the hallmarks of his description—amyloid plaques and neurofibrillary tangles. Alzheimer’s disease is the main common form of Dementia(4).

Alzheimer's disease (AD) being a neurodegenerative disorder it is clinically characterised by functional impairment without change in consciousness. Clinically dementia is also defined as a deficit of memory function and at least one other cognitive domain (language, praxis, gnosis, executive function, judgement, and abstract thought(5). The majority of cases of dementia occur in older age groups, and as people age, so do their incidence and prevalence rates; low- and middle-income nations and areas tend to see this tendency more frequently(6).

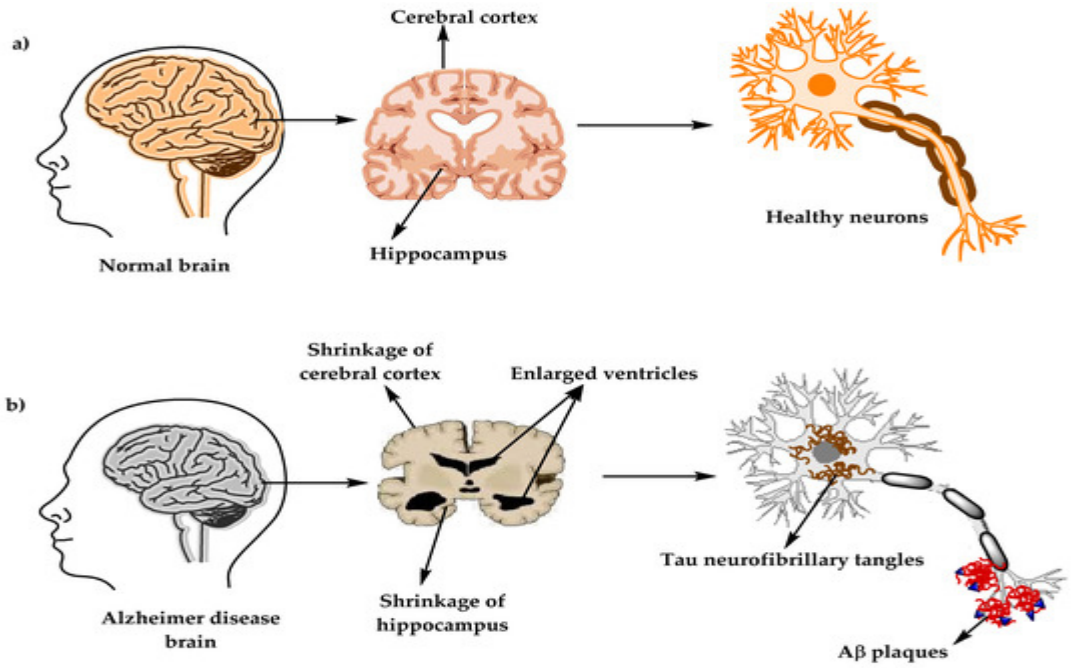


Figure 1 : The physiological structure of the brain and neurons.

The physiological structure of the brain and neurons in (a) shows a healthy brain with the hippocampus shown as the normal usual size, with healthy neurons, we take note of absence of any irregularities. (b) shows a brain attained by Alzheimer's disease, there is representation of a smaller brain due to shrinkage of the hippocampus, cerebral cortex and enlarged ventricles. The neurons present in the brain show presence of Tau neurofibrillary tangles and Alpha beta plaques indicating presence of Alzheimer's disease (AD) in the brain(2).

Recalling freshly learned material is the most prevalent early indication of AD. As the illness worsens, symptoms include losing motivation, becoming increasingly confused about what happened, becoming disoriented, neglecting to take care of oneself, and eventually losing the ability to conduct basic bodily functions and dying(7).

1.2 Epidemiology

According to estimates, about 47 million individuals worldwide suffer from dementia, and as of 2018, it was predicted that the yearly expense of these illnesses will exceed $1 trillion. With the incidence of all dementias doubling every 6.3 years from 3.9 per 1000 for ages 60–90 to 104.8 per 1000 above age 90, ageing is the major risk factor for AD(7).

It is anticipated that as the population ages and life expectancy rise, the illness burden would rise because the onset is directly correlated with age. A new study published in the Lancet Commission by Professor Gill Livingston, MD et al., has identified additional risk factors for

dementia in addition to age, such as hypertension, obesity, diabetes, physical inactivity, hearing loss, smoking, depression, low level of education, and a low socialisation frequency(5,9).

Alzheimer's disease (AD) has a major global impact. Approximately 6.2 million Americans suffer with AD dementia, and the disease claims more lives than both prostate and breast cancer put together. According to estimates from the National Institute on Aging, the prevalence of AD doubles every five years in people over 65, and the disease affects a larger percentage of the population as people age and by 2050, it will cost more than $1.5 trillion(10).

Though the increase and crisis associated with providing care persist, the incidence of dementia may not be as high as previously projected, according to certain recent demographic studies that have shown a lower incidence than previously predicted from previous projections. Since the 1980s, there has been a rise in epidemiological dementia research, with an effort to standardise diagnostic criteria and procedures across geographic regions. These studies' estimates served as the foundation for reviews such as Delphi(11,12).

According to estimates, the prevalence of dementia in adults 60 years of age and older was 3.9% globally. Regional prevalence rates were 1.6% in Africa, 4.0% in China and the Western Pacific, 4.6% in Latin America, 5.4% in Western Europe, and 6.4% in North America(13).

The percentage of dementia patients who lived in low- and middle-income nations was 58% in 2010, and it is projected to increase to 63% in 2030 and 71% in 2050. In the past, estimates of the global dementia population have typically applied a uniform age-specific prevalence and assumed little geographic variation(12,14).

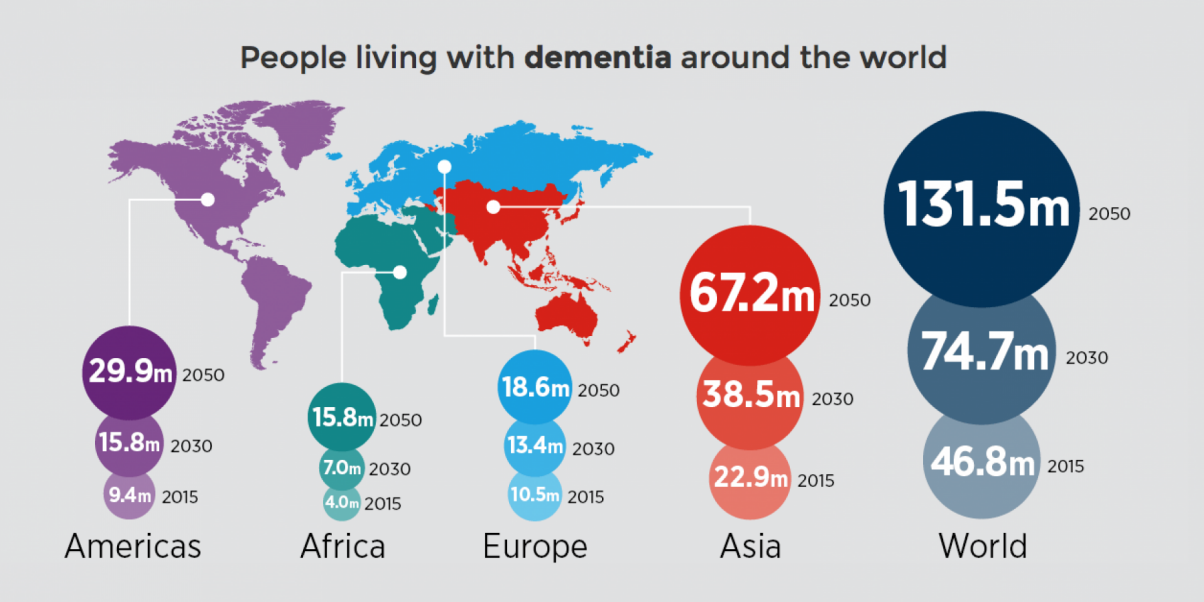


Figure 2 : Alzheimer's disease Age-specific prevalence

This image extracted from the report of the World Alzheimer Report 2015, The Global Impact of Dementia, is an analysis of prevalence, incidence, cost and trends. This image illustrates the present and future aspects of Alzheimer's disease worldwide(15).

1.3 Aetiology

1.3.1 Age

The age-specific incidence of dementia has declined over the past 20 years, according to findings from many European population-based cohort studies conducted in the last five years. This has raised expectations for preventive therapies. Age-specific incidence was 24% lower in the 2000 cohort than in the 1990 cohort in a study that directly evaluated incidence across sub-cohorts(16,17). Alzheimer's affects persons mostly over 65, but it can strike younger people as well. Alzheimer's affects about one in three persons who have young-onset dementia(18). The effects of ageing are particularly noticeable in tissues like the brain that are predominantly made up of postmitotic cells. This makes age a big risk factor by definition since in AD neurodegeneration particularly takes place in the brain(19).

1.3.2 Genes

Most of the time, there is more than one hereditary component to Alzheimer's. Rather, a variety of genes as well as environmental and lifestyle variables may have an impact. As a result, an

individual may possess multiple genetic variants or a combination of variants that either raise or lower the risk of Alzheimer's disease(20).

As of right now, early onset hereditary Alzheimer's disease has been associated with three genes. Presenilin 1 (PSEN1), presenilin 2 (PSEN2), and amyloid precursor protein (APP) are the names of these genes. Cells that make the amyloid protein have these genes implicated. When a gene is malfunctioning, the brain experiences an abnormal build-up of amyloid that results in clumps or "plaques" that harm brain cells and contribute to the progression of Alzheimer's disease(21).

1.3.2.1 Familial AD

Mutations in the presenilin 1 (PSEN1), presenilin 2 (PSEN2), or amyloid precursor protein (APP) genes can result in dominantly inherited familial AD (FAD). Less than 1% of instances of AD are caused by these uncommon familial variants. FAD can manifest as early as 20 years old, with an average onset age of 46.2 years(4,22).

Age-related cognitive decline and Alzheimer's disease are prevented by inheriting a missense mutation in APP that reduces Amyloid beta (Aβ) synthesis and aggregation over time. The most frequent cause of early-onset AD is missense mutations in presenilin 1 or 2, which is the catalytic subunit of γ-secretase. Relative increases in the generation of Aβ42/43 peptides are the outcome of the mutations. Midway through their lives, these hydrophobic organisms self-aggregate, resulting in significant Aβ accumulation(23). Furthermore, it has been demonstrated that the presenilin and APP autosomal dominant variants linked to the familial types of early-onset AD increase the generation of aggregation-prone Amyloid beta and/or increase the production of amyloid beta(7).

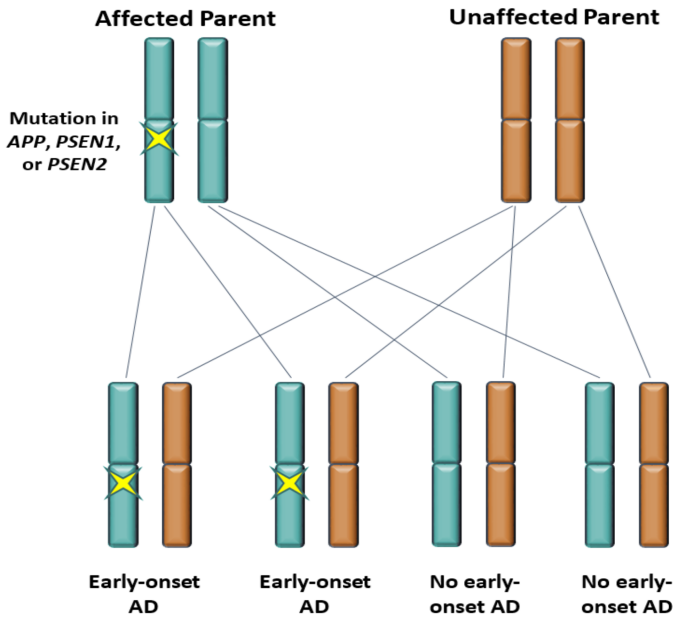


Figure 3 : Autosomal dominant inheritance of *APP, PSEN1, and PSEN2* gene mutations

This is a representation of some patients with early-onset familial AD who have been shown to have mutations in three distinct genes. These genes are known as presenilin 1 (PSEN1), presenilin 2 (PSEN2), and amyloid precursor protein (APP)(24).

1.3.2.2 Trisomy

The finding that the APP gene is located on chromosome 21 contributed to the original development of the amyloid hypothesis, which postulated that people with Down's syndrome experience typical Alzheimer neuropathology as a result of lifetime overproduction of Aβ. The finding of persons with various segmental microduplications of sub-regions of chromosome 21 has provided evidence for this hypothesis. Down's attributes are present in rare individuals with translocation Down's syndrome that only affects the distal region of chromosome 21 telomeric to the APP gene, but they do not develop AD. Due to trisomy 21, APP is expressed more frequently in Down syndrome (DS) patients; AD-type disease is known to manifest in Down syndrome patients significantly earlier(8,29).

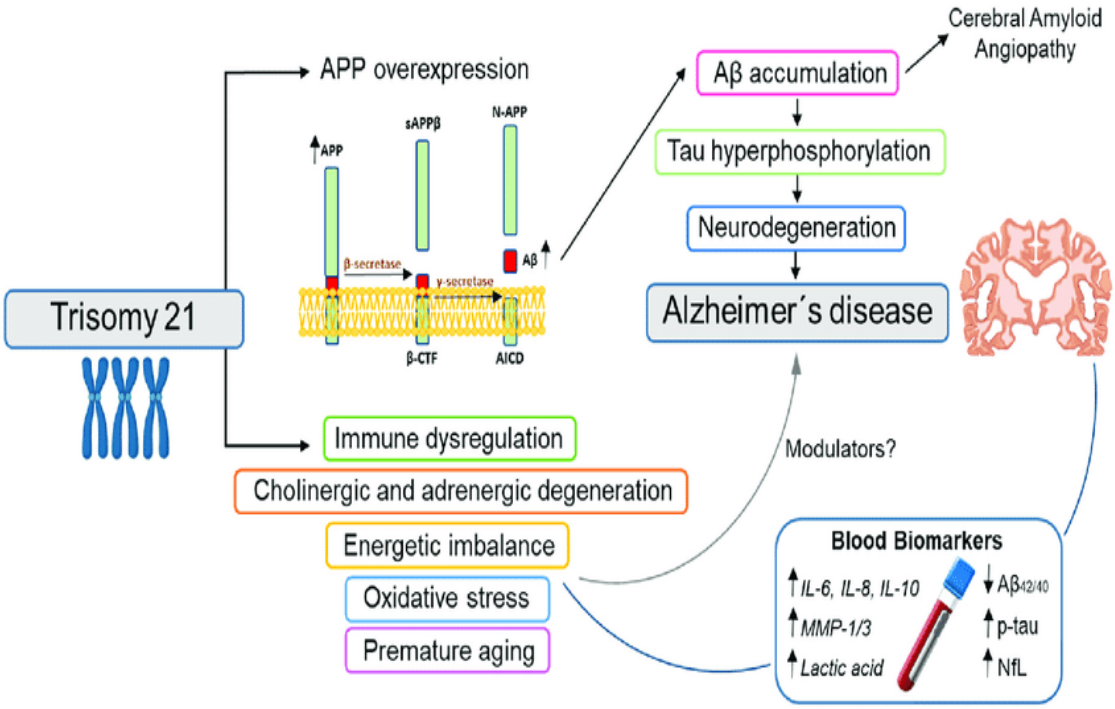


Figure 4 : How trisomy 21 affects Alzheimer's disease susceptibility

This image shows how trisomy 21 affects Alzheimer's disease susceptibility and how it relates to possible blood-based biomarkers. Chromosome 21 partial or complete triplication is the cause of Down syndrome (DS). The overexpression of APP and subsequently the overproduction of amyloid-β (Aβ) peptide are caused by the triplication of the amyloid precursor protein (APP) gene. As a result, the brain experiences an increase in the deposition and accumulation of Aβ (A)(32).

1.3.2.3 APOE4

The apolipoprotein E (APOE) gene is one well-known gene that affects the risk of Alzheimer's disease. The APOE gene contributes to the production of a protein that aids in the bloodstream's transportation of fats other than cholesterol. It is believed that issues with this process have a role in the onset of Alzheimer's. There are various APOE alleles, such as ε2, ε3, etc (20).

The primary genetic risk factor for Alzheimer's disease is APOE4. Regardless of APOE genotype, the lifetime risk for Alzheimer's disease is 11% for men and 14% for women. For APOE4 homozygous, the risk is greater than 50%, and for APOE3 and APOE4 heterozygotes, it is between 20% and 30%. There are several effects of APOE4 in Alzheimer's disease. It also breaks down into neurotoxic pieces and obstructs the brain's ability to remove Aβ(26).

The genetic association of ApoE with AD and the differing effects of cholesterol loading or depletion on amyloid pathology in APP tg mice have long suggested a role for cholesterol in the illness. Research conducted on APP mice that express distinct human ApoE alleles has demonstrated that varied isoform effects on the clearance of Aβ are a key pathogenic influence of ApoE. Traditionally, ApoE4 carriers were part of the late-onset AD population. This genotype was discovered to significantly raise the risk of AD and reduce the amount of Aβ cleared from the brain, which results in excess Aβ accumulation and typical downstream AD neuropathology(23).

Due to the genetic implication of ApoE in AD and the differing effects of cholesterol loading or depletion on amyloid pathology in APP tg mice, a role for cholesterol in AD has long been recognized. Research using APP mice that express distinct human ApoE alleles has demonstrated that varied isoform effects on the clearance of Aβ are a key pathogenic consequence of ApoE(29). It would be appropriate to state as a conclusion that although APOE4 is a risk factor for Alzheimer's disease, not everyone with APOE4 gets the illness, and not everyone who gets Alzheimer's disease carries the APOE4 allele(26).

1.4 Pathophysiology

AD is characterised by two neuropathological features which are amyloid plaques and neurofibrillary tangles (NFTs). There are further signs of inflammation, amyloid angiopathy, cerebral shrinkage, and neuronal death. The loss of synapses in the brains of AD patients is well documented, and it is the brain change that most closely corresponds with cognitive impairment(4,7).

Amyloid-β peptide (Aβ) and tau protein have been identified as the main players in the patho-physiology of Alzheimer's disease (AD) based on data from thousands of basic, pre-clinical, and clinical studies. This is primarily due to their deposition in the characteristic histopathological brain lesions, which include senile plaques for Aβ and neurofibrillary tangles (NFTs) for tau, as well as an increase in their soluble forms in the brains of AD patients. Nevertheless, attempts at therapy targeted at lowering Aβ levels have not succeeded thus far. In a similar vein, positive results from tau-based clinical trials have not yet been obtained(27).

The disease's clinical manifestation is a reflection of the neurochemical and structural brain networks, particularly the "cholinergic system," malfunctioning and ultimately failing. Several competing theories on the underlying biology of the neurodegeneration have guided research

into interventions to modify, arrest, or delay the progression of the disease and its clinical manifestations, even though the key events in the pathogenesis of Alzheimer's disease remain poorly understood(28).

1.4.1 Changes in the Brain

Alzheimer's disease typically first affects the connections between neurons in the entorhinal cortex and hippocampus, two regions of the brain linked to memory, causing them to shrink in size. Later on, it impacts parts of the cerebral cortex linked to logic, language, and social interaction. Numerous other brain regions and the surrounding neurons eventually sustain damage and cease to function properly(29).

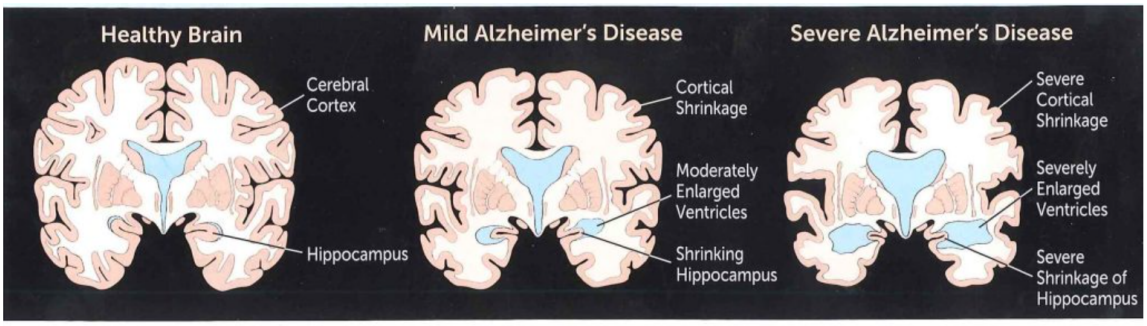


Figure 5 : A comparison of a healthy brain and an Alzheimer's disease-affected brain.

