Efficacy of Rivastigmine in Alzheimer's Disease- A Structured Review

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School of Pharmacy

BRAC University

30 October, 2022

Declaration

It is hereby declared that-

1. The thesis submitted is my own original work while completing degree at Brac University.

2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.

3. The thesis does not contain material, which has been accepted, or submitted, for any other degree or diploma at a university or other institution.

4. I have acknowledged all main sources of help.

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Approval

The project titled "Efficacy of Rivastigmine in Alzheimer's Disease- A Structured Review" submitted by Abdul Alim (18346011) of summer, 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on 30.10.2022.

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Ethics Statement

The project did not involve any human participants or animals at any stage of the study.

Abstract

Rivastigmine is an anti-cholinesterase agent, used to treat mild to moderate dementia of Alzheimer's disease (AD). Its efficacy and tolerability increase the treatment compliance. This study focused on determining the efficacy of Rivastigmine by reviewing data from the clinical trials. A structured search was conducted through PubMed up to September 2022 to identify randomized controlled trails (RCT) evaluating the efficacy of oral capsule and transdermal patch of Rivastigmine for AD. The efficacy was assessed using the primary end point, Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog) and secondary end point, Mini Mental State Examination (MMSE). It was suggested that Rivastigmine capsule 12 mg/d (twice daily) and Rivastigmine patch 9.5 mg/d (Once daily) is the optimal dose for 24 weeks in mild to moderate AD. Though cholinesterase inhibitors have limited activity, Rivastigmine still represents a positive effect for the treatment of AD.

Dedication

Dedicated to my faculty members, family and friends.

Acknowledgement

All praises for Almighty Allah. I would like to express my sincere gratitude to my project supervisor, Professor Dr. Hasina Yasmin (Assistant Dean and Program Director, School of Pharmacy, BRAC University) for providing the guidance and support in completing my project. I also sincerely thank for her precious time spent on making me understand the pros and cons also correcting my mistakes. I would like to acknowledge Professor Dr. Eva Rahman Kabir (Dean, School of Pharmacy, BRAC University) for her support and encouragement to complete my project. I would also like to acknowledge Dr. Mesbah Talukder, Associate Professor, School of Pharmacy, BRAC University for his valuable suggestions and encouragement.

I would like to thank to my family members, friends, all faculty members and all teacher assistants for their motivation and support.

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List of Acronyms

AD: Alzheimer’s Disease

ACh: Acetylcholine

AChE: Acetylcholine Esterase Inhibitors

ADAS-cog: Alzheimer's Disease Assessment Scale–Cognitive Subscale

AEs: Adverse Events

BID: Bis In Die

ADL: Activities of Daily Living

BuChE: Butyrylcholine Esterase Inhibitors

ChE-Is: Choline Esterase Inhibitors

MCI: Mild Cognitive Impairment

MMSE: Mini Mental State Examination

Chapter 1

Introduction

1.1 Alzheimer's disease (AD)

AD is considered as one of the most frequent causes of dementia which is currently represented a rising health risk. The WHO declared AD as a global health concern in 2006 (Lane, 2018). AD is one of the most prevalent neuro-degenerative diseases which are identified clinically by observable decrease in memory loss, ability in learning, capacity to do regular activities of living. A wide range of neuropsychiatric symptoms were observed including apathy, agitation, physical and verbal agitation, irritability, depression etc. In last ten years, pharmacotherapy of AD getting more advantageous than using psychotropic medications as it has sedative effect. The FDA approved only one class of drugs ChE-Is for treating AD that has been thoroughly investigated in patients during clinical trials (Stepankova & Komers, 2008). It was found that lack of Acetylcholine (ACh) leads to faulty cholinergic signaling in brain mainly hippocampus and cortex area, considering as the source of cognitive impairment (Hsieh et al., 2021).