The disease manifested brain manifests in two distinct stages: mild and severe. In the brain of someone with mild Alzheimer's disease, we observe shrinkage of the cerebral cortex and hippocampus; in the brain of someone with severe Alzheimer's disease, we notice substantial shrinkage for both, together with a greatly enlarged ventricle. As Alzheimer's spreads throughout the cerebral cortex, shrinking hippocampus cells cause ventricles to enlarge, brain tissue to shrink, language, judgement, behaviour, and body functions to decline along with memory until death, which typically occurs eight to ten years after diagnosis(30).

1.4.2 Amyloid Hypothesis

The development of possible treatments for AD is being guided by the amyloid (or Aβ) hypothesis, which has emerged as the predominant model of AD pathophysiology(23). It has been reported that the intraneuronal accumulation of Alpha beta peptides may occur before the formation of extracellular amyloid plaques and NFTs(7).

Positive lesions (due to accumulation), which are characterised by the accumulation of neurofibrillary tangles, amyloid plaques, dystrophic neurites, neuropil threads, and other

deposits found in the brains of AD patients, are one of two types of neuropathological changes in AD that provide evidence about the course of the disease and its symptoms. Together with negative lesions (caused by losses), these lesions are marked by significant atrophy brought on by a loss of neurons, synapses, and neuropils. In addition, neurodegeneration can also result from other conditions such as oxidative stress, neuroinflammation, and damage to cholinergic neurons(31).

The amyloid precursor protein (APP) and the production of Alpha beta according to Kang et al., (1987),(32) amyloid precursor protein (APP) is a ubiquitous single-pass transmembrane protein with three distinct domains: intracellular, hydrophobic, and extracellular. Under healthy settings, soluble APP (sAPP) modulates gamma-aminobutyric acid receptors and N-methyl-D-aspartate receptors, which preserve intracellular calcium homeostasis, and is involved in neurite outgrowth, synaptogenesis, synaptic plasticity, and cell survival(33,34).

A variety of distinct secretase complexes can cleave APP in two different ways which are the amyloidogenic pathway and the non-amyloidogenic pathway **(Figure below)**(7).

In the amyloidogenic pathway, the cleavage of APP by b and g-secretases results in the release of neurotoxic Ab peptides, which then aggregate into oligomeric aggregates and as part of the non-amyloidogenic route, a-secretase preferentially cleaves APP(35).

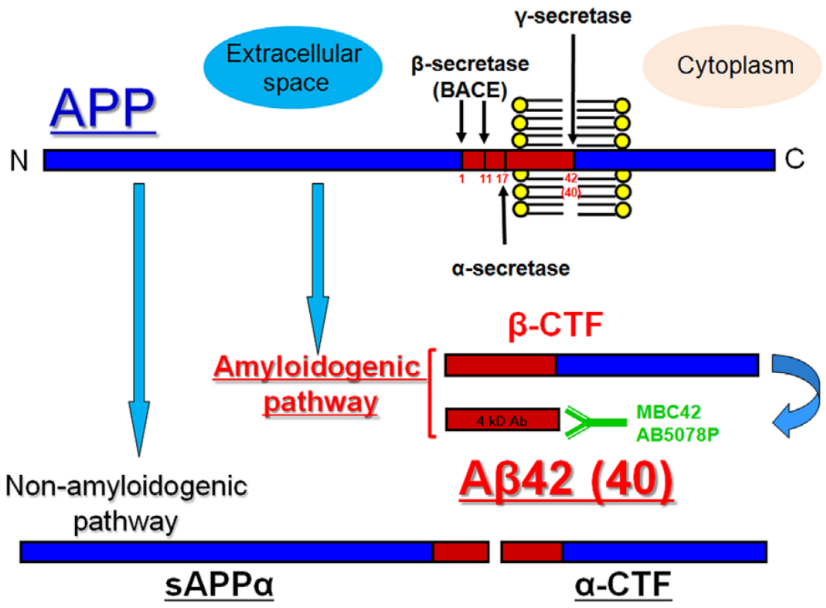


Figure 6 : An outline of APP and APP fragments

This is an outline of APP and APP fragments, comprising APP b-CTFs and Ab. Ab is found in both the APP's transmembrane domain and its exposed ectodomain to the cytoplasm and extracellular environment. The N-terminus of Ab is used to identify the locations at which a-, b-, and g-secretases cleave APP. A-secretase inside Ab cleaves APP mostly in the non-amyloidogenic route, preventing Ab formation. The amyloidogenic pathway's b- and g secretase sequentially process APP to create Ab(7).

1.4.2.1 Senile Plaques (SP)

Senile plaques also known as amyloid plaques are extracellular deposits of the amyloid beta protein in the grey matter of the brain(36).

The breakdown of a bigger protein known as the amyloid precursor (APP) yields the beta-amyloid protein implicated in Alzheimer's disease. It accumulates between neurons in a variety of chemical forms. It is believed that among the beta-amyloid proteins, the beta-amyloid 42 type is particularly harmful. Abnormal amounts of this naturally occurring protein clump together to produce senile plaques in the Alzheimer's brain, which impair cell function(29). Age-related plaques do develop in the brain, but Alzheimer's disease is characterised by a high number of plaques and neurofibrillary tangles(37).

Numerous factors, including the existence of risk genes linked to Alzheimer's disease, can lead to an overproduction of Aβ42. The synthesis of Aβ42 may also be elevated by other disorders, such as type 2 diabetes, circadian rhythm instability, and a history of traumatic brain damage(38).

Beta-amyloid protein (Aβ), can take on several morphological forms, such as neuritic, diffuse, dense-cored, classic, or compact type plaques. The transmembrane amyloid precursor protein (APP) is the source of Aβ deposits, which are produced by proteolytic cleavage enzymes such as β- and γ-secretase. These enzymes break down APP into fragments of amino acids (43, 45, 46, 48, 49, and 51), which combine to generate the final forms of Aβ40 and Aβ42. Aβ monomers come in many forms: soluble oligomers that can proliferate throughout the brain and massive, insoluble amyloid fibrils that can build up to create amyloid plaques. Because Aβ plays a significant role in neurotoxicity and neuronal function, the buildup of thicker plaques in the cerebral cortex, hippocampus, and amygdala can result in cognitive deficits as well as activation of astrocytes and microglia, damage to axons and dendrites, and loss of synapses(7).

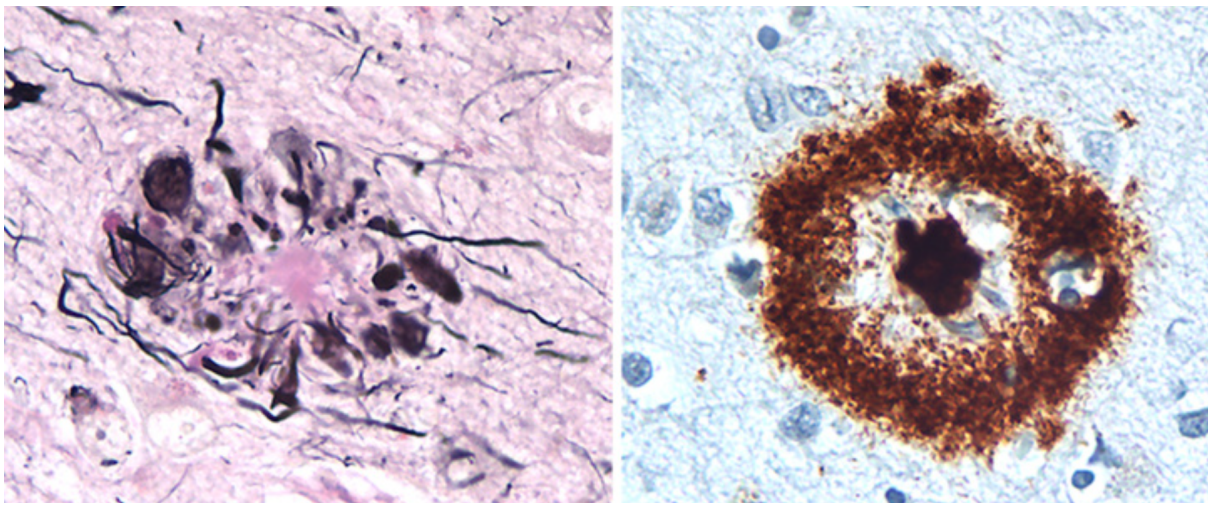


Figure 7 :"Classical" Aβ (senile) plaques in the cortex of Alzheimer's disease (AD)

This is an image showing "Classical" Aβ (senile) plaques in the cortex of Alzheimer's disease (AD) victims who had passed away. On the left, a plaque is stained with periodic acid-Schiff (PAS) counterstain and the Naoumenko-Feigin silver method; an amyloid core (dark pink) is encircled by many aberrant neurites (black). On the right, glial nuclei are seen in the area between the plaque core and outer corona as well as inside and around the corona(36).

The intraneuronal labelling of Ab was once thought to be an artefact, which is one of the reasons why the intraneuronal accumulation of Ab has not been a major problem in AD research, despite the fact that there are now many reports of its presence in the brains of human AD, DS, and transgenic models of AD. The majority of researchers found it difficult to understand intraneuronal Ab labelling in the postmortem AD brain. But just because intraneuronal Ab is difficult to see in certain brain regions doesn't indicate that it doesn't exist in the neurons. In amyloid plaques, extraneuronal aggregates of Ab peptides are also significantly more prevalent than intraneuronal Ab accumulation. Consequently, extracellular deposits have been thought to be more significant than intraneuronal accumulation(7).

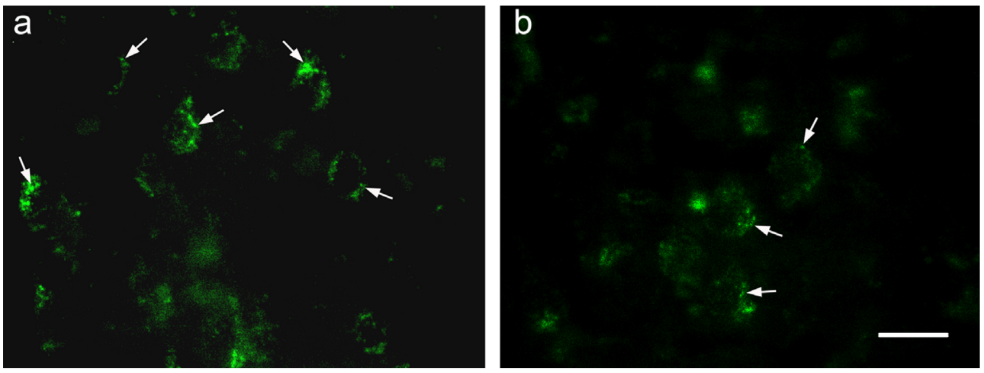


Figure 8 : An 11-month-old wild-type mouse's brain stained with immunofluorescent dye.

Antibodies (a) MBC42 and (b) AB5078P identify the intracellular accumulation of Ab42 peptides in the pyramidal neurons of the cortex of wild-type mice. Ab42 peptides build up in the cytoplasm around the nucleus in a granule/vesicular pattern. The scale bars are 5 mm(7).

1.4.2.2 Neurofibrillary Tangles (NFTs)

Tau NFTs are the other well-known neuropathological characteristic of AD, in addition to amyloid plaques. In the brains of AD patients and transgenic mice carrying the APP mutation, some dystrophic neurites around plaques were found to contain hyperphosphorylated tau(7).

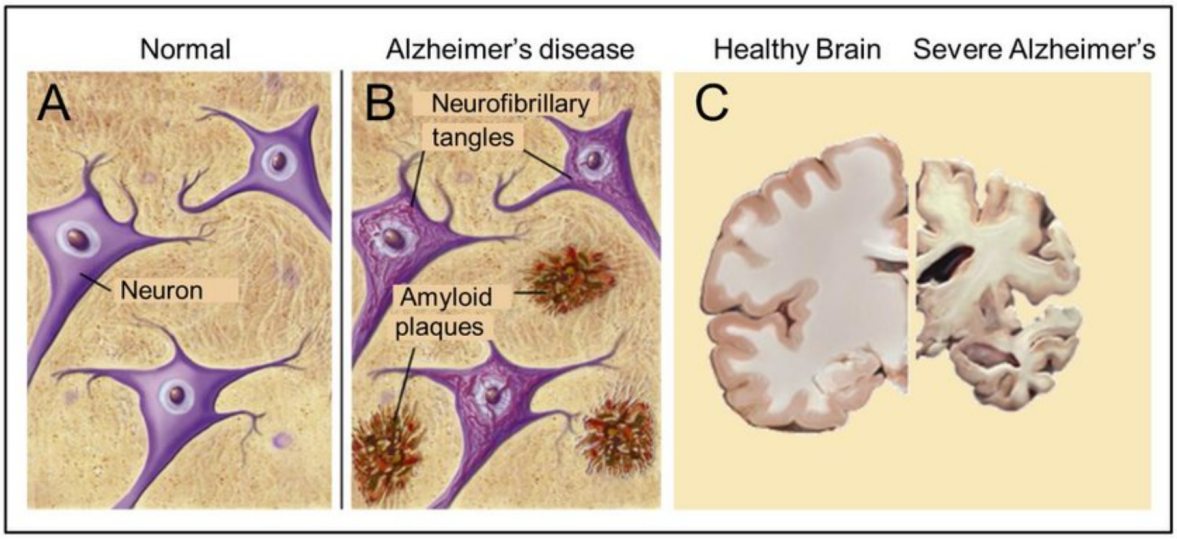


Figure 9 : Amyloid plaques and neurofibrillary tangles shown in neurons inside the brain

Amyloid plaques and neurofibrillary tangles shown in neurons inside the brain (B), which are lacking in healthy brain tissue (A), are major pathological hallmarks of Alzheimer's disease (AD). Later stages of AD development in human brain slices are characterised by massive

apoptosis (C). Sources: A and B: Amyloid plaques and neurofibrillary tangles in Alzheimer's disease(39).

Abnormal tau protein accumulations inside neurons are known as neurofibrillary tangles. Microtubules are internal support structures in healthy neurons that aid in directing chemicals and nutrients from the cell body to the axon and dendrites. Tau typically attaches to microtubules in healthy neurons and stabilises them. However, aberrant chemical alterations in Alzheimer's disease led tau to separate from microtubules and adhere to other tau molecules, creating threads that ultimately come together to create tangles inside neurons. The neuron's transport mechanism is obstructed by these tangles, impairing synaptic transmission between neurons(29).

1.4.2.3 Synaptic Loss

Memory impairment results from synaptic loss in the neocortex and limbic system, which is typically seen in the early stages of AD. Defects in axonal transport, oxidative stress, mitochondrial damage, and other processes that might lead to small fractions, such as the accumulation of tau and Aβ at the synaptic sites, are examples of synaptic loss mechanisms(2).

Alzheimer's disease causes damage to and malfunctions in the brain's neurons, which can lead to a breakdown in the connections between neural networks and the shrinking of certain brain regions. This process, known as brain atrophy, is prevalent by the time Alzheimer's reaches its terminal stages and is caused by considerable cell death as well as the decrease of brain volume(29).

1.4.3 Clinical Signs and symptoms

1.4.3.1 Cognitive symptoms

Alzheimer's disease symptoms can differ from person to person. Usually, one of the first indications of the illness is memory loss. Alzheimer's disease may also be detected in its early stages by a decline in non-memory cognitive functions, such as difficulty choosing the proper word, problems comprehending visual imagery and spatial relationships, and problems with reasoning or judgement. The symptoms worsen with time and include greater disorientation and behavioural abnormalities(40).

The severity of dementia varies, with the least severe stage occurring when a person's functioning is just starting to be affected and the most severe stage necessitating total reliance on others for assistance with daily activities(41).

Since Alzheimer's is a progressive disease, a person with Alzheimer's typically lives for four to eight years after being diagnosed, but they may survive up to twenty years, depending on other circumstances(42).

It is important to distinguish between the symptoms of Alzheimer's disease and those of mild cognitive impairment (MCI). (MCI) is a disorder where affected individuals experience greater cognitive or memory issues than average for their age. When compared to the symptoms of Alzheimer's disease or a similar dementia, MCI symptoms are less severe. Most people with MCI are able to take care of themselves and go about their everyday lives normally(43).

1.4.3.2 Behavioural and Psychological Symptoms

1.4.3.2.1 Agitation and aggression

Agitation, abnormal motor behaviour, anxiety, elation, irritability, despair, apathy, disinhibition, delusions, hallucinations, and changes in eating or sleep patterns are among the behavioural and psychological symptoms of dementia (BPSD)(44). Aggression and agitation are among the behavioural and psychological symptoms of dementia (BPSD) that many people encounter. About 20% of community-dwelling individuals with Alzheimer's disease experience these symptoms. They create serious therapeutic issues, put the person at risk for harm, and are distressing for them as well as others(45).

Typically, verbal abuse and yelling, together with physical acts like biting, striking, and object throwing, are indicative of aggression. They are especially prevalent when taking care of oneself. Additional signs of agitation include pacing and restlessness, excessive fidgeting, and motor activity linked to worry. These symptoms have a big impact on their day-to-day activities(46). Either verbal or physical aggression is possible. They may happen unexpectedly, for no apparent reason, or as a result of an annoying circumstance(47).

1.4.3.2.2 *Hallucinations and delusions*

There will be encounters in dementia, when perceptual abnormalities can arise in all sensory modalities. Determining whether a patient is experiencing a hallucination or a perceptual disorder in the absence of sensory stimuli might be challenging in some situations(48). False beliefs that a person believes to be true are called delusions. For instance, the individual can believe that their partner is in love with someone else(49).

False impressions of things or happenings that involve the senses are known as hallucinations. Alzheimer's disease-related brain alterations, which typically occur in the latter stages of the

illness, are the source of these misleading perceptions. A curtain may reveal the face of a past acquaintance, or the person may see insects scuttling across their palm(50).

Delusions and strange mental content the degree of delusional ideas' complexity, systematisation, conviction, and the level to which they motivate patients to act can vary greatly. Delusional ideas are false beliefs that are deeply held, persistent, and irrefutable. Compared to non-demented psychotic patients, delusional beliefs usually contain suspicion, abandonment, and misidentification and are generally less ordered and complicated(44,51).

1.4.3.2.3 Personality and mood changes

Behaviour and personality often change with dementia. Families and friends may find it difficult to cope with a person who has dementia since they frequently behave in ways that are very different from their "old self." There are numerous reasons why behaviour varies. Dementia is typically caused by a person losing neurons, or brain cells, in specific areas of their brain. Which area of the brain is losing cells often determines the behavioural changes you observe(52).

Typically, Alzheimer's initially affects the area of your brain responsible for memory. Later on, there is damage to the cerebral cortex that impacts your language, communication, and social behaviour—the core aspects of your personality. You may observe changes such as their loss of interest in previously enjoyed activities or their suspicious, perplexed, or nervous behaviour(53). You may notice common changes in personality and behaviour, such as an increased sensitivity to stress and anger, a gloomy or uninterested demeanour, hiding things or suspecting others of hiding things(54).

1.4.3.2.4 Sleep disturbances

Alzheimer's disease (AD) has been the primary focus of research on sleep in dementia. Between 25 and 35 percent of AD participants have sleep problems. Disturbances, both subjective and objective, are explained. Sleep is disrupted by prolonged nighttime awakenings, which also lowers sleep efficiency and overall sleep time. Slow wave sleep is diminished and occasionally nonexistent(55).

Deep sleep and paradoxical sleep deprivation are common disruptions of the neurophysiological sleep architecture during AD. The most common sleep abnormalities that affect AD patients are restless legs syndrome and sleep breathing disturbances(56).