1.2 Prevalence of AD

Nowadays, an approximately 6.2 million Americans of 65 years and above are estimated to be living with AD dementia. By 2060 this figure can increase to 13.8 million unless any development of medical advances to stop, steady or treat AD. A recent study stated that there were 121,499 official death certificates recorded in 2019 for AD which makes Alzheimer's the 6^{th} leading cause for death in USA. Between 2000 and 2019, reported deaths from AD increased to more than 145% whereas other death causes like stroke, heart attack and HIV decreased.

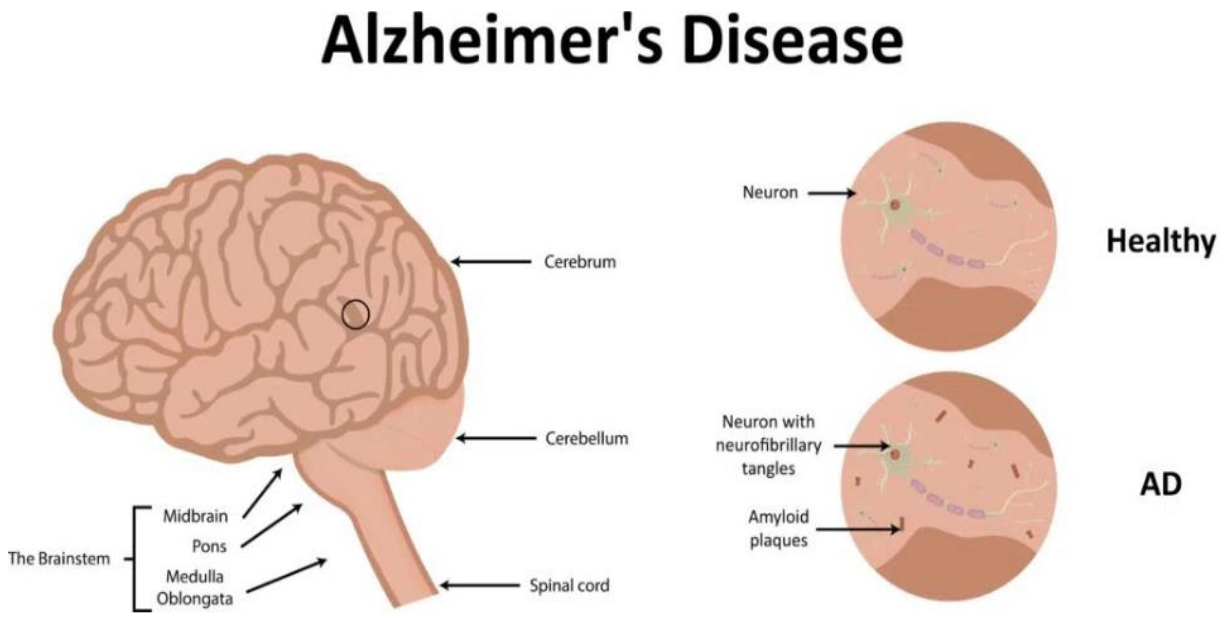


Figure 01: Schematic illustration of Alzheimer's Disease (Jakob-roetne & Jacobsen, 2009).

During the COVID-19 pandemic deaths due to AD were increased. During 2021, about 11 million care provider and family members give a predicted 15.3 billion hours to Alzheimer's or dementia patients. According to a telephone survey study organized in Canada, it was found that AD prevalence was 31% for women and 27% for men (Eldufani & Blaise, 2019). In Wales and England, dementia is the main reason of death where 11.6% deaths were registered in 2015 due to dementia. In countries with lower middle income, which indicate patterns of highly growing diseases like diabetes, hypertension and other cardiovascular diseases are estimated to increased prevalence of Alzheimer, mostly in each 5 years twice in prevalence after 65 years (Lane, 2018).

1.3 Etiology

The causes of AD are multifactorial which include genetics, cardiovascular disease, Down syndrome, head injury, environmental toxins, genetic factors and aging. Also other factors like diabetes mellitus, depression are the disease conditions which cause AD. The various etiological factors are showed in Figure 2.