1.4.3.3 Functional Symptoms

1.4.3.3.1 Impaired Activities of Daily Living

Alzheimer's disease frequently results in functional impairment, which is linked to institutionalisation and an increased caregiver load(57). Activities of Daily Living (ADLs), which are more fundamental, and Instrumental Activities of Daily Living (IADLs), which are more advanced and required for self-care, are the two tiers of instruments used to measure functional capacity(58).

Activities including cooking, cleaning, and maintenance around the house, driving or taking public transit, grocery and clothing shopping, and money management are examples of instrumental ADLs. Since moderate difficulties in instrumental ADL are allowed under its diagnostic criteria, amnestic MCI is commonly considered to be the precursor stage of AD dementia(59).

Actually, the main distinction between AD and mild cognitive impairment (MCI) is the deterioration in instrumental and fundamental activities of daily life(60). The capacity for physical activity, self-maintenance, and self-care can be viewed as functional status. A person suffering from dementia typically needs assistance with more difficult duties, such keeping track of finances and bills or just keeping up with daily chores(61).

1.4.3.3.2 Communication difficulties

People with Alzheimer's disease find it difficult to communicate since they have memory problems. They can have trouble speaking or forget what they want to say. They can't say what they want to say, which may make you feel impatient(62).

Language problems are a common symptom of dementia and may even be a sign of the disease. The capacity to put concepts into words in order to communicate with others is known as language(63,64). A person's capacity for communication steadily declines with dementia such as Alzheimer's disease. Being able to communicate with someone who has Alzheimer's involves tolerance, comprehension, and attentive listening. The following techniques can improve communication between you and the dementia patient(65).

1.4.3.3.3 Inability to recognise familiar objects or people

A person suffering from dementia may still have normal eyes, but if there is damage to the brain, it could impair their vision. Different kinds of information are processed by different brain regions.The temporal and parietal lobes of the brain are used to judge distances and

recognize faces and things. Therefore, a person suffering from dementia may have trouble recognizing faces or objects if those lobes are destroyed. Misidentification results from this(66). Deficits in face recognition are commonly observed in Alzheimer's disease (AD) and are commonly linked to memory impairment. But since there is evidence of a decreased inversion effect for faces but not for automobiles in AD, it has also been suggested that deficiencies in higher-level perceptual processes may be the cause of the inability to recognize familiar faces(67).

1.5 Diagnosis

The diagnosis of Alzheimer's disease or any other dementia cannot be made by a single test. To accurately diagnose patients, doctors use a variety of diagnostic methods in addition to the patient's medical history and other data. These tools include neurological exams, cognitive and functional assessments, brain imaging tools like Magnetic Resonance Imaging (MRI), Computed Tomography (CT), Positron Emission Tomography (PET), cerebrospinal fluid testing, and blood tests(68).

Prior to the early 2000s, examining molecular and cellular alterations in brain tissue under a microscope after death was the only reliable method of determining whether a person had Alzheimer's disease or another type of dementia. Research has made it possible for physicians and researchers to identify biomarkers linked to dementia in a living individual by using diagnostic tools like blood tests and brain Positron Emission Tomography (PET) scan imaging. This has allowed for more accurate and timely diagnosis. Research is being done to identify the changes that could lead to Alzheimer's and those that could be a consequence of the illness(29). When AD is suspected, a patient should have a number of tests performed, such as a neurological examination, neuronal magnetic resonance imaging (MRI), laboratory testing (such as vitamin B12), and other tests not related to the patient's family history or medical history(2).

Launched in 1984, the initial set of diagnostic criteria for Alzheimer's disease concentrated solely on clinical symptoms. Alzheimer's degenerative alterations could not be measured in vivo at the time; hence a definitive diagnosis of the disease could only be made after death(16). Advanced brain imaging techniques and neuropsychological testing are possible additional instruments. Once reversible causes have been ruled out, clues for specific causes of major neurocognitive disorder are sought. A history of multiple strokes, for example, may point towards a diagnosis of vascular dementia. A history of head trauma may suggest traumatic

encephalopathy. A history of prolonged alcohol use disorder may support the diagnosis of alcohol-related dementia. In adults over 60, the most frequent cause of progressive cognitive decline is AD(10).

1.5.1 Physical and Neurological exam

A physical examination will be conducted by a medical practitioner. Testing reflexes, muscular tone, and strength may be part of it. the capacity to go across the room and get out of a chair testing the senses of balance, coordination, and hearing and sight. Examining the neural system's potential effects on physical abilities like muscle strength, coordination, and gait (the capacity to walk) is known as a neurological test(69). The doctor may advise a patient to stop taking certain medications or switch to another medication if they believe it is the cause or aggravating their symptoms(70).

1.5.2 Cognitive Functional and behavioural tests

Before sending a patient for neuropsychological testing to be done by qualified specialists—many clinics offer training on using simple questionnaires—physicians must analyse the patient's mental state(71).

These exams determine if a person requires a full dementia evaluation or additional evaluation. Cognitive tests often assess a variety of mental capabilities, including language and communication proficiency, short- and long-term memory, and orientation—the awareness of people, places, and things(72). If your doctor has reason to believe you might be confused, like in the case of a head injury or during an acute sickness such an infection, they may administer the Mini-Mental State Examination (MMSE). It is also occasionally used in the process of figuring out whether a person has dementia or another type of cognitive impairment. (MMSE) is a battery of 11 questions that medical practitioners frequently use to assess patients for cognitive impairment (difficulties with comprehending, thinking, speaking, and remembering)(73).

The test has been proven valid across several demographics. Normality is defined as 25–30 out of 30, mild impairment as 21–24, moderate impairment as 10–20, and severe impairment as less than 10. The test is limited because it cannot identify mild memory loss, especially in people with higher levels of education, even though it only takes approximately ten minutes(74).

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

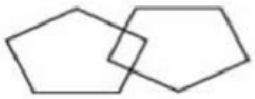
Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Figure 10 : illustrates the MMSE test

Illustration of the MMSE test, a 30-point assessment tool commonly used in clinical settings to screen for dementia-related cognitive impairment and gauge its severity, is shown in Figure.

1.5.3 Brain Imaging

The evaluation of volume change in typical regions is the main function of MRI (and CT, for that matter) in the diagnosis of Alzheimer disease, with a diagnostic accuracy of up to 87%.

Regretfully, during the initial stages of the illness, this kind of volume reduction is not noticeable. Two characteristics—temporoparietal cortical atrophy and mesial temporal lobe atrophy, specifically in the entorhinal cortex, perirhinal cortex, and hippocampal regions—should be used to make the diagnosis(75).

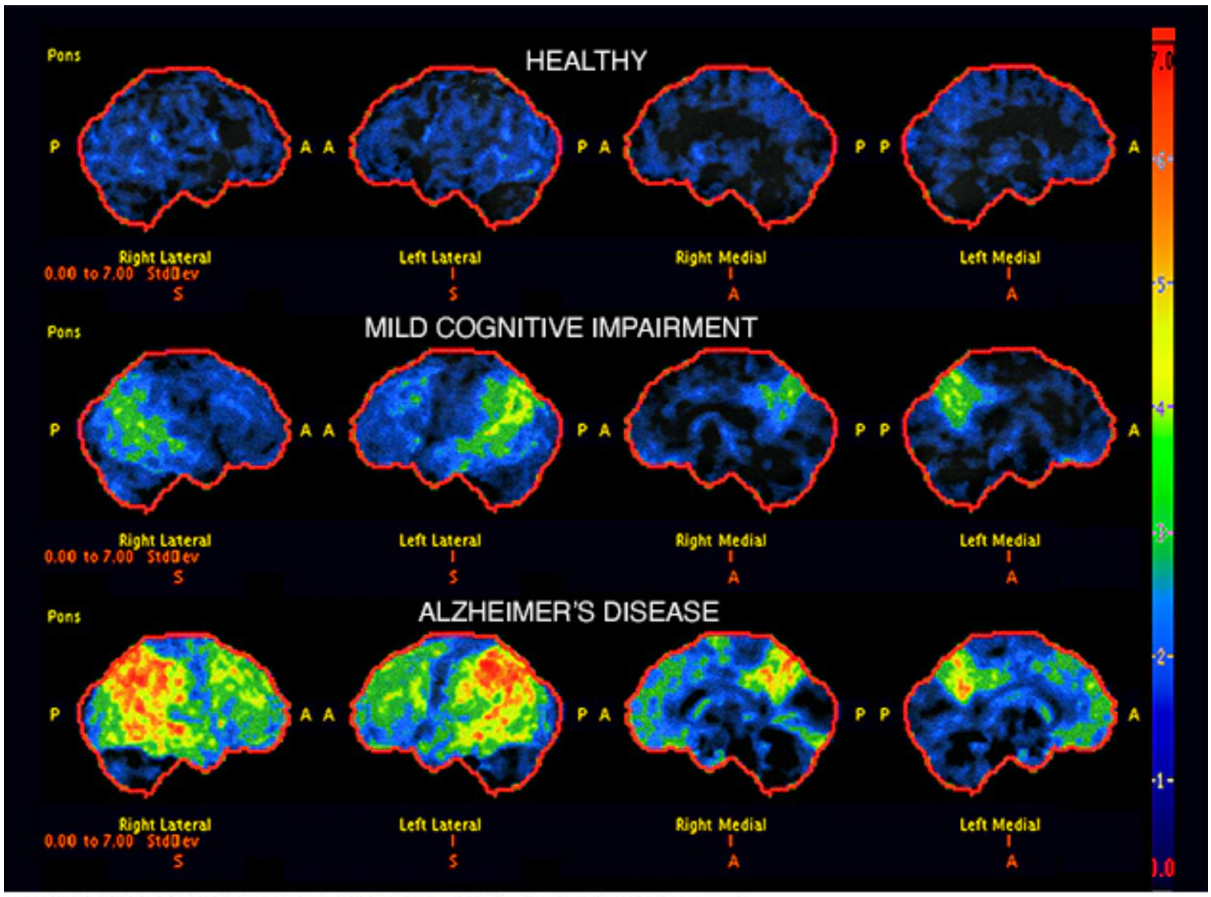


Figure 11 : Alzheimer's disease diagnosis using brain scan images

Alzheimer's disease is diagnosed using FDG PET brain imaging. The brains with mild cognitive impairment, Alzheimer's disease, and a healthy brain are all visible on the scans. Blue and black areas show a healthy brain metabolism. As the condition worsens, areas that are green, yellow, and red indicate deteriorating brain metabolism(76).

One can measure mesial temporal lobe atrophy directly or indirectly. An increase of the parahippocampal fissures is used in indirect assessment, whereas hippocampal or parahippocampal volume loss is assessed directly. The former is more precise and sensitive, although it should ideally involve volumetric calculations as opposed to just "eyeballing" the scan(77).

Mesial Temporal atrophy can be measured using a straightforward method called the MTA score. Atrophy is rated in five classes (0–4) based on the height of the hippocampus formation, the temporal horn, and the breadth of the choroidal fissure. Atrophy is indicated by a score of 0; choroidal fissure widening is indicated by a score of 1; further lateral ventricle widening and slightly reduced hippocampal formation height are indicated by a score of 2; moderate loss of hippocampal formation volume is indicated by a score of 3; and an increase in all of these findings in the final stage is indicated by a score of 4(78).

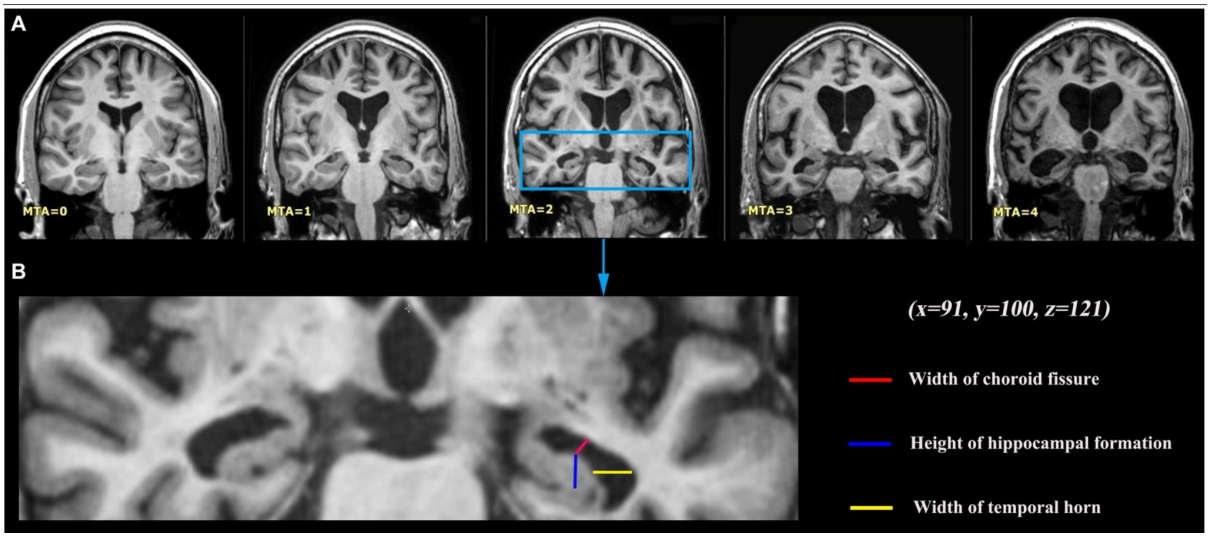


Figure 12 : Grading standards for medial temporal lobe atrophy (MTA)

This figure shows Grading standards for medial temporal lobe atrophy (MTA). (A) Hippocampus body coronal T1-weighted slices of five distinct study participants with varying MTA levels: 0 no atrophy; 1 choroid fissure widening; 2 additional lateral ventricle temporal horn widening and slightly reduced hippocampal height; 3 moderate hippocampal volume loss; and 4 end-stage increase of all these findings(79).

Furthermore, Alzheimer's disease can be distinguished from other neurodegenerative diseases using a PET scan, which measures brain function(69). PET scans can identify abnormalities in brain function by detecting variations in blood flow, oxygen metabolism, glucose metabolism, and the presence of amyloid proteins. MEG displays the electromagnetic fields that result from neural activity in the brain. PET can only be used in research settings at the moment to identify the tau protein(70).

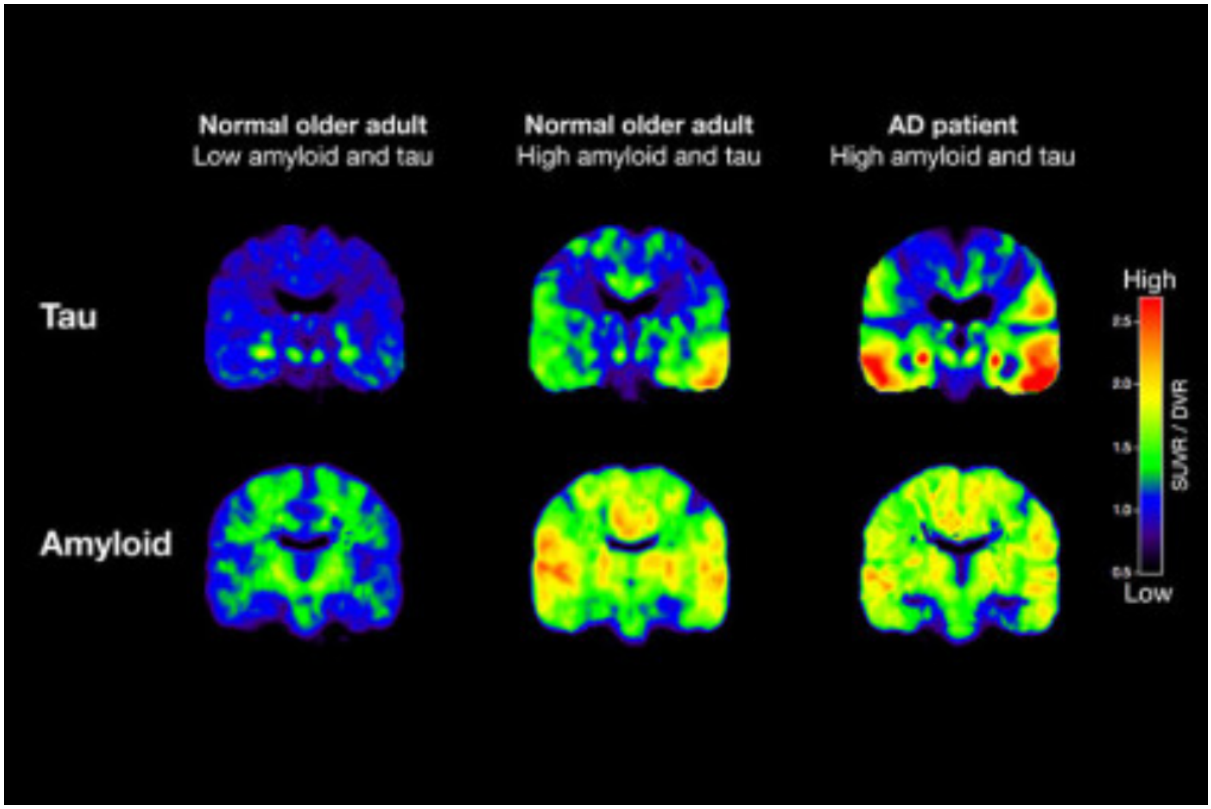


Figure 13 : PET scans from two healthy older individuals and one Alzheimer's patient (AD)

Top row: tau and bottom row: beta-amyloid PET scans from two healthy older individuals and one Alzheimer's patient (AD) are displayed. The left normal older adult shows minimal tau in the medial temporal lobe and no amyloid accumulation in the brain. Amyloid deposition is seen throughout the brain of the middle-aged, typical adult, and tau has expanded into the temporal cortex. Both tau and amyloid are dispersed throughout the brain in AD patients(80).

1.5.4 Blood Tests

Additional blood tests may be conducted to help rule out infectious diseases or metabolic and endocrine disorders as potential reasons of brain dysfunction, depending on what blood tests have been completed before the patient's appointment(69).

1.5.5 Cerebrospinal Fluid (CFS) and Blood Tests and biomarkers

Measurements of Tau proteins, including both total and phosphorylated forms of Tau (p-Tau), and Ab peptides, particularly Ab42, in cerebrospinal fluid (CSF) have been proposed as a substitute for PET imaging in evaluating AD pathology in recent years(81).
Numerous research on human biomarkers indicates that positive amyloid-PET scan results and low CSF Aβ42 occur years before other AD-related alterations, such as increased CSF tau, poor cerebral glucose metabolism, brain shrinkage, and clinical dementia. Post hoc

assessments of patients with mild Alzheimer's disease (AD) have indicated a slowdown of cognitive deterioration, based on trials including three different Aβ monoclonal antibodies: solanezumab, crenezumab, and aducanumab. Progressive human organ failure has been linked to additional amyloidogenic proteins; patients respond therapeutically to therapeutic reductions of amyloid or its precursor protein(22,23).

The three main CSF biomarkers for Alzheimer's disease are phosphorylated tau (p-tau), which is correlated with neurofibrillary degenerative alterations, total tau (t-tau), which reflects the degree of neurodegeneration, and Aβ42, which displays cortical amyloid accumulation(16,22).

The continuum of pathological changes (e.g., plaque counts) that exist without a clear distinction between patients with Alzheimer's disease and cognitively healthy elderly people who died from other causes must be taken into account when evaluating the diagnostic performance of Alzheimer's disease biomarkers(22). In order to define the early stages of the illness, new study criteria for AD in people without dementia place a strong emphasis on the existence of amyloid pathology(82).

1.5.6 Differential Diagnosis

Understanding the distinguishing characteristics and underlying pathologies of each type of dementia can aid in the precise diagnosis of patients, ensuring that they receive the assistance and care that is best suited to their needs and preserve the best quality of life possible. Some of the clinical distinctions between the main dementias are shown in the following table(83).

Table 1 : Differential diagnosis

Disease	First Symptom	Mental Status	Neuropsychiatry	Neurology
AD	Memory loss	Episodic memory loss	Initially normal	Initially normal
FTD	Apathy: poor judgement/insight, speech/language: hyperorality	Frontal/executive, language: spares drawing	Apathy disinhibition, hyperorality, euphoria, depression	May have vertical gaze palsy, axial rigidity, dystonia
LBD	Visual hallucinations, delirium, Capgras' syndrome, parkinsonism	Drawing frontal/executive; spares memory; delirium prone	Visual hallucinations, depression, sleep disorder, delusions	Parkinsonism

CJD	Dementia, mood, anxiety, movement disorders	Variable, frontal/executive, focal cortical memory	Depression, anxiety	Myoclonus rigidity parkinsonism
Vascular	Often but not always sudden; variable; apathy, falls, focal weakness	Frontal/executive, cognitive slowing; can spare memory	Apathy, delusions, anxiety	Usually, the motor slows down. Spasticity can be normal

Abbreviations: AD, Alzheimer's disease; CBD, corticobasal degeneration; CJD, Creutzfeldt-Jakob disease; DLB, Lewy body dementia; FTD, frontotemporal dementia; MND, motor neuron disease; PSP, progressive supranuclear palsy(83).

Two types of dementia can be distinguished: dementia without noticeable motor symptoms and dementia with noticeable motor indications. Alzheimer's disease, frontotemporal dementia, Creutzfeld-Jakob disease, and other prion disorders are examples of dementias that do not exhibit noticeable motor symptoms(84).

2 CHAPTER II:

Pharmacological Treatments

2.1 Cholinesterase inhibitor's introduction

To slow down their cognitive deterioration, patients with dementia are typically started on a cholinesterase inhibitor. The way this inhibitor functions is by preventing the hydrolysis of the neurotransmitter acetylcholine by the enzyme acetylcholinesterase(85).

The main treatments for AD are cholinergic medications, which work by making more ACh available to neurons that are still alive. Examples of these medications are galantamine, rivastigmine, and donepezil. They haven't, however, been demonstrated to stop the course of the disease or neuronal death. Cholinergic neurons in the basal forebrain area die, which is a major contributing factor to cognitive impairment in AD. As a result, acetylcholine (ACh) deficiency and conventional cholinergic indicators, such as choline acetyltransferase and acetylcholinesterase, are well-characterised in the AD brain(86).A substantial body of research indicates that excitotoxicity and neurodegenerative diseases are pathophysiologically related to dysregulated glutamate. As a result, apart from cholinesterase inhibitors, glutamate NMDARs have also become important AD treatment targets(46). However, for therapeutic efficacy, treatment for AD should begin when neuronal loss is still minimal, at the predementia stage(82,88).

Currently approved medications for the treatment of Alzheimer's disease are only intended to treat its acute symptoms; they are not intended to treat the illness's clinical dementia stage, which is divided into three stages: mild, moderate, and severe. They focus on the neurochemical pathways that underlie behavioural symptoms and cognitive decline(89). However available treatment options are not 100% effective (90).It is also important to note that the impact of early therapy or preventive actions for asymptomatic persons may not show obvious changes right away for medicines that have the potential to alter the course of the disease. However, with ongoing, long-term care, these interventions could still show their worth and significance(91). Alzheimer's disease has a complex, heterogeneous, progressive, and interacting pathophysiology, which raises the possibility that different combination therapies will be required depending on the patient's needs as well as the stage of the disease(28).Family and other caregivers' supportive care is the cornerstone of Alzheimer's disease treatment. When living in a routine and well-equipped home, patients suffering from dementia have a higher quality of life. In addition to assistance in mobilising resources to continue caring for their loved one while maintaining their own well-being, family caregivers require education on how to deal with the illness's progressive nature(92).

2.2 Acetylcholine

The cholinergic hypothesis that acetyl deficiency is critical in the onset of AD symptoms emerged as a result of the selective acetylcholine deficiency in AD and the observation that central cholinergic antagonists, such as atropine, can induce a confused state that results in similarities between Alzheimer's and dementia(93).

One of the most significant neurotransmitters in the central cholinergic system is acetylcholine (ACh), which is selectively bound to nicotinic and muscarinic receptors and broken down by acetylcholinesterase (AChE). ACh is essential for memory and learning. It is widely accepted that ACh speeds up information transfer and encourages brain nerve conduction in the central nervous system. Moreover, raising central ACh levels can improve brain function overall and increase memory(94).

Acetylcholine is hydrolyzed by two distinct cholinesterase enzymes in the brain. These two enzymes are acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). AChE is largely prevalent at the synaptic neuron connections, as well as places that exhibit significant activity in the cerebral cortex. BuChE is located in the glial cells of the brain and helps mediate cholinergic action. The liver is the primary organ where pseudocholinesterase (BuChE, EC 3.1.1.8), often referred to as plasma cholinesterase, butyrylcholinesterase, or acetylcholine acylhydrolase, is present. BuChE hydrolyzes butyrylcholine more quickly than AChE does(95).

As humans age, the activity of both of these cholinesterase enzymes increases. Cholinesterase enzymes are significantly overexpressed by Alzheimer disease(96). The biosynthetic enzyme choline acetyltransferase catalyses a one-step reaction that synthesises ACh; the presence of this enzyme is the "marker" that indicates a neuron is cholinergic(95). Numerous studies have demonstrated that a distinct loss of cholinergic neurons in the hippocampus and a sharp decline in ACh levels are seen in individuals with age-related memory loss and Alzheimer's disease (AD). The hippocampus is a key component of the central nervous system (CNS), which collaborates in the formation of memory. Cholinergic neurons that originate from many brain regions, including the prefrontal cortex, intervals basal forebrain(94,97).

ACh is released from the nerve into the synaptic cleft during neurotransmission, where it binds to the muscarinic and nicotinic ACh receptors on the postsynaptic membrane to transmit the signal from the nerve(96). The postsynaptic membrane contains AChE as well, which hydrolyzes ACh to stop the signal from being sent. AChE's main function is to stop synapses

from communicating with one another and spreading ACh, which would otherwise activate surrounding receptors. The presynaptic neuron absorbs the freed choline from the ACh breakdown once more, and choline acetyltransferase facilitates the synthesis of the neurotransmitter by joining it with acetyl-CoA(93).

The breakdown of the neurotransmitter acetylcholine (ACh) into choline and acetic acid is catalysed by the cholinesterase enzyme family. This reaction is required for a cholinergic neuron to be able to return to its resting state following activation(97). Acetylcholinesterase has one of the quickest reaction times; it can hydrolyze a molecule in around 80 microseconds. This is primarily because of where it is located, as nerves have to be able to communicate quickly(100).

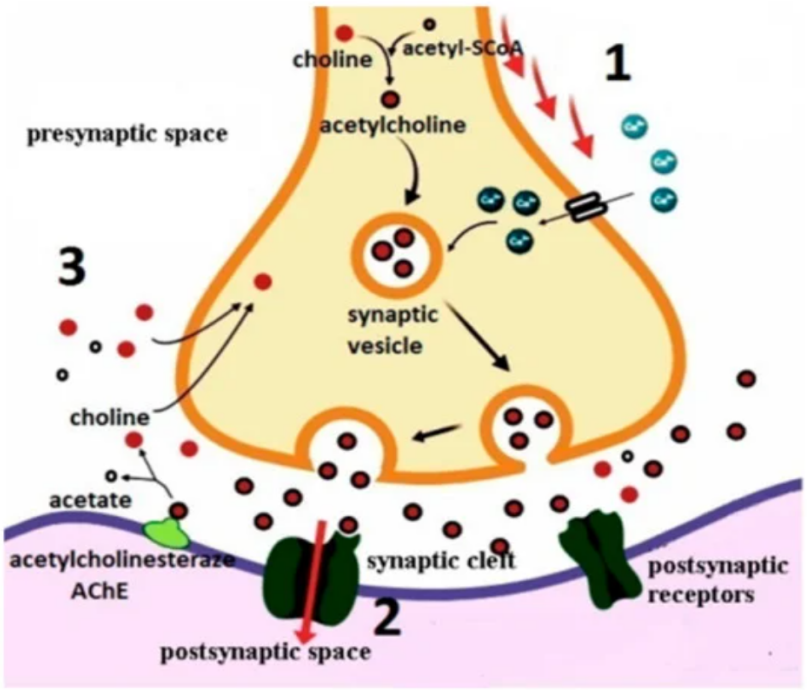


Figure 14 : AD cholinergic hypothesis and the acetylcholine release path

This shows a schematic illustration of the AD cholinergic hypothesis and the acetylcholine release path (3). AChE catalyses the breakdown of acetylcholine, and choline molecules are reabsorbed by the presynaptic neuron. (1) Action potential causing an influx of Ca2+ and subsequent membrane docking of synaptic vesicles; (2) acetylcholine binds to receptors initiating a graded depolarization in the postsynaptic cell. Acetyl-CoA is acetyl coenzyme A; ACh stands for acetylcholine; and AChE for acetylcholinesterase(91).

2.3 Acetylcholinesterase

Acetylcholinesterase is a synthetic enzyme (AChE) that helps cholinergic neurons produce acetylcholine from acetyl coenzyme A and choline(101). AChE is found in the synapse that connects animal nerve and muscle cells. There is also acetylcholinesterase in the space between two nerve cells(102).

AChE's exceptional catalytic efficiency, designing drugs logically, and treatment methods to organophosphorus toxin intoxication all depend on knowledge of its three-dimensional structure. Furthermore, understanding the molecular basis for the recognition of ACh by other ACh-binding proteins, such as the muscarinic and nicotinic ACh receptors, can be aided by structural data regarding the ACh-binding region of AChE(103). Amyloid-beta and AChE appear to interact directly in a way that promotes the peptide's deposition into insoluble plaques. This novel function raises the possibility that well formulated AChE inhibitors could function as drugs that change the disease rather than only acting as palliatives(104).

2.4 Acetylcholinesterase inhibitors

A cholinesterase inhibitor is a medication that improves cognitive function and is used to treat dementia-related cognitive loss(85). The discovery that cholinergic pathways in the cerebral cortex and basal forebrain are disrupted in AD, and that the ensuing cholinergic deficit adds to the cognitive impairment of these patients, led to the development of acetylcholinesterase (AChe) inhibitor medications. While many consider this "cholinergic hypothesis" to be substantial, others think it just makes up a small part of the illness process. There are numerous additional neurotransmitters that are impacted by AD, and it is yet unclear how important each one is in relation to the clinical results(105).

In addition to being used to treat human illnesses and manage insect pests, cholinesterase inhibitors have also—and maybe most infamously—been employed as chemical warfare agents and terrorist weapons(101). In 1999, early AChe inhibitor research looked at physostigmine, velnacrine, and tetrahydroaminoacridine (tacrine). The only medication to pass comprehensive clinical testing and be approved for sale in the USA and other European countries was tacrine. This was followed by the more recent drugs donepezil, rivastigmine, and metrifonate. When taken together, these medications exhibit a dose-dependent reduction in AD symptoms along with differing degrees of systemic cholinergic effects(105).

In 1999 a study was done and they found out that acetyl cholinesterase inhibitors mainly tacrine, Donepezil, Rivastigmine and Metrifonate, when taken together, they exhibit a dose-

dependent reduction in AD symptoms along with differing degrees of systemic cholinergic effects. Physostigmine, velnacrine, and tetrahydroaminoacridine (tacrine) were investigated in the early stages of AChe inhibitor research. Only tacrine made it through extensive clinical testing before going on sale in the USA and several regions of Europe. The more modern medications donepezil, rivastigmine, and metrifonate have come after this(105).

The basic mode of action of these medications is depicted in Fig. below.

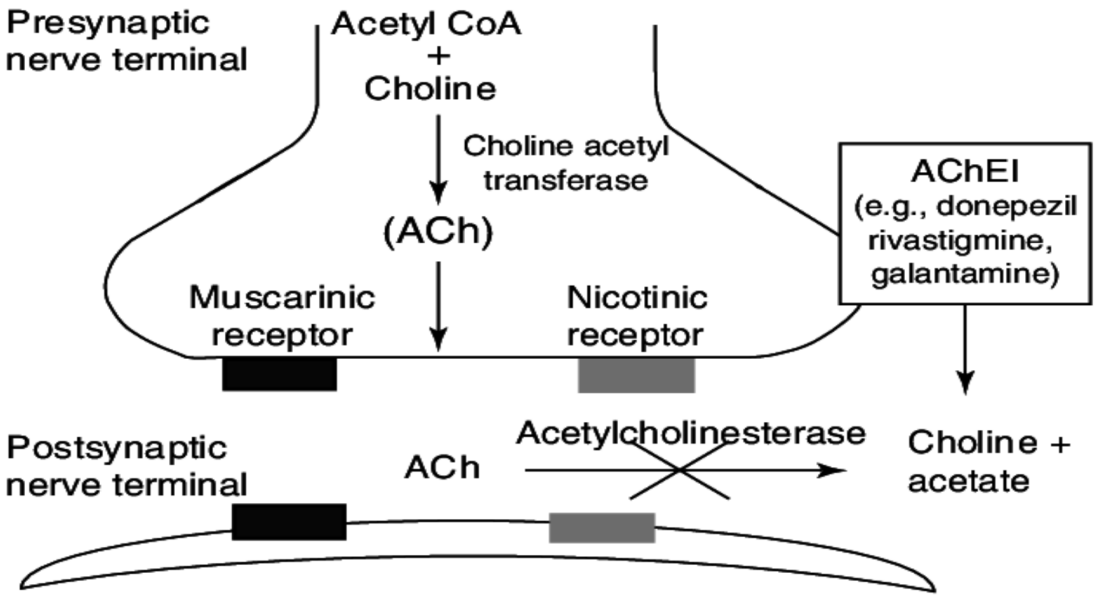


Figure 15 : Cholinergic synapse and cholinesterase inhibitors,

Cholinergic synapse and cholinesterase inhibitors, as seen in Figure 1. The presynaptic terminal releases acetylcholine, formed by (Acetyl Coa +Choline) this reaction is catalysed by Choline Acetyltransferase. The released ACh which is normally efficiently hydrolyzed by acetylcholinesterase (AChE) to form choline acetate is not hydrolyzed because of the inhibition of Acetylcholinesterase, thus preserving the amount of Acetylcholine(106).

2.4.1 Donepezil

The leading component of the second generation of acetylcholinesterase inhibitors (AChEIs), which includes galantamine, rivastigmine, and donepezil, is donepezil. These drugs were created to treat Alzheimer's disease (AD) in response to the hypothesis that the disease was linked to a central cholinergic deficit in the early 1980s(107). Because donepezil is a selective and reversible inhibitor of acetylcholinesterase (AChE), it may be able to offset the loss of functional cholinergic brain cells by raising the amount of acetylcholine that is readily

available(108). While donepezil does not appear to be able to slow down the disease's progression, it can enhance behaviour and cognition, which can help with some symptoms(109).10 mg pills containing donepezil hydrochloride is the recommended dosage. Must be administered orally right before going to bed. Modification of dosage if liver failure occurs must be implicated(110).

The medication's notable upregulation of nicotinic receptors in cortical neurons may be a factor in its neuroprotective qualities. The medication also shows delays in rectifier potassium currents and fast transient potassium currents, as well as reversible suppression of voltage-activated sodium currents. But it's unlikely that these activities will have a major impact on the medication's therapeutic benefits(109). When compared to tacrine, it has a significantly better specificity for acetylcholinesterase inhibition. Additionally, its lack of activity in peripheral tissue, such as heart tissue or gut smooth muscle, emphasises its CNS selectivity. Peak plasma levels are reached after about 4 hours, and the pharmacokinetics are dose-proportional and linear. With a long half-life of more than 70 hours, plasma steady state appears to be reached between 14 and 21 days. Excretion is gradual and happens through the cytochrome P450 system and the kidneys, however it is unaffected in patients with renal or hepatic impairment(105).

2.4.2 Rivastigmine

Rivastigmine was developed in 1985 and was approved by the FDA in 1997.Rivastigmine is recommended for the treatment of mild to moderate Alzheimer's-type dementia. Treatment of mild to severe dementia linked to Parkinson's disease is another one of its indications(96).

A unique "pseudo-irreversible" inhibitor of acetylcholinesterase that selectively targets the brain, rivastigmine virtually entirely bypasses the hepatic cytochrome P450 system in its metabolism(111).The carbamate AChe inhibitor rivastigmine selectively inhibits the brain. Due to its ability to connect with the enzyme AChe and create a carbamylated complex, it mimics ACh, earning it the moniker "pseudo-irreversible" inhibitor. This stops more ACh from being hydrolyzed by enzymes for a few hours after the medication has left the plasma. Thus, rivastigmine has an approximately 10-hour half-life despite this. Rivastigmine exhibits strong CNS selectivity, similar to donepezil, with animal studies demonstrating a particular impact in the cortex and hippocampus. Rivastigmine is inactivated by cleavage during the inhibition of an enzyme and does not bind significantly to plasma proteins. As a result, the medication is quickly eliminated by the kidneys and avoids hepatic metabolism(105).

For patients with mild to moderate Alzheimer's disease, rivastigmine transdermal patches offer a helpful therapy alternative. They are more tolerable than rivastigmine capsules, which offer similar medication exposure and efficacy. This inhibitor is pseudo irreversible and noncompetitive(112). Rivastigmine is a carbamate-type inhibitor of butyrylcholinestérase and acetylcholinesterase. It is thought to facilitate cholinergic neurotransmission by slowing down the breakdown of acetylcholine released by intact cholinergic neurons on a functional level. Therefore, rivastigmine may benefit cognitive deficits reliant on these cholinergic pathways along the course of Alzheimer's disease. Rivastigmine acts on target enzymes by forming a complex with them by a covalent bond, which causes the enzymes to become transiently inactive. In a young subject(113). There are three forms of rivastigmine available: transdermal patches, oral liquid, and capsules. 1.5 mg, 3 mg, 4.5 mg, and 6 mg capsules are available. 2.0 milligrams per millilitre is the oral solution. The dosage for transdermal patches is 4.6, 9.5, and 13.3 mg per 24 hours(96).

There aren't enough studies on women to assess the harm to the unborn child when taking this medicine while nursing. The use of this medication may be impacted by the existence of additional medical issues. Any additional medical issues, particularly an application site reaction from the rivastigmine skin patch, should be reported to the doctor; patients with this condition should not use the skin patch. Asthma, a history of heart issues, such as hypotension (low blood pressure) or a weak heartbeat, lung or breathing issues (such as obstructive pulmonary disease), a history of seizures(114).

2.4.3 Galantamine

Galantamine is a centrally acting, neuromuscular drug that was developed in the 1960s using its cholinergic action. Its beneficial effects on artificially impaired human memory were found in 1977, but it wasn't until the early 1990s that it underwent systematic redevelopment as an Alzheimer's disease drug. First used in Bulgaria in the early 1950s, it was primarily used to treat neuropathic and paralytic diseases. However, its potential applications were greatly expanded when the cholinergic hypothesis of Alzheimer's disease emerged(115).

In nature, galantamine is a tertiary alkaloid. Early in the 1950s, it was identified and isolated from plant sources, including Galanthus nivalis. Galantamine was first investigated for neuropathic and paralytic disorders, such as myopathies, reversal of neuromuscular inhibition, and paralytic illnesses following polio(116,117).

Galantamine is used to treat mild to moderate dementia, which is a symptom of Alzheimer's disease and is characterised by memory loss and mental abnormalities. Alzheimer's disease cannot be cured, nor can it be prevented from getting worse by galantamine. However, it has been shown that this treatment helps certain Alzheimer's patients think more clearly. Galantamine allows ACh to accumulate and exert its full potency by delaying its breakdown. But as Alzheimer's progresses, the amount of ACh produced decreases, which could mean that galantamine's effectiveness is compromised(118).

Galantamine functions as a cholinesterase inhibitor through two different mechanisms. It is a reversible acetylcholinesterase (AChe) inhibitor that increases acetylcholine's intrinsic action on nicotinic receptors, increasing cholinergic neurotransmission in the central nervous system. Galantamine exhibits a high bioavailability, low plasma protein binding, and large volume clearance(119).

Reports have lately started to surface on galantamine's long-term effectiveness in postponing cognitive function decline, activities of daily living, and behavioural disorders(117). The suggested range for dosage is 16–24 mg/day, administered in two separate doses with food in order to minimise or prevent gastrointestinal side effects such nausea and vomiting.