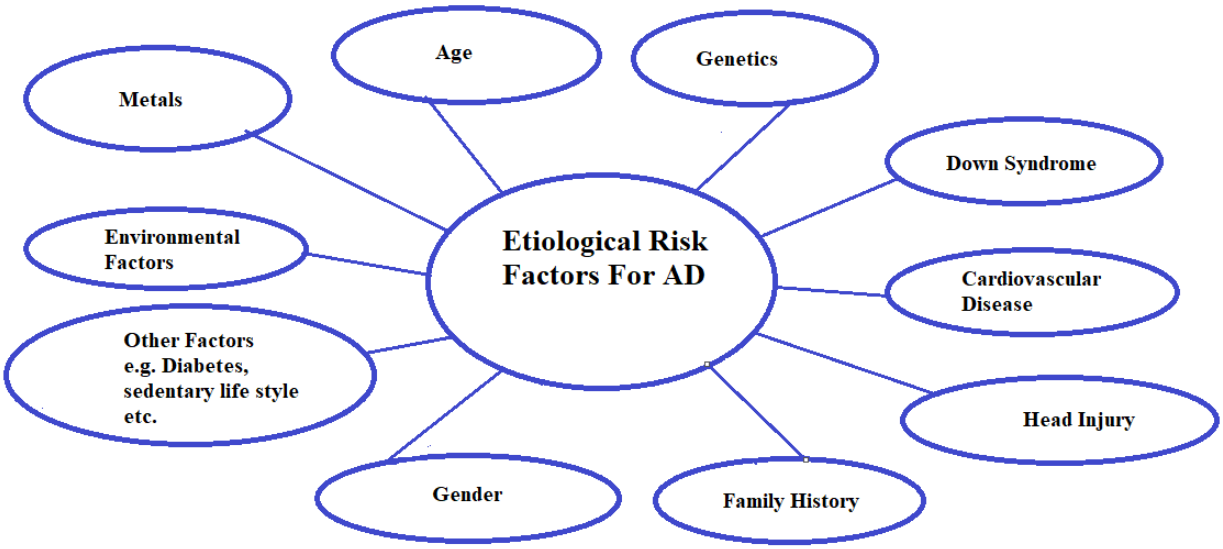


Figure 2: Etiological risk factors for AD (Duggal & Mehan, 2019).

Risk Factors

Age- The single most important factor is age. Risk for Alzheimer's goes up as person gets older. Aging affects AD by two mechanisms as free radicals produce through cellular respiration in aging results AD and another one is mutation in messenger RNA of Aβ protein precursor and ubiquitin B. For most people, it starts going up after age 65. After age 65 the risk of developing AD

doubles in every 5 years. However, people at any age are susceptible to developing AD. Roughly 1 in 20 persons under 65 are found to have AD which is known as early or young onset AD. Around the age of 40 years it can start affecting people.

Genetics- Genetics is a crucial factor in the development of AD. Amyloid precursor protein (APP), Presenilin 1 (PSEN 1) and Presenilin 2 (PSEN 2) mutations are linked to early-onset AD, or familial AD which develop the risk of the disease before the age of 65 years.

Down syndrome- Persons with Down's syndrome have a greater chance of acquiring AD at the age of 30 or 40 years. This is because some persons who have down syndrome can develop AD as a result of genetic abnormalities which cause amyloid plaques to accumulate in the brain over time (Duggal & Mehan, 2019).

Cardiovascular Disease (CVD) - Three explanations are most frequently suggested to explain CVD which could develop the risk of AD. Firstly, CVD and AD normally share the same risk factors which independently increase the rates of CVD and AD. Secondly, brain vascular damage could indirectly contribute to the development of conditions that predispose to neurodegeneration. Lastly, vascular factors can contribute to the development of AD by causing neuronal death, and buildup of plaques and tangles (Stampfer, 2006).