It is advised to start the treatment at the lowest possible dosage and gradually increase it after thoroughly evaluating the patient's response to the preceding dosage in terms of clinical advantages and tolerability. Starting treatment involves taking 4 mg twice a day, which should be taken with food in the morning and evening. The dosage can be raised to 16 mg/day, which is the first maintenance dose, after at least 4 weeks(118).

2.5 NMDA Receptor Antagonists

2.5.1 NMDA

NMDA receptors (NMDARs) are a subset of iGluRs that are preferentially gated by certain agonists, such as N-methyl-d-aspartate (NMDA). The voltage-dependent activation of NMDAR through the elimination of Mg2+ blockage, its high Ca2+ permeability, and its comparatively slow ligand-gated kinetics set it apart from other iGluRs(121). The main excitatory neurotransmitter in the human brain, glutamate, binds to the N-methyl-D-aspartate (NMDA) receptor. It is essential to synaptic plasticity, a neuronal process thought to constitute the foundation of memory formation by releasing calcium ions into nerve cells(122). Increased brain glutamate levels can lead to an overabundance of calcium being released, which can harm nerve cells. NMDA antagonists attach to NMDA receptors and block glutamate from binding,

which stops calcium from entering nerve cells(123). This receptor affects numerous central nervous system activities because it permits a fine control over calcium entrance into the cell and a graded response to stimuli. The formation of new memories is a well-known illustration of NMDA receptor action. Long-term potentiation is the method by which this memory encoding takes place. The hippocampus is thought to be a crucial brain region for this process(124). It is important to highlight the critical role played by Mg2+ ions, which act as a switch that blocks NMDA receptors under "normal" circumstances but permits ion flux when the activation exhibits characteristics typical of learning processes, such as temporal and spatial convergence (cooperativity). In reality, there is experimental evidence that amply supports the claim that synaptic plasticity is impaired when Mg2+ concentration is lowered(125). The two main experimental models that underpin learning and memory are long-term potentiation (LTP) and long-term depression (LTD) of hippocampus synaptic transmission. Alzheimer's disease (AD) is one of the neurodegenerative diseases that is known to alter synaptic plasticity(126). Synaptic plasticity is a theory about the brain underpinnings of learning and memory processes. The two main types of persistent alterations in synaptic strength in the central nervous system that have been extensively researched in the hippocampus region are long-term depression (LTD) and long-term potentiation (LTP)(127).

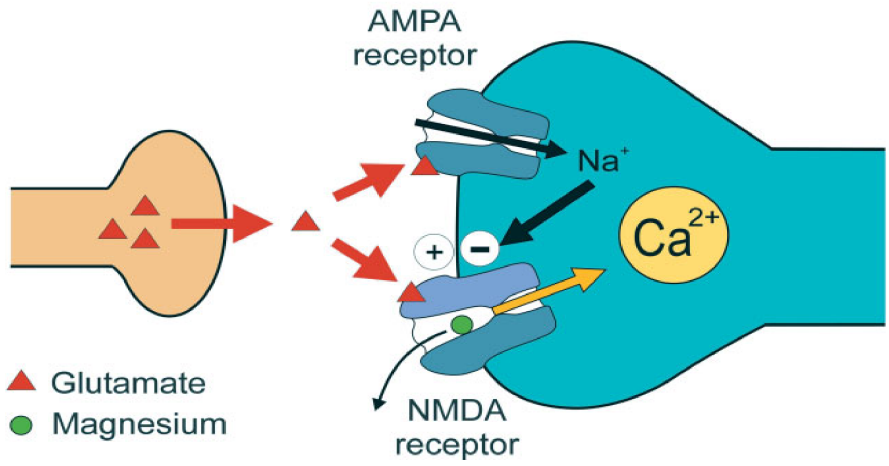
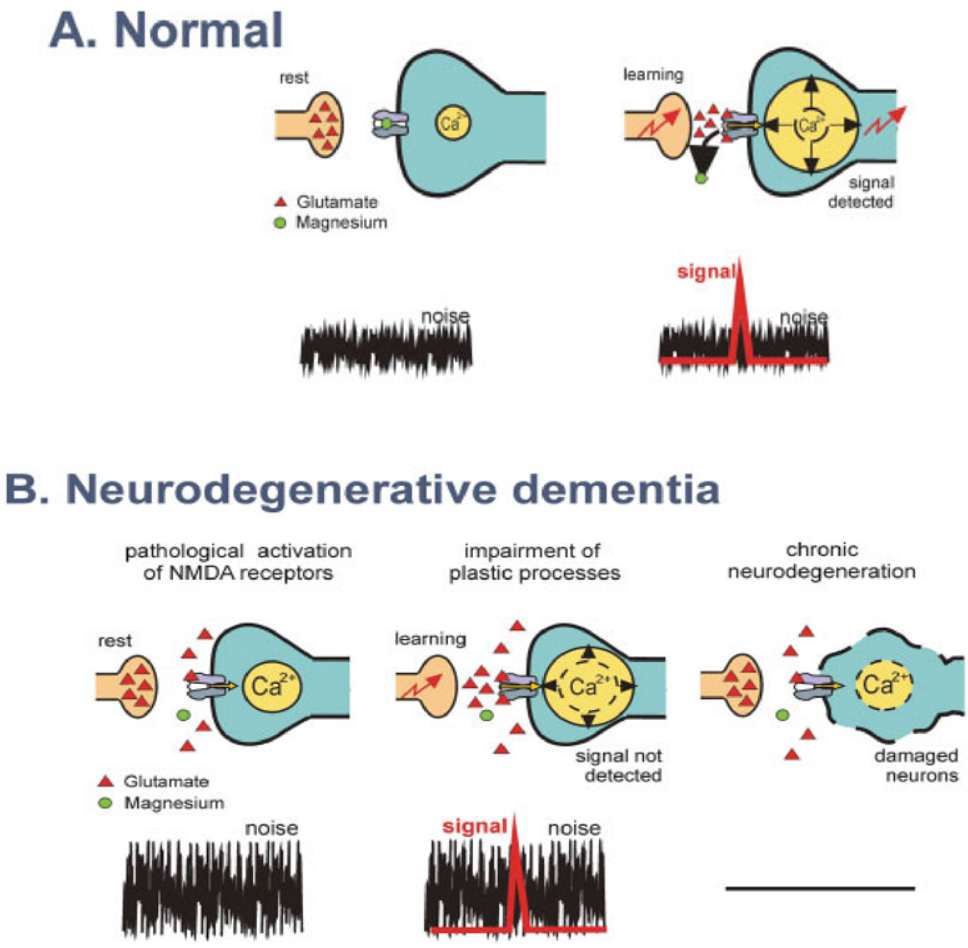


Figure 16 : Long Term Potentiation (LTP)

Long Term Potentiation (LTP) is a neural model of memory formation that involves NMDA receptors(125).

2.5.2 Memantine

Memantine is a potent voltage-dependent, noncompetitive antagonist of the N-methyl-D-aspartate receptor (NMDA) with modest affinity. Since 1989, it has been used to treat Alzheimer's disease (AD). It rose to the position of the second most widely used medication worldwide in 2018 for the treatment of dementia(128). The development of the NMDA agonist memantine resulted from the glutamatergic system's potential involvement in neurodegeneration(129). Memantine belongs to a class of drugs known as NMDA receptor antagonists, which function by reducing aberrant activity in the brain and is believed to have neuroprotective effects for the management of dementia. However, it is not the cure of Alzheimer's disease(85).The magnesium cation channel of the NMDA receptor is bound by memantine, a main aliphatic three-ring structure. Acetylcholinesterase inhibitors like donepezil, rivastigmine, or galantamine can be administered with memantine alone or in combination(130).



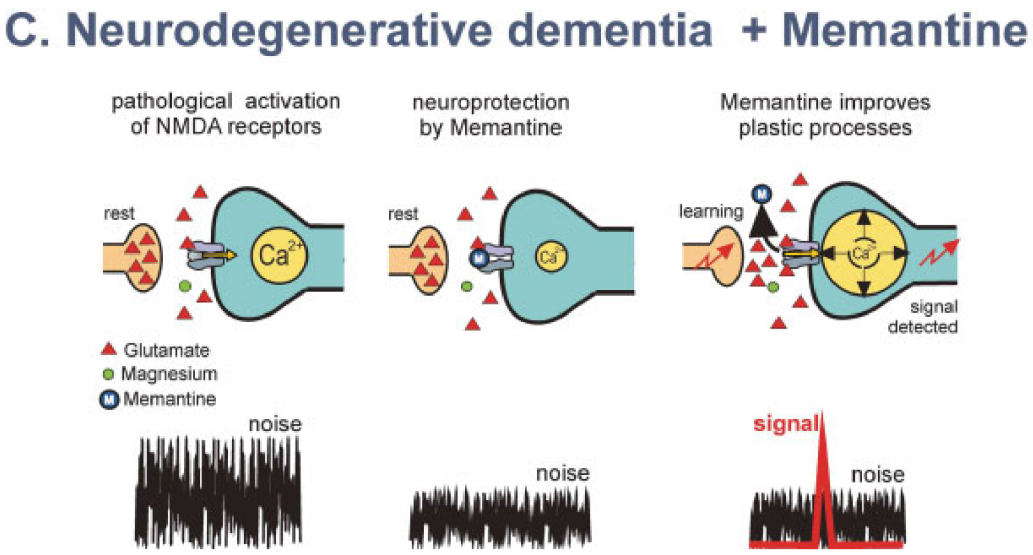


Figure 17 : Illustration of Memantine in Alzheimer's Disease

Under typical circumstances, learning relies on identifying a significant (strong enough) signal above baseline activity (in this case, Ca2+ fluctuations), or an appropriate signal-to-noise ratio. B. According to our signal-to-noise ratio hypothesis, Mg2+ is not effective enough to perform its "filtering" function in Alzheimer's disease because of an overactive glutamatergic system. Consequently, synaptic noise increases, reducing identification of the pertinent signal, as in education. C. Diagram illustrating how the signal-to-noise hypothesis explains how memantine works in Alzheimer's disease. Memantine functions as a filter by obstructing "synaptic noise," which permits the detection of the desired signal and restores synaptic plasticity(125).Memantine's low affinity and quick off-rate kinetics at the level of the NMDAR-channel (*N*-methyl-D-aspartate receptor) preserve the physiological function of the receptor, which underpins memantine's tolerability and low adverse event profile. This uncompetitive binding to the NMDAR is the key to memantine's therapeutic action(86).

2.5.3 Neurotoxicity

One type of brain injury that may be brought on by exposure to excessive doses of NMDA receptor antagonists is known as Olney's lesions. Alternatively, "NMDA receptor antagonist neurotoxicity," or NAN, is another term occasionally used to describe similar injuries(131).

2.5.4 Glutamate

With regard to excitatory neurotransmitters, glutamate and its receptors, primarily ligand-gated ionotropic glutamate receptors (iGluRs), is the most prevalent one in the mammalian central nervous system (CNS). Although it is nearly entirely found intracellularly, it is widely dispersed throughout the central nervous system. Glutamate synthesis can occur via several different metabolic processes. Its receptors are essential for synaptic plasticity, the underlying chemical process that underlies memory and learning(122).

2.6 Combination Therapies

Priorities in AD research are the creation of therapeutic medicines that modify the disease that can be employed in the early stages of the disease and the improvement of symptomatic treatments that are primarily intended for the more advanced stages of the disease. As of the present, the only therapeutic medicines for AD that are accessible treat its symptoms. Given the complex nature of AD pathogenesis, the most realistic strategy for altering the trajectory of AD progression appears to be the implementation of a multimodal therapeutic intervention that targets many molecular targets of AD-related degenerative processes(132).

Priorities in AD research are the creation of therapeutic medicines that modify the disease that can be employed in the early stages of the disease and the improvement of symptomatic treatments that are primarily intended for the more advanced stages of the disease. As of the present, the only therapeutic medicines for AD that are accessible treat its symptoms. Given the complex nature of AD pathogenesis, the most realistic strategy for altering the trajectory of AD progression appears to be the implementation of a multimodal therapeutic intervention that targets many molecular targets of AD-related degenerative processes(132). Combining medications or creating therapies that focus on several routes may be useful therapeutic strategies. Based on the differentiation between combination and added therapies, it may be inferred that the majority of trials belong to the added therapy category(133).

The demand for novel therapeutic strategies is very pressing. Drug therapies that cause accidents are being found and are at different levels of approval. However, clinical practice has to rely on currently available, mostly symptomatic pharmacological therapy alternatives until those causal drug agents are definitively established. It is possible to try to make the most of those current medications' limited capabilities by assessing novel combinations of them(134).

It is flexible to employ combination therapy to address the pharmacological target, delivery mechanism, or timing of delivery. Therapeutic drugs may target amyloid, tau, or other disease mechanisms, like inflammation, as part of AD disease modifying treatments (DMT) development projects. This kind of combination therapy has the advantage of being able to target at least two of these targets (such as tau and amyloid-targeting therapies) or one target in two different ways (two amyloid-targeting therapies, for example)(135). In 2014, donepezil and memantine together received approval for the treatment of moderate-to-severe AD cases. Nonetheless, research into numerous additional potential combination treatments for the treatment of AD has not stopped(136).

2.6.1 Synergistic effects

Because memantine and AChEIs have complementary modes of action, they can be used in conjunction. Patients benefit from their combination, which typically has synergistic advantages with no rise in negative consequences(90).

In a combination therapy, each medication should address a different cause of Alzheimer's disease rather than the same one. One medication might, for instance, address both inflammation and the other vascular problems. By addressing the condition from several angles, we hope to improve the chances of delaying its progression(137).

The illness stage must be taken into account when choosing therapies that are likely to have a synergistic or cumulative effect. Targeting amyloid alone with a monotherapy may work well in the early stages of AD, or more than 20 years before the disease starts. Combining an amyloid plaque removal agent with a soluble Aβ production modulator may be recommended when the plaque load increases (about 10 to 20 years before onset). Additionally, a tau production inhibitor may be added when biomarkers show an increase in the production of soluble tau isoforms(138). Combination therapy using memantine and donepezil improves resting and movement times, potentially enhancing spatial learning and retrieval(139).

2.6.2 Delaying disease progression

Still, it is critical to find strategies that could benefit individuals who have already received a diagnosis. Extensive study has been conducted in addition to pharmacological studies to identify potential techniques that could decelerate the advancement of AD(140).

2.7 Combination Therapy Donepezil and Memantine

Combination medication therapy is one way to treat AD with appropriate pharmacological efficacy but at a reduced dosage schedule(141). When it came to improving cognition, activities of daily living, global assessment, and neuropsychiatric symptoms in patients with AD (mostly moderate-to-severe AD), the combination therapy of donepezil and memantine was the most successful. Its acceptability was marginally higher than that of donepezil and lower than that of memantine(142).To add on memantine and donepezil did not interact, according to the study done in the US in 2003 were there were no notable pharmacokinetic interactions between a single dose of memantine and several doses of donepezil, according to the 19 participants who finished the trial. This meant that the pharmacokinetic and pharmacodynamic data collected indicated that their use together may be both safe and beneficial(143).

Memantine and donepezil each have respectable adverse event (AE) profiles on their own. Nonetheless, the question of whether combining them directly is safe must be taken into account. No pharmacological or pharmacokinetic interactions between memantine and donepezil were seen, as reported by Periclou et al.,(144) indicating that combination use of the two medications is safe(134).

2.8 Pharmacotherapy with non-pharmacological interventions

Non-pharmacological or behavioural interventions aim to maintain or improve a person's cognitive function, allow them to carry out their regular activities of daily living, and/or address behavioural symptoms (such as depression, wandering, agitation, aggression, or sleeplessness) that frequently accompany memory impairment(145). The role of individual characteristics (such as age and education level), environmental stimuli (such as participation in familiar, professional, and leisure activities), lifestyle factors (such as physical exercise and a balanced diet), expertise and experience, and other factors as protective agents against the development of dementia have all contributed to the growing interest in non-pharmacological interventions for people with AD in recent years(146).

Non-pharmacological strategies for managing dementia centre on the following issues: Early detection of the illness and assistance for the patient during its early stages. supplying knowledge, maintaining or enhancing cognitive abilities. Maintaining or enhancing the patient's independence. reducing or getting rid of troublesome behaviour as well as dementia's

psychological symptoms(147). Reality orientation training is another popular strategy. Enhancing people's spatial and temporal orientation is the goal of this strategy. Giving fundamental information to persons with Alzheimer's disease on a regular basis, like their name, the date, and the time, is part of it. This is accomplished either talking to the person or by putting orientation tools all over their house. Large calendars or door signs with the names of the rooms written on them are examples of orientation aids(148).

2.9 Alzheimer's prescription in the neuropsychiatry department in Tlemcen CHU

We got the chance to see patients and talk with the medical professionals in charge of treating Alzheimer's disease (AD) when we visited the neuropsychiatry department of the Central University Hospital (CHU) in Tlemcen. Here are our thorough results:

1) Pharmacological treatments administered:

- **Donepezil (10 mg):** For the mild to moderate stage of Alzheimer's disease.
- **Memantine (10 mg):** For the moderate to severe stage of Alzheimer’s disease.

It was clear that this medication worked well for treating AD patients. After taking the medicine, patients' cognitive states were assessed and found to have significantly improved. The lack of adverse effects was indicative of the medication's excellent effectiveness in the department.

2) Associations of Medications:

- Benzodiazepines is only occasionally used in addition to therapies for AD. Sertraline and paroxetine are two specific antidepressants that are used. They cause memory problems.

Remarks on Enhancement of Patients:

- Cognitive State: The Mini-Mental State Examination (MMSE) revealed stqability in patients' cognitive states following drug administration.
- Behavioural Problems: The drugs also assisted in preventing behavioural problems and an exacerbation of insomnia.

- Demographics: Age, sex, or gender did not seem to have an impact on the improvement in cognitive evolution that occurred after treatment.

Evaluation and Assessment:

- MMSE: The main tool used to evaluate patients' cognitive states as new patients and evaluating state during or after treatment.
- MRI: Used to rule out Lewy bodies and other possible differential diagnosis.

Particular Therapy Regimens:

- Patients with moderate to severe AD are administered memantine.
- Patients diagnosed with mild to moderate AD are treated with donepezil.
- Paroxetine: Acting as an anxiolytic, this medication is used for people with amnesia.

The cost of the treatments varies; however, most patients receive financial assistance from Carte Chiffa issued by the Algerian government.

Extra Attention to Detail Lewy Bodies:

- Use of Antipsychotic Medication in LBD: Caution Antipsychotic drug sensitivity is common in patients with Lewy Body Dementia. Typical antipsychotic use can have serious side effects, including severe drowsiness, worsening of motor symptoms, and neuroleptic malignant syndrome.

In summary:

Upon visiting the CHU Tlemcen neuropsychiatry department, we discovered a methodical and efficient approach to Alzheimer's disease treatment. Memantine and donepezil, which have demonstrated considerable advantages in patient cognitive improvement with negligible side effects, are the department's main medications. The department's procedures, which include the use of MRI and MMSE, guarantee thorough patient evaluation and customised treatment plans, improving the general health of AD patients. This study emphasises the necessity of customised treatment plans for Alzheimer's patients, taking into account the particular difficulties caused

by diseases like Lewy Body Dementia, which calls for the careful administration of antipsychotic drug.

3 CHAPTER III:

Meta-analysis

Principal Objective:

Bibliographic research and a systematic analysis of the efficacy of treatments available for alzheimer's disease.

Secondary Objective :

- Evaluation of pharmacological treatments, looking into the influence of lifestyle modifications and assessing alternative therapies
- Conduct a literature review and provide suggestions for clinical practice while evaluating the effects of treatment.

3.1 Introduction

We conducted a meta-analysis to gather and analyse data from multiple studies with the primary objective of reviewing various articles on prominent science research platforms such as Pubmed and Science direct, in order to do an assessment of the effectiveness of available treatments for Alzheimer's disease. The secondary objectives included evaluating the efficacy of pharmacological treatments, exploring the impact of lifestyle modifications, and assessing alternative therapies. In addition to that, we conducted a comprehensive literature review and presented recommendations for clinical practice, all while examining the treatment effects.

The selection of studies was done according to predefined criteria.

A Meta-analysis is a structured, quantitative epidemiological study design employed to systematically evaluate prior research studies, aiming to draw comprehensive conclusions from the collective body of research. The results of a meta-analysis may yield a more accurate estimation of the treatment effect, the risk factor for a disease, or other outcomes, compared to any single study contributing to the combined analysis(149). Pharmaceutical corporations employ meta-analysis to secure regulatory bodies' clearance for new treatments; in certain cases, the approval process necessitates a meta-analysis(150).

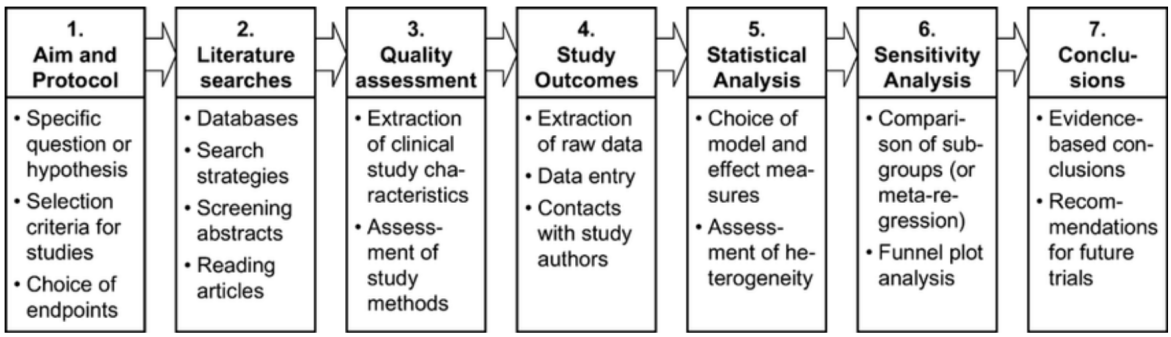


Figure 18 : Illustration of the seven steps taken when doing a meta- analysis(151).

In this study we performed a specific type of meta-analysis called meta-analyses of aggregate data. A meta-analysis of aggregate data uses the analysis of statistics to construct a summary or pooled estimate using effect estimates of individual studies reported in the published literature. Therefore, the values used were taken directly from the individual studies involved(152).

Effectiveness in medical terms is how well a particular treatment or drug works when people are using it, as opposed to how well it works under carefully controlled scientific testing conditions(153). The difference between efficacy and effectiveness is that the latter considers a drug's performance in actual use. A medication that performs well in clinical trials frequently performs poorly when used as prescribed. For instance, a medication may be very efficient in lowering blood pressure, but its effectiveness may be low if patients stop taking it due to the numerous side effects(154).

For a drug to be put on the market, it has to undergo various regulatory testing like clinical trials in order to be deemed safe for public consumption. Clinical trials are investigations conducted on human subjects to evaluate medical interventions intended to cure, diagnose, or prevent diseases or other health issues. To determine whether a medication or treatment is both safe and effective for use in humans(155). The drug manufacturer or sponsor conducts laboratory and animal experiments to determine the medicine's mechanism of action and whether it is likely to be safe and effective when tested in humans before allowing it to be tested in humans. The next step is to start a series of human trials to evaluate the drug's safety in treating diseases and its potential for actual health benefits(156).

In this meta-analysis we will be focusing on analysing the effectiveness of available treatments for Alzheimer's disease. Our focus is mainly on the pharmacological FDA approved treatments that are Memantine, Donepezil, Rivastigmine and Galantamine.

3.2 Material and Methods

Search Engines PubMed, Science Direct

Key Words :

- First Combination: Alzheimer's disease and effectiveness of pharmacological treatments and MMSE and acetylcholinesterase inhibitors.
- Second Combination: Combined drug therapy for Alzheimer's disease and pharmacological treatments.
- Third Combination: Effectiveness of pharmacological treatments of Alzheimer's disease and acetylcholinesterase inhibitors and improvement.

Research data sources

For the first combination the results found on PubMed were 197 articles after using filters which are articles submitted during the years 1991 to 2024, articles with Full text available as well as clinical trials. On ScienceDirect we found 88 articles after applying filters which are articles submitted in the period of 1991 to 2024 which were only research articles.

For the second combination the results found on PubMed were 263 articles after using filters which are articles submitted during the years 2000 to 2024, articles with Full text available as well as clinical trials. On ScienceDirect we found 1703 articles after applying filters which are articles submitted in the period of 2000 to 2024 which were free access, open archives and only research articles.

For the third combination the results found on PubMed were 79 articles after using filters which are articles submitted during the years 1990 to 2024, articles with full text available as well as clinical trials. On ScienceDirect we found 444 articles after applying filters which are articles submitted in the period of 1991 to 2024 which were only research articles.

The titles of articles identified as potentially pertinent were initially chosen for examination. Subsequently, a comprehensive analysis of the full text was undertaken to assess their validity.

3.3 Criteria of evaluation

3.3.1 Inclusion criteria

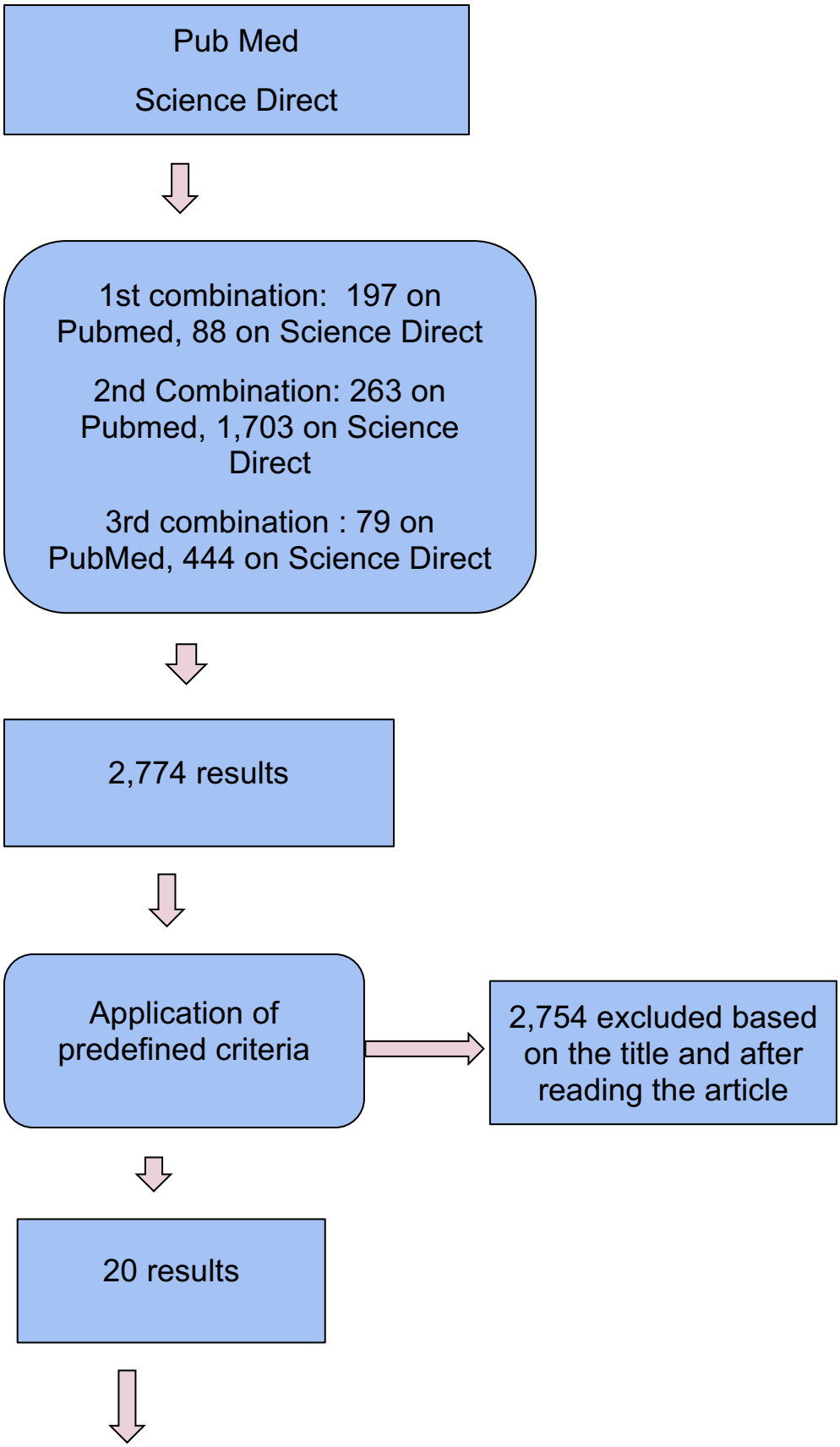
The chosen articles were required to pertain to clinical studies or randomised trials, whether controlled or uncontrolled, focusing on individuals diagnosed with Alzheimer's disease rather than other forms of dementia such as vascular dementia. Additionally, the selected studies focused on patients who were not concurrently receiving medications for chronic diseases. This was to allow us to have concrete results on the effectiveness of treatments for Alzheimer's disease. Individuals who were concurrently prescribed a psychotropic medication needed to maintain a consistent dosage for one month or more before entering the study.

We implemented exclusion criteria to omit literature reviews, article responses, and experimental or in vitro studies from consideration.

3.3.2 Exclusion Criteria

Excluded were studies involving treatments for Alzheimer's disease other than FDA-approved Cholinesterase inhibitors such as galantamine, rivastigmine, donepezil, and NMDA memantine. Likewise, individuals who were not in a medically stable condition or were undergoing palliative care were excluded.

Studies with patients with Lewy bodies dementia were excluded.


Pub Med
Science Direct
1st combination: 197 on Pubmed, 88 on Science Direct
2nd Combination: 263 on Pubmed, 1,703 on Science Direct
3rd combination : 79 on PubMed, 444 on Science Direct
2,774 results
Application of predefined criteria
2,754 excluded based on the title and after reading the article
20 results

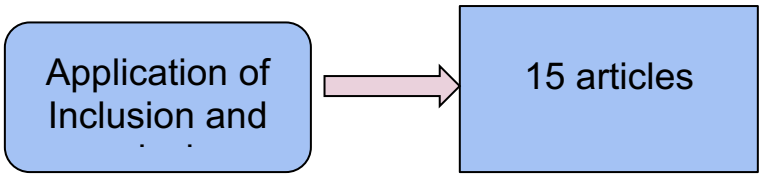


Figure 19 : Diagram illustrating the inclusion of articles

3.4 Results

Our research on the databases PubMed and ScienceDirect yielded a total of 2,774 results. Following a meticulous review of article titles and thorough examinations of abstracts and, where necessary, full articles, 2,759 studies were subsequently excluded. Ultimately, 15 studies were selected, comprising a cohort of approximately 7,342 individuals diagnosed with Alzheimer's disease. The studies that we are analysing involve patients from the United States of America (USA), Korea, United Kingdom, Sweden and Spain respectively.

The fundamental characteristics of the studies are outlined in the table.

Table 2 : Summarised data from the selected studies

Study	Country	Study Design	Study Population	Scale	Placebo Control	Duration	Treatment
David Wilkinson *et al.,* 2009 (157)	United States of America	randomised, double-blind, placebo-controlled parallel-group	1,049 patients were randomised to donepezil or placebo in the original trials	MMSE	Yes	24 weeks	Donepezil 10mg
Adam Rosenblatt *et al.,* 2010 (158)	United States of America	Open-label study	Male or female ambulatory participants residing in an ALF aged 50 and 90 years, with a diagnosis of AD	MMSE LOCF	No	12 weeks	Donepezil 10mg
Marwan Sabbagh*et al.,*2013	Spain	randomised, double-blind, international study enrolling patients with	57 subjects with mild to moderate AD	MMSE ADCS-ADL	No	24 weeks	Donepezil 23 mg

(159)		moderate to severe Alzheimer's disease		SIB CIBIC+			
Carina Wattmo *et al.,* 2012 (160)	Sweden	prospective, non-randomised, multicentre study in a routine clinical setting included 784 AD patients	784 community dwellers with mild to moderate AD treated with donepezil for 3 months	MMSE ADAS-cog IADL PSMS	No	6 months	Donepezil 10 mg, Rivastigmine 1.4 mg or Galantamine 4 mg
Suh *et al*., 2008 (161)	Korean	double blind, community -controlled study	138 patients with mild to moderate AD	MMSE BADL IADL DAD-K	Yes	52 weeks	Galantamine 4 mg
Farlow *et al*., 2010 (99)	United States of America	double blind, community -controlled study	1371 patients, patients ranging from 45 to 90 years of age diagnosed with probable Alzheimer's disease (AD).	MMSE CIBIC+ SIB	Yes	2 years	Donepezil 10mg
Clara Vila-Castelar *et al.,* 2019 (162)	United States Of America	longitudinal, randomised, double-blind, placebo -controlled pilot trial	23 participants diagnosed with AD initiating de novo donepezil treatment (5 mg) for the first time	MMSE ADAS Cog	Yes	6 weeks	Donepezil 10 mg
Martin Knapp *et al.,* 2016 (163)	United Kingdom	52-week, multicentre, double-blind, placebo-controlled, factorial clinical	295 patients with moderate to severe	MMSE	Yes	52 weeks	Donepezil 10 mg

		trial.					
Robert J. Howard *et al.,* 2007 (164)	United Kingdom	multicenter, blinded, randomised, parallel-group trial	272 Alzheimer's disease patients with clinically significant agitation	MMSE SIB	Yes	12 weeks	Donepezil 10 mg
Michael Rosler *et al.,* 1999 (111)	Canada	Prospective, randomised, multicentre, double blind, placebo controlled, parallel group trial.	725 patients diagnosed with mild to moderately severe Alzheimer's disease	ADAS Cog	Yes	12 weeks	Rivastigmine 1-4 mg 6-12mg
Rachelle S Doody *et al.,*2012 (165)	United States of America	randomised, double-blind trial	1,467 patients were randomised to donepezil treatment	MMSE CIBIC + SIB	Yes	24 weeks	Memantine 20mg Donepezil 10-23 mg
Robert Howard *et al.,* 2015 (166)	United Kingdom	randomised, double-blind, placebo-controlled	295 community-living patients with moderate-to-severe Alzheimer's disease	MMSE	Yes	24 weeks	Memantine 20mg Donepezil 10mg
Seong Hye Choi *et al.,* 2011 (167)	South Korea	randomised, multicenter, parallel group, open-label study	172 patients diagnosed with Alzheimer's disease	MMSE	Yes	16 weeks	Memantine 5-20mg Donepezil 10mg
Martin Farlow et al., 2009 (168)	United States of America	randomised open label prospective parallel study	261 patients 50 years of age or older who have been diagnosed with mild-to-moderate	MMSE	Yes	25 weeks	Rivastigmine 4.6mg Memantine 5-10mg

Anton P. Porsteinsson *et al .,* 2008 (169)	United States of America	a double-blind, randomised, placebo-controlled trial	433 people with suspected AD and MMSE scores ranging from 10 to 22	MMSE	Yes	24 weeks	Donepezil 10 mg Memantine 20mg

3.5 Statistical Analysis

The variables studied are presented in the form of MMSE and SIB scores of the patients. The forest plots and graphs were done using the software SPSS.

The statistical analysis has been grouped into four segments. In each segment there is a certain theme of analysis represented by a table followed by a graph as well as a forest plot.

It can be challenging to try to browse through a large number of distinct articles that pose the same question. This is particularly relevant if the analyses' articles reach conflicting findings and present varying statistical evidence supporting or refuting an association.

A forest plot gathers all the pertinent research that addresses a certain topic, finds a common statistic among the publications, and arranges them on a single set of axes. By doing this, we may compare directly the results of the studies and the calibre of the outcome in one location(170). The ability to compare effect sizes and confidence intervals across studies, evaluate the consistency and strength of the evidence, spot potential sources of bias, and make well-informed decisions about the impact of interventions or exposures are just a few advantages of using forest plots(171).

3.6 Mean calculation

These values were used in the First and Second segment of the practical part of this thesis respectfully.

In the selected studies they provided the baseline mean of MMSE scores, that is the mean recorded at the beginning of the study. In some studies, they provided the mean at the end of the study which we recorded as the new mean of the MMSE scores. In some studies, in place of providing the mean at the end of the study, they provided a change in mean from the baseline mean, so in order to calculate the mean at the end of study we merely added the new change in mean to the baseline mean in order to get the mean which we recorded as the new mean.

New Mean = Baseline mean + Change in mean

Table 3 : Mean calculation results

Study	**Baseline mean**		**Change in mean**		**New mean**	
	Placebo	**Treatment**	**Placebo**	**Treatment**	**Placebo**	**Treatment**
Farlow *et al*.,2010 (172)	19.1	16.7	0	0.9	19.1	17.6
Clara Vila-Castelar *et al.,*2019(162)	25.4	24.3	-1.1	-0.1	24.3	24.2
Martin Knapp *et al.,*2016(173)	6	8	-1	2	5	6
Robert J. Howard *et al.,*2007(164)	8.2	8	−0.96	0.54	7,24	8.69
Rachelle S Doody *et al.,*2012 (174)	13.8	11.9	0.6	–0.1	13.2	11.8
Robert Howard *et al.,*2015 (175)	9.0	9.1	0.7	1.9	7.24	8.00
Seong Hye Choi *et al.,*2011 (176)	16.7	16.9	0.1	0.3	16.8	16.6
Anton P. Porsteinsson *et al.,*2008 (169)	17.0	16.7	-0.6	-0.1	16.4	16.6

David Wilkinson *et al.,* 2009 (157)	18.4	18.0	0.8	0.8	18.48	18.08
Guk Suh Hee *et al*., 2008 (161)	15.4	16.4	0/0	-0.1	15.4	16.3

3.6.1 First segment

The first segment explores analyses between the treatment group and placebo group in regards to monotherapy. The variables are the differences in the average of cognitive ability measures by MMSE test after the end of the clinical trial for each study.

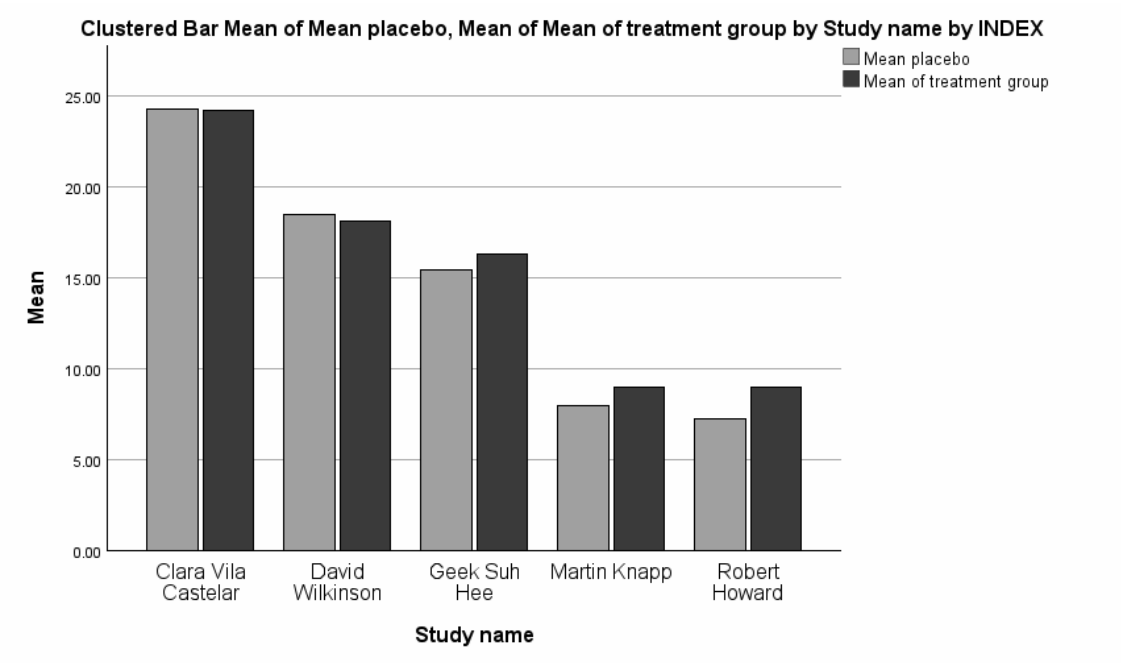
In this segment we will be looking at monotherapy as a treatment for Alzheimer's disease. The data is divided into two groups which are the treatment group (ChEI) and the placebo group not being a ChEI treatment.