Head injury- Several studies have identified the indications of dementia who have experienced traumatic brain injuries. Many years after the injury, researchers have identified the accumulation of amyloid plaques and neurofibrillary tau tangles in the brain. There is a greater chances of people who have suffered from severe brain injury than those who have not

experienced brain injury (similar to the microscopic changes in the brain observed in AD and other types of dementia) (Shimura et al., 2021).

Family history- People who have a parent, siblings or other relatives with AD are more prone to develop AD. If more than one family member is affected, the risk of developing AD increases. Either environmental factors, genetics or both can play a vital role when diseases tend to run in families (Manuscript, 2013)**.**

Gender- Several studies have shown that women are at higher risk of AD dementia than men. Approximately two thirds of people diagnosed with AD dementia are women. However, women have greater life expectancies than man. As a result, women have a greater risk of developing AD dementia (Mielke & Clinic, 2019).

Metals- Exposure to neurotoxic metals such as lead, mercury, arsenic, aluminum and copper has been linked to AD because of their tendency to rise amyloid plaques and tau protein phosphorylation (Blackman et al., 2021).

Environmental Factors- Environmental toxins such as smoke, tobacco or nicotine and pesticide like carbofuran and deltamethrin are involved in hampering tau function which leads to AD.

Other factors- High cholesterol levels, untreated depression (although this condition can be one of the signs of AD) and leading sedentary lifestyle may also raise person's risk of AD (Duggal & Mehan, 2019).

1.4 Pathology

The pathophysiology of AD is complicated, including some neurotransmitter systems and pathophysiologic processes.

Amyloid Plaques Formation

Amyloid fibril formation is a multiple state process which begins with the cleavage of the amyloid fragments from the trans membrane APP, misfolding of Aβ monomers that form several structures like unfolded clusters, beta sheet oligomers, larger fibrils and Amyloid plaques. These amyloid aggregates have a strong interaction with the membrane because of the close proximity to the cell surfaces (figure 3). The hypothesis that the state of the cell membrane (composition, morphology and other physicochemical properties) plays a significant role in AD which is supported by several studies (Drolle et al., 2014).

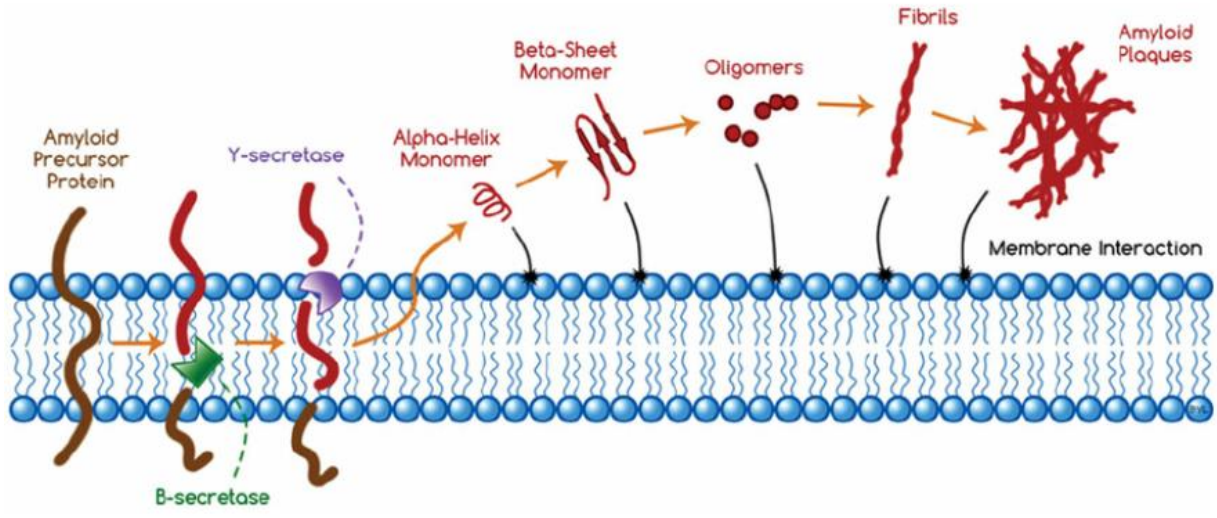


Figure 3: Schematic showing amyloid origin and the mechanism of the amyloid fibril formation (Drolle et al., 2014).