Table 4 : Placebo vs Treatment monotherapy

Study	**Treatment (ChEI)**		**Placebo**	
	No of patients	MMSE mean/sd	No of patients	MMSE mean/sd
Clara Vila-Castelar *et al.,*2019 (162)	13	24.2 / 2.8	13	24.3 /1.9
Martin Knapp *et al.,*2016 (173)	73	9 /4	72	8 /4
Robert J. Howard *et al.,*2007 (164)	128	8.69 / 2.4	132	7,24 / 2.5

David Wilkinson *et al.,*2009 (157)	388	18.08 /4.7	518	18.48 /4.7
Geek Suh Hee *et al*.,2008 (161)	66	16.3 /3,4	72	15.4 /3.9

This table shows the difference between the number of patients as well as the mean cognitive state and standard variation (sd) at the end of the clinical trial for each study, this information is shown as a comparison between the treatment group and the placebo.



Mean = MMSE mean

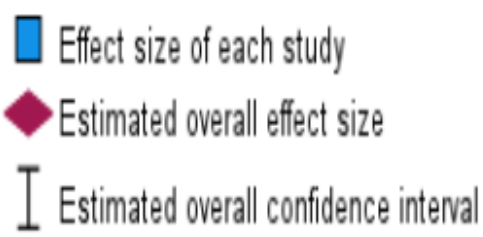
Figure 20 : Graph representing treatment group vs placebo group

This is a graphic representation of the differences between the placebo group and the monotherapy group. There are five studies with information provided in the table above. The X axis shows the studies involved in this segment. The Y axis represents the mean cognitive state of the patients in each study. The higher the value for the y axis, the better the cognitive state the patients of each study were in after the end of the clinical trial.

There is little difference between the treatment group and placebo group for studies of *Clara Vila-Castelar et al., 2019 and David Wilkinson et al., 2009* (157,162). For the remaining studies we observe a difference of the treatment group having higher cognitive levels compared to the placebo group.

We went on to do a forest plot of the results of the studies. A forest plot is a crucial tool for providing, in a single figure, information on individual research data, a visual indication of the degree of study heterogeneity, and the estimated common effect(177).

When conducting a forest plot, we aim to see if the results from the research done are statistically significant. A set of observed data is said to be statistically significant if it can be linked to a particular cause rather than being the product of chance. The analyst uses statistical hypothesis testing to arrive at this conclusion. In the event that the results are indeed the product of pure chance, this test yields a p-value, which is the likelihood of seeing outcomes as extreme as those in the data. Typically, a p-value of 5% ($p \leq 0.05$) or less is regarded as statistically significant(178). This indicates that there is sufficient evidence to reject the null hypothesis and accept the alternative(179). A non-significant p-value does not always mean that the data have no influence or difference. It indicates that there is insufficient evidence in the observed data to rule out the null hypothesis. Though it might be more or less variable than what the study was able to identify, there might still be a true effect or difference. The p-value can also be impacted by other elements such as measurement accuracy, study design, and sample size(180).



ID	Cohen's d	Std. Error	Lower	Upper	p-value	Weight	Weight (%)
Clara Vila Castelae	-0.04	0.39	-0.81	0.73	0.92	5.01	7.36
Martin Knapp	0.25	0.17	-0.08	0.58	0.13	13.59	19.97
Robert J. Howard	0.47	0.13	0.22	0.72	0.00	16.23	23.86
David Wilkinson	-0.09	0.07	-0.22	0.05	0.21	19.88	29.22
Geek Suh Hee	0.25	0.17	-0.09	0.58	0.15	13.32	19.59
Overall	0.18	0.12	-0.06	0.42	0.13		

Model: Random-effects model

Heterogeneity: Tau-squared = 0.05, H-squared = 3.38, I-squared = 0.70

Test of overall effect size: z = 1.50, p-value = 0.13

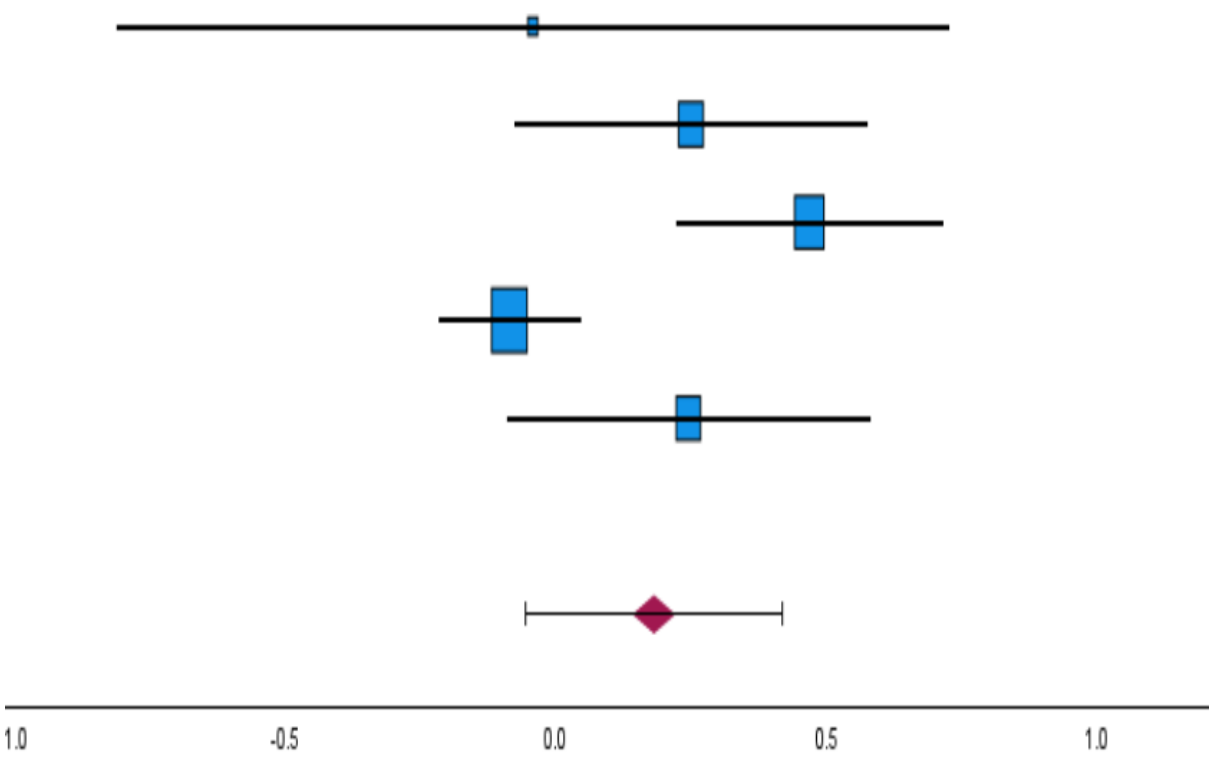


Figure 21 : Forest plot of treatment vs placebo

In the forest plot above after doing the meta-analysis we found a p value of 0.13 (p = 13%) . Since our p value is higher than 5% ($p > 0.05$) this leads us to the conclusion that our results are not statistically significant.

We can therefore conclude that treatment with cholinesterase inhibitors showed no efficacy on MMSE scores compared with placebo in these studies.

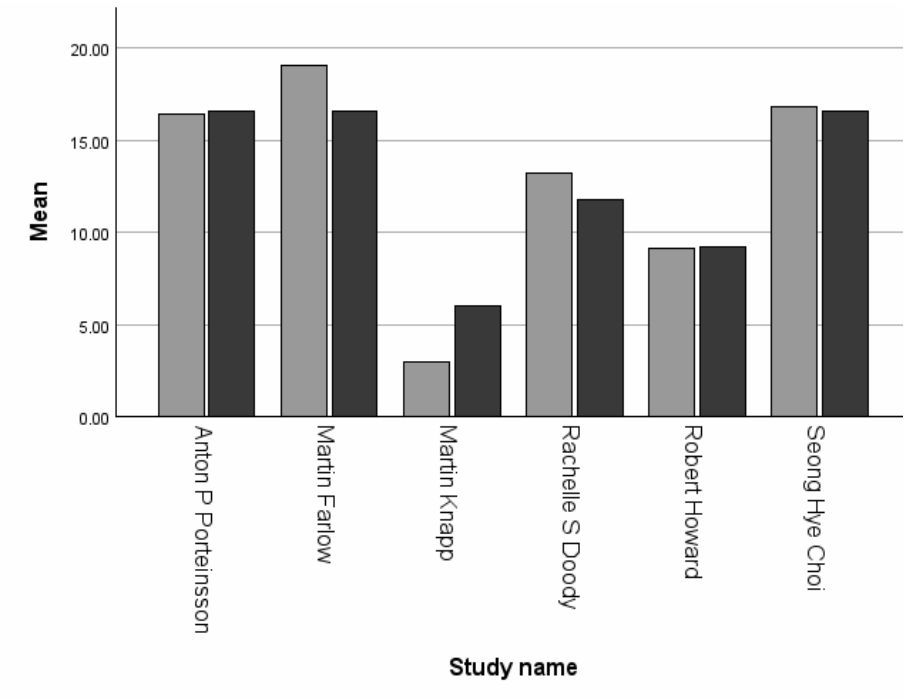
3.6.2 Second segment

In this segment we will be looking at the drug combination theory as a treatment for Alzheimer's disease. The data is divided into two groups which are the treatment group (Memantine + ChEI) and the placebo group being just a ChEI treatment.

Table 5 : Combined Therapy (Memantine + ChEI) vs Monotherapy (ChEI)

Study	**(Memantine + ChEI)**		**ChEI**	
	Number of patients	MMSE mean/sd	Number of patients	MMSE Mean/sd
Rachelle S Doody *et al.,*(174) 2012	352	11.8 / 0.36	611	13.2 / 0.19
Robert Howard *et al.,*(181) 2012	73	8.00 / 2.8	73	7.24 / 2.6
Seong Hye Choi *et al.,* (176) 2011	88	16.6 / 2.9	84	16.8 / 2.9
Martin Farlow et al., (99) 2009	135	16.7 / 3.79	126	19.1 / 3.91
Anton P. Porsteinsson *et al.,* (169) 2008	216	16.6 / 5.41	217	16.4 / 5.08
Martin Knapp *et al.,* (173) 2016	73	6 / 4	73	3 / 3

This table shows the difference between the number of patients as well as the mean cognitive state and standard variation (sd) at the end of the clinical trial for each study, this information is shown as a comparison between the treatment group and the placebo.



= Memantine + ChEI

= ChEI

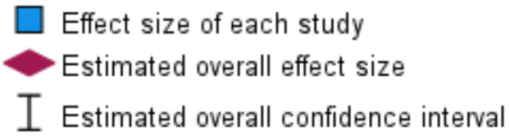
Mean = MMSE mean

Figure 22 : Graph of Combination treatment vs Monotherapy treatment group

This is a graphic representation of the Differences between the combined treatment group and the monotherapy treatment group. There are six studies with information provided in the table above. The X axis shows the studies involved in this segment. The Y axis represents the mean cognitive state of the patients in each study. The higher the value for the y axis, the better the cognitive state of the patients of each study were in after the end of the clinical trial.

There is little to difference between the combined treatment group and mono therapy group for studies of *Seong Hye Choi et al, Robert Howard et al, Anton P Porteinsson et al*(166,167,169) There is however a notable difference between the two groups in *Rachelle S Doody and Martin Farlow et al* (99,165) with the treatment group showing higher cognitive levels compared to *Martin Knapp* (163) in which the mono therapy showing a higher cognition level of the patients.

We went on to do a forest plot of the results of the studies illustrated in the next page.



ID	Cohen's d	Std. Error	Lower	Upper	p-value	Weight	Weight (%)
Rachelle S Doody	-5.58	0.14	-5.87	-5.30	0.00	0.18	16.67
Martin Knapp	0.85	0.17	0.51	1.19	0.00	0.18	16.64
Robert Howard	0.04	0.17	-0.29	0.36	0.82	0.18	16.65
Seong Hye Choi	-0.04	0.15	-0.34	0.25	0.77	0.18	16.66
Martin Farlow	-0.64	0.13	-0.89	-0.39	0.00	0.18	16.68
Anton P Porteinsson	0.04	0.10	-0.15	0.23	0.69	0.18	16.70
Overall	-0.89	0.96	-2.77	0.99	0.35		

Model: Random-effects model
Heterogeneity: Tau-squared = 5.49, H-squared = 291.45, I-squared = 1.00
Test of overall effect size: z = -0.93, p-value = 0.35

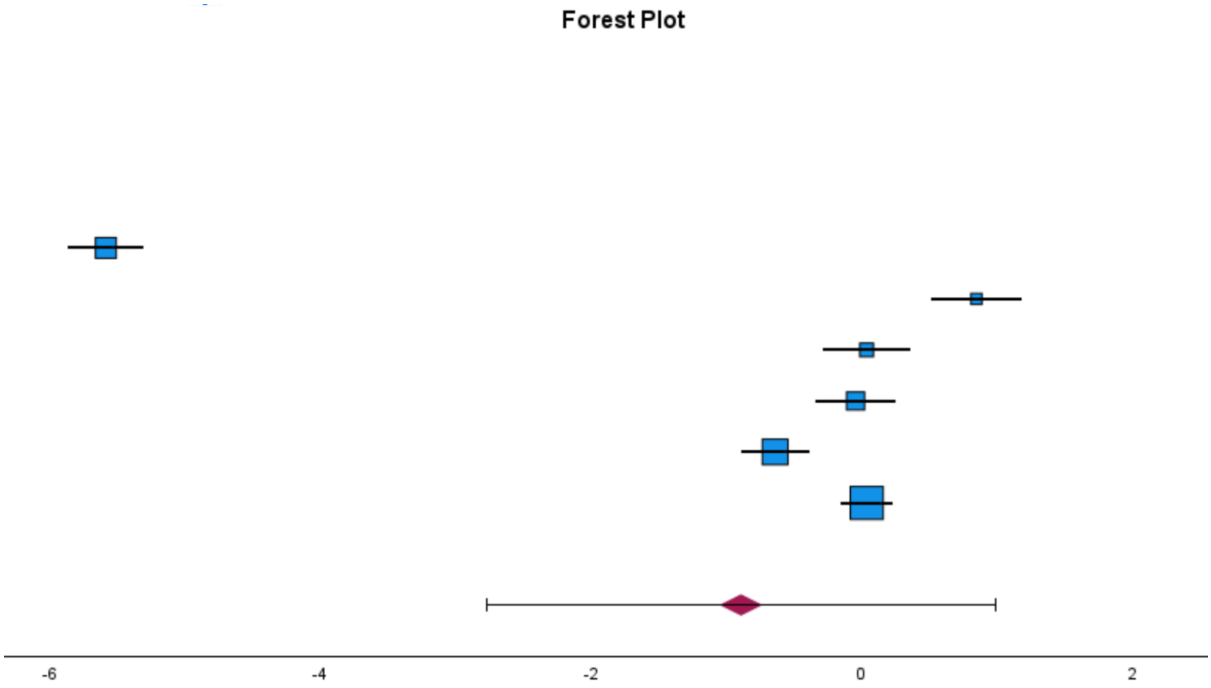


Figure 23 : Forest plot of monotherapy vs combination therapy

In the forest plot above after doing the meta-analysis we found a value of 0.35 (p = 35%). Since our p value is higher than 5% ($p > 0.05$) this leads us to the conclusion that our results are not statistically significant. This will mean that combination therapy did not show a significant advantage over monotherapy.

3.6.3 Third segment

In this segment we will be looking at the improvement or worsening of patients after using ChEI as treatment for Alzheimer's disease. The data is divided into two groups which are the improvement group and the worsening group.

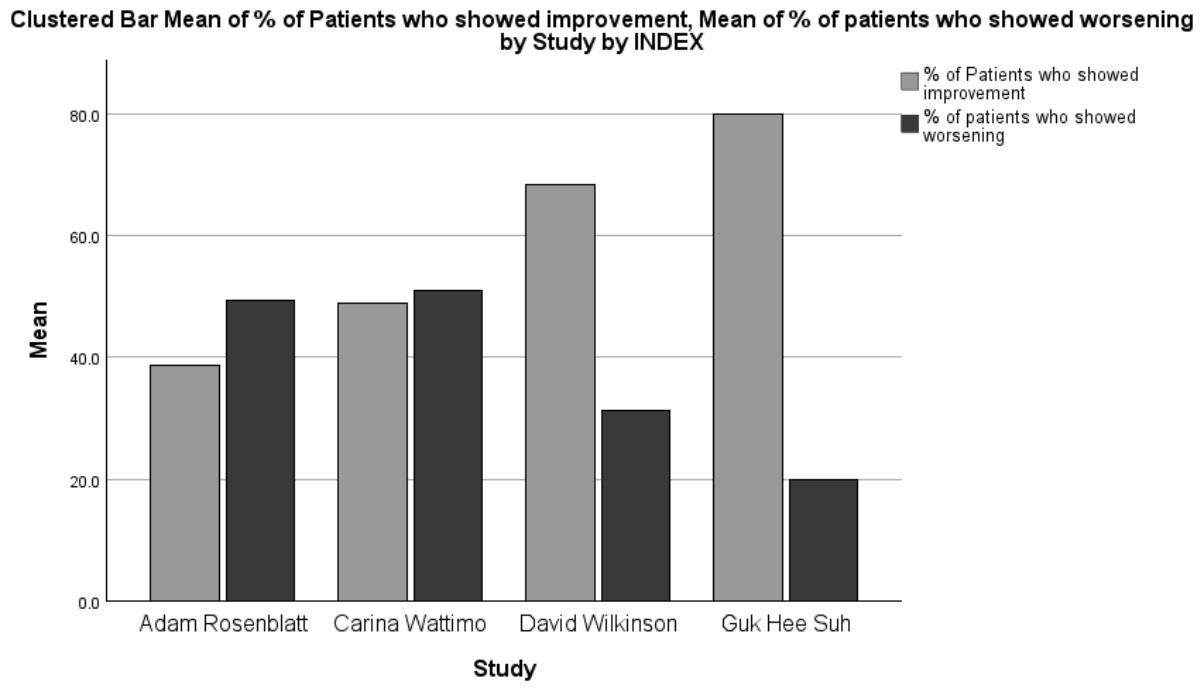
Table 6 : Improvement vs Worsening

	Mild to Moderate MMSE / ADL		Moderate to severe MMSE / ADL	
	Improvement		Worsening	
Study	Placebo	Study	Placebo	Study
David Wilkinson et al., (157) 2009	207/388 (53.3%)	356/518 (68.5%)	181/388 (46.6%)	162/518 (31.2%)
Adam Rosenblatt et al., (158) 2010	N/L	36 (38.7%)	N/L	46 (49.5%)
Guk-Hee Suh et al.,(161) 2008	37/72 (51.3%)	45/66 (80%)	35/72 (49.7) %	21/66 (20%)
Carina Wattmo et al., (160) 2012	N/L	383/784 (49%)	N/L	401/784 (51%)

This table summarises analytic information on four studies that we did as part of our research. In all studies there were patients categorised as mild to moderate and moderate to severe using the MMSE (Mini Mental State Examination) score. The numbers and percentages represent the number of patients who showed improvement or worsening after intake of Acetylcholinesterase drugs. we looked at the number of people that improved after administration of ChEI's and

changed the value into a percentage using the total number of patients involved in the treatment group. The same requirements were done for the worsening group.

In each study improvement and worsening were measured using different cognitive tests, in some studies more than one cognitive test was used. We choose to stick to results based on the cognitive test of MMSE.



Mean = MMSE mean

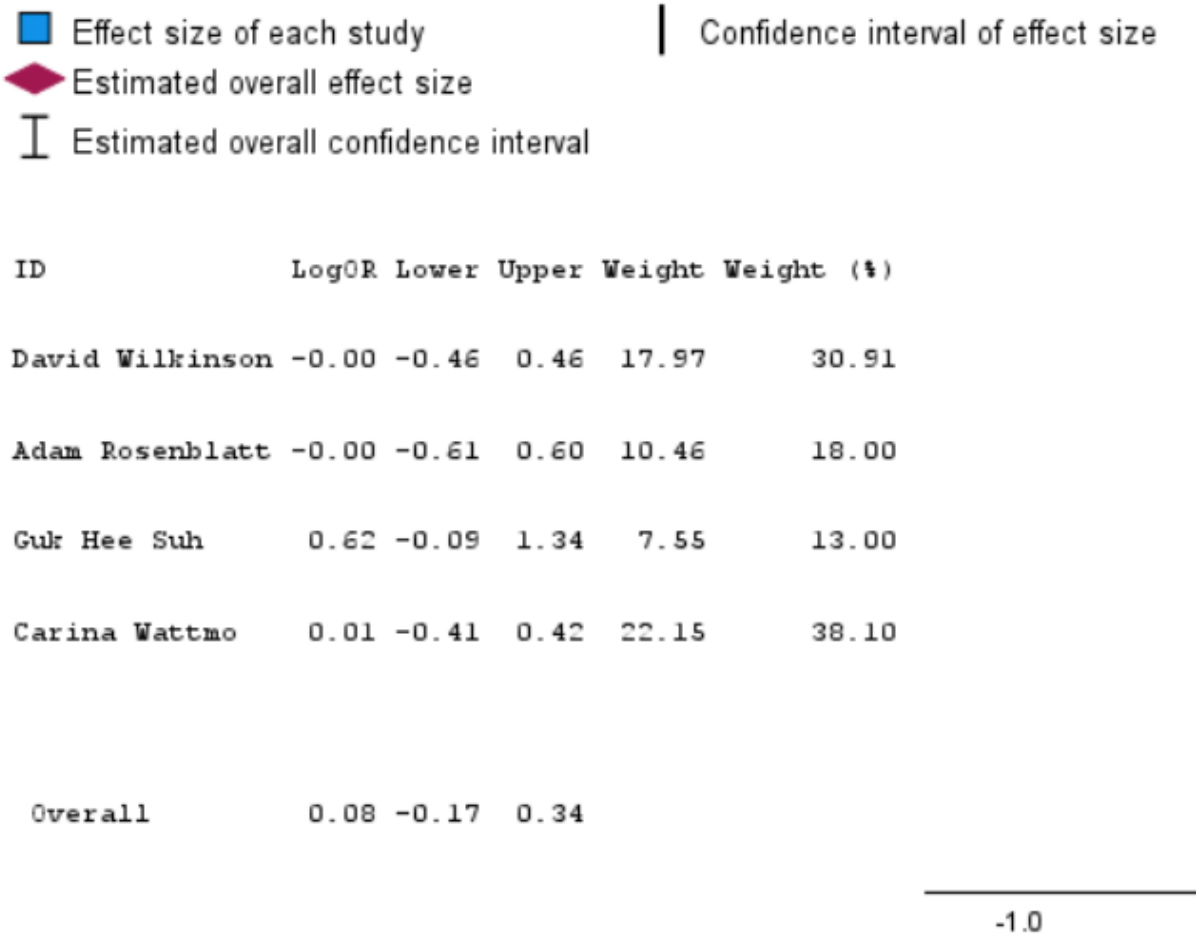
Figure 24 : Graph of worsening group vs Improvement

This is a graphic representation of the comparison between the patients who showed improvement in cognitive ability and patients who showed worsening in cognitive ability for each study.

The X axis shows the studies included in the bar graph, David *Wilkinsonet al., 2009,* Adam Rosenblatt *et al.,* 2010, Guk-Hee Suh *et al*., 2008, Carina Wattmo *et al.,* 2012 Each study is represented in turn by two columns, one for worsening and the other for improvement.

In this bar graph we remark how all the grey columns are represented as a higher percentage compared to the black columns representing worsening. From this graph we can conclude that a greater percentage of patients improving was noticed in all studies compared to the patients showing worsening.

Using statistical data from the four studies (120,157,158,160) We managed to make the Forest plot showing that the treatment of Alzheimer's disease by ChEI's has shown benefits using the improvement of patients against the worsening of patients. Because the p value is 0.53, we can conclude that there is no significant difference among the studies, indicating that there is no large difference between the percentage of patients who experienced improvement in cognitive ability vs the patients who experienced worsening of their cognitive ability.



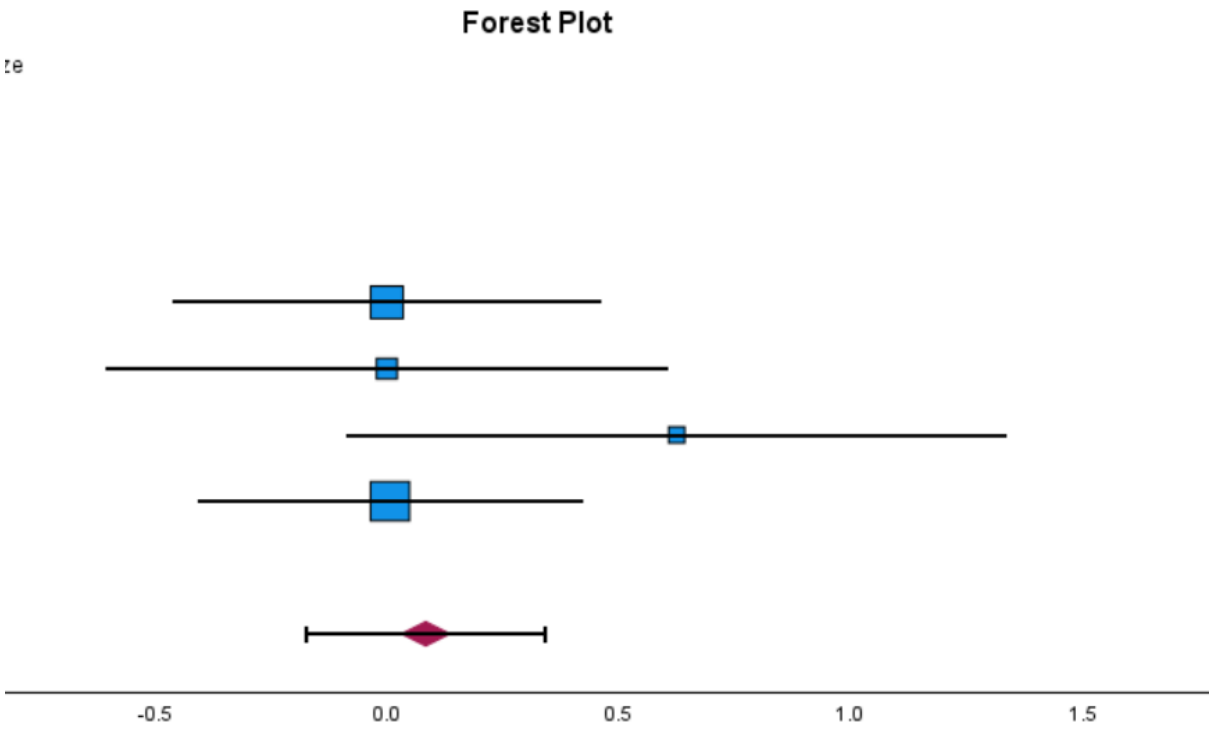


Figure 25 : Forest plot of results of improvement group vs worsening group

In the forest plot above after doing the meta-analysis we found a p value of 0.53 (p = 53%). Since our p value is higher than 5% ($p > 0.05$) this leads us to the conclusion that our results are not statistically significant.

3.6.4 Fourth segment

Table 7 : Donepezil 10 mg vs 23 mg

	Moderate to severe MMSE (0-9)	
Study	Dosage 10 mg	Dosage 23 mg
Marwan Sabbagh et al.,2013 (159)	462 LS score -3.8 points	909 LS score +0.1 points
Farlow et al., 2010 (99)	471 LS score +0.4	963 LS score +2.6
Rachelle S Doody et al., 2012 (174)	299 LS score +1.3	569 LS score +3.1

LS score = SIB score

This table shows a comparison between two different dosages of Donepezil, the statistical analysis is based on the test of SIB (Severe impairment Battery), using the difference of the LS score from the baseline score to the post hoc analysis score.

To add on to the results we got from the comparison between the improvement of cognitive ability vs the worsening of cognitive ability we also did a comparison including three studies comparing the improvement or worsening of cognitive ability, in relation to different dosages as well as different stages of Alzheimer's disease.

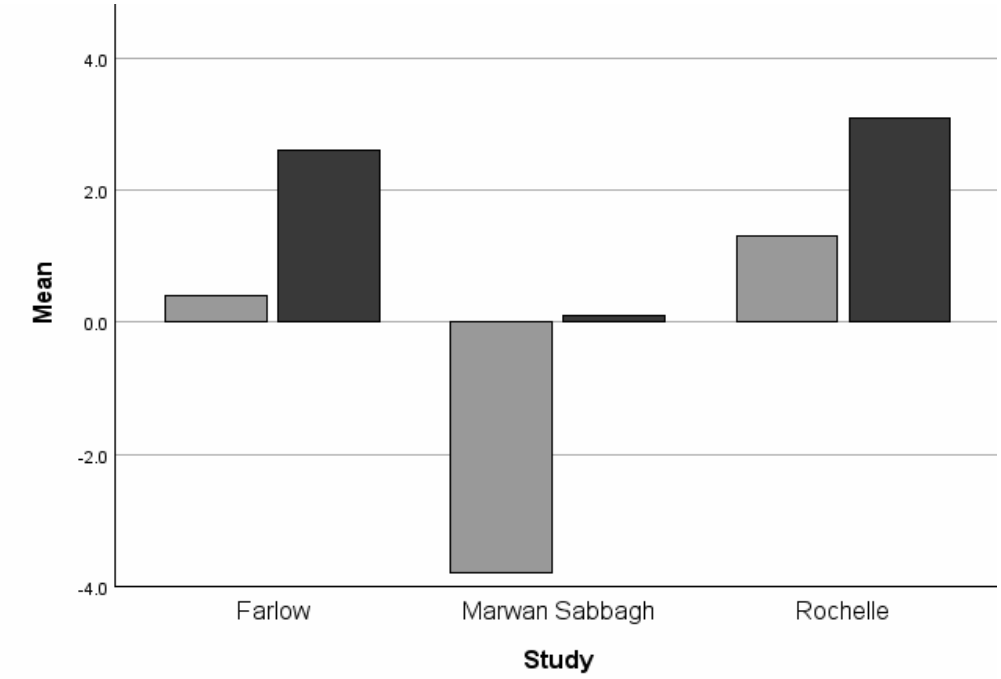


Figure 26 : Graph of Donepezil 10 mg vs 23 mg

LS score of patients who took 10 mg Donepezil

LS score of patients who took 23 mg Donepezil

Mean = MMSE mean

This is a graphic presentation of the LS scores of the treatments who took Donepezil at 10mg and those who took Donepezil at 23 mg of the information shown in the table above. There are three studies involved. The variable used in this study is the LS score representing the (Severe Impairment Battery Scale) SIB scale. The main purpose of the Severe Impairment Battery (SIB) scale was to address floor effects, which had restricted the usefulness of instruments previously employed to assess cognitive alterations in patients with moderate to severe Alzheimer's disease (AD) participating in clinical studies(182).

3.7 Discussion

Even though AD is a progressive condition, it is commonly believed that a patient's ability to improve or stabilise their cognitive, functional, and/or behavioural symptoms is the only way to show the advantages of treatment(157).

The information about the clinical efficacy of treatments for individuals with severe dementia is still lacking, despite the fact that a sizable fraction of dementia patients advances into the disease's severe phases(183). Therapeutic targets based on decreased clinical deterioration constitute realistic and clinically relevant aims for AD treatment(157).

The results shown in the first segment express how after performing the forest plot no significant difference in results are noted between the placebo group and the monotherapy treatment group. This is also a similar instance in some of our studies like Robert Howard et al 2007(164). There was no significant difference observed in the estimated mean reduction in the CMAI score between the donepezil and placebo groups from baseline to 12 weeks(164).

These among others include improvement in Daily Living Activities and reducing caregiver time. This enables us to see that regardless of there not being significant differences between the placebo and treatment group, we cannot conclude the treatment to not be effective based on that factor alone.

Guk-Hee Suh et al., 2008 (161)conducted a prospective study in Korea with a focus on society to determine whether ChEI's galantamine, in particular, can improve progressive functional ability and reduce caregiver time. The study also sought to determine the annual cost of patients who had more or less caregiver time(120). After this analysis it is inevitable to note that treatment of Alzheimer’s disease is also of economic interest as it can help prevent extra costs on caregiver expenses.

Acetylcholinesterase inhibitor monotherapy for Alzheimer's disease can help with symptoms, although patient response is frequently inconsistent(181). However, the AChEIs are efficacious for mild to moderate AD. Memantine has a beneficial effect in moderate to severe AD and is generally well tolerated, with a low incidence of adverse events (AEs). In contrast,

AD tends to affect mainly the senior citizens, according to prevalence statistics, approximately 12.5% of adults over 60 and 17.3% of those over 85 have severe Alzheimer’s disease(120).

The results retrieved from the forest plot in the second segment show us how there wasn't a significant difference over the use of ChEI's in monotherapy and with memantine in combination therapy on MMSE score. This would indicate that the addition of memantine did not add any significant advantage and patients who took ChEI's alone as treatment were doing well. According to this investigation, the cognitive benefits of donepezil did not seem to be significantly impacted by concurrent usage of memantine. In individuals receiving both donepezil alone and in combination with other medications, donepezil 23 mg was typically safe and well tolerated(174). *Carina Wattmo et al.,2012* also looks into how clinical and sociodemographic characteristics, which in this case include six months of ChEI therapy, affect the functional response after a given amount of time. In most studies most patients were above the age of 65 years and had gone through some kind of evaluation to attest their attainment of the alzheimer's disease in some studies like *Carina Wattmo et al.,2012* (160)*, Marwan Sabbagh et al., and Martin R Farlow et al.,2010* (159) incorporating patients in their late forties and early fifties. Cognitive benefit is seen in the studies regardless of age, weight or gender.

When compared to monotherapy, the use of the rivastigmine transdermal patch seemed to be well-tolerated in patients on established memantine, with only moderate, non-significant increases in adverse events (AEs). Additionally, there was no discernible negative impact on cognition or overall functioning(99).

The total magnitude of the deterioration in cognitive and functional status observed in all patients was greater than the gains in cognition and function linked to donepezil and memantine. The cognitive benefits of memantine treatment were lower and did not meet the minimum clinically important difference, but the benefits of donepezil therapy exceeded a minimum clinically important difference based on distribution(181).

In relation to combination therapy, it seems that adding the rivastigmine patch to patients who are already receiving memantine medication is well tolerated. Despite the fact that the combination regimen was linked to a higher number of adverse effects, these were not statistically different from the side effects recorded in patients taking rivastigmine by themselves or in earlier clinical trials using rivastigmine patches(99).

In *Seong Hye Choi*., et al 2011 memantine + rivastigmine patch combination therapy did not have a worse tolerability profile than rivastigmine patch monotherapy(176).

The total magnitude of the deterioration in cognitive and functional status observed in all patients was greater than the gains in cognition and function linked to donepezil and memantine. The cognitive benefits of memantine treatment were lower and did not approach the minimum clinic(181).

The continuation of donepezil is more cost-effective than stopping it altogether due to improved clinical outcomes and a reasonable(163).

In the third segment in relation to different dosages of Donepezil, Donepezil is usually dispensed as 10mg or 23 mg. Based on analysis, it appears that patients with more advanced AD may benefit more from donepezil 23 mg/d than donepezil 10 mg/d in terms of cognitive function. These benefits may be seen regardless of a patient's age, gender, weight, or history of donepezil 10 mg/d treatment(159)**.**

Marwan Sabbagh et al., 2013 and *Martin R. Farlow et al.,2010* examined the connections between easily recognizable baseline traits, demographics and the patients' cognitive reaction when they were receiving either a 10 mg/d or a 23 mg/d dose of donepezil.

Since 1997, donepezil 5 and 10 mg/d has been demonstrated to offer therapeutic benefits and tolerable tolerability in the primary symptom areas of cognition, general functioning, and function in everyday activities. The US Food and Drug Administration approved a higher daily dose of donepezil (23 mg) in 2010 for the treatment of moderate to severe AD(159).

We were able to identify inconsistent findings on the efficacy of treatments for Alzheimer's disease (AD) by examining the findings of studies that sought to assess the efficacy of medicines currently available. Actually, the majority of research we found was based on the fact that the use of ChEIs improved cognitive function overall, but they were unable to prevent AD from progressing into a severe stage. (160)**.**

It is imperative to note that different assessment techniques were used in some research, such as *Guk Hee Suh et al.,2008*, to increase the effectiveness of treatment in addition to the MMSE scale. Galantamine was found in the latter study to be advantageous for patients with mild to moderate AD. It not only slowed the rate of functional decline but also resulted in significant financial savings, which is directly related to a reduction in the time and cost of caring for the patient. If the MMSE scores are not acceptable to us, this measure allows us to examine the efficacy of the treatment for Alzheimer's disease in greater detail.

3.8 Conclusion and perspectives

The importance of memantine and cholinesterase inhibitors in the symptomatic treatment of Alzheimer's disease (AD) is highlighted by this meta-analysis. Even though these pharmaceutical therapies have limited advantages, they are vital in helping patients live better lives and lighten the load on caregivers. These conclusions are supported by data from our study conducted at the Central University Hospital (CHU) in Tlemcen, which shows significant improvements in cognitive function in individuals using memantine and donepezil with little side effects.

Notwithstanding these encouraging results, the data also show that additional extensive, rigorous trials are required to validate the slight variations noted between the treatment and placebo groups. For these treatments to be shown safe and effective on a larger scale, such studies are necessary.

This argument has also emphasised the necessity of ongoing innovation in the treatment of AD. A greater comprehension of the physiopathology of the disease and the development of novel therapies are necessary due to the rising global burden of Alzheimer's disease. Given the complexity of Alzheimer's disease, comprehensive approaches and alternative therapeutics beyond symptomatic treatment should be investigated.

Perspectives

Going ahead, this study offers the following perspectives:

- Improved Clinical Trials :

More extensive and varied clinical trials are required to validate the advantages of existing pharmaceutical interventions. To guarantee that the findings can be applied to a large population, these trials ought to try to enrol a diverse selection of individuals.

- Creation of Innovative Medicines:

The creation of novel therapeutic approaches that can more successfully address the underlying pathophysiology of Alzheimer's disease is desperately needed. Instead of just focusing on treating symptoms, research should be done on novel treatments that can alter the course of a disease.

- All-inclusive Approaches to Treatment:

Examining and incorporating complementary therapies, such cognitive therapies, lifestyle adjustments, and other non-pharmacological approaches, may provide extra advantages and enhance patient results.

- Comprehending Pathophysiology

It is imperative that the pathophysiological mechanisms of Alzheimer's disease are further investigated. Developing targeted treatments will be aided by a deeper comprehension of neurofibrillary tangles, amyloid plaques, and other pathological alterations.

- Support for Caregivers and Policy:

Supporting carers and putting in place laws that enable better care should be priorities as the number of cases of Alzheimer's disease rises. This entails guaranteeing access to efficient therapies and offering tools for caregiver education.

- All-encompassing Medical Care :

The quality of life for Alzheimer's patients can be improved by emphasising a holistic approach to patient care that takes psychological, social, and physical factors into account. Neurologists, psychiatrists, and other medical specialists might work in multidisciplinary teams to provide comprehensive care.

In summary, this thesis has shed important information on the efficacy and security of the available therapies for Alzheimer's disease, but it has also underlined the need for continued investigation and creativity. Improving treatment options and patient care necessitates a persistent, cooperative effort to address the complex difficulties of Alzheimer's disease.

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