The amyloid β peptide is a critical initiator that triggers the progression of AD via accumulation and aggregation. Amyloid β peptide is a vital component of senile plaques that frequently exist in the brain of AD patients. Aggregation (such as oligomer, pro-fibril and filamentous fibril formations) and accumulation of Amyloid-β in the brain has been suggested to play an important role in the pathogenesis of AD. Amyloid β plaques have the ability to destroy nerve cells which causes thinking and memory loss in AD.

The loss of memory and cognitive ability that is linked to AD is assumed to be caused by neurodegenerative processes that are triggered when amyloid-β clumps together and deposits in the brain (Chen & Wang, 2015).

Tau Neurofibrillary Tangles (NFTs) Formation

Tau is a protein found in neuronal microtubules which facilitates tubulin self-assemble microtubules as well as regulates the stability of axonal microtubules. Tau proteins conformational changes and hyper phosphorylation help in the generation of tau aggregates which results in formation of NFTs. Extracellular amyloid-β plaques and intracellular neurofibrillary tangles (NFTs) are two pathologic features of AD. It has long been predicted that the build-up of tau into NFTs which results in neuronal malfunction and death and it is one of the major causes of dementia in AD patients.

The development of NFTs- tau proteins self-aggregate to form loosely intertwined paired helical filaments (PHFs) and the tightly wrapped straight filaments (SFs), which results to the formation of NFTs plays an important role in AD (Jie et al., 2021).

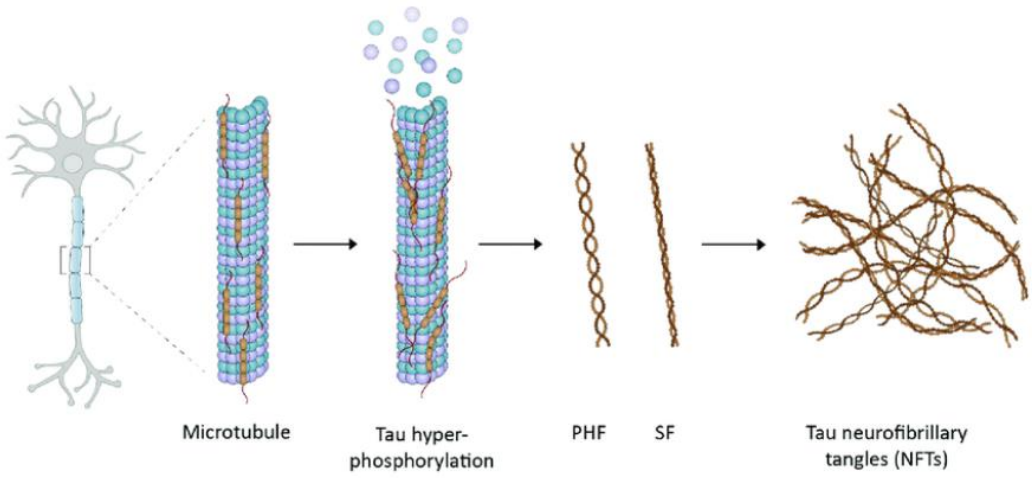


Figure 4: Schematic showing tau neurofibrillary tangles (NFTs) formation (Jie et al., 2021).

The Role of ACh

The figure 5 shows how the cholinergic pathway is linked to AD. Amyloid-beta plaques and NFTs are formed when AChE reduces the ACh levels. The AChE-Is block the AChE enzyme which blocks the cholinergic pathway of AD thus increasing the level of ACh that facilitates in the treatment of AD.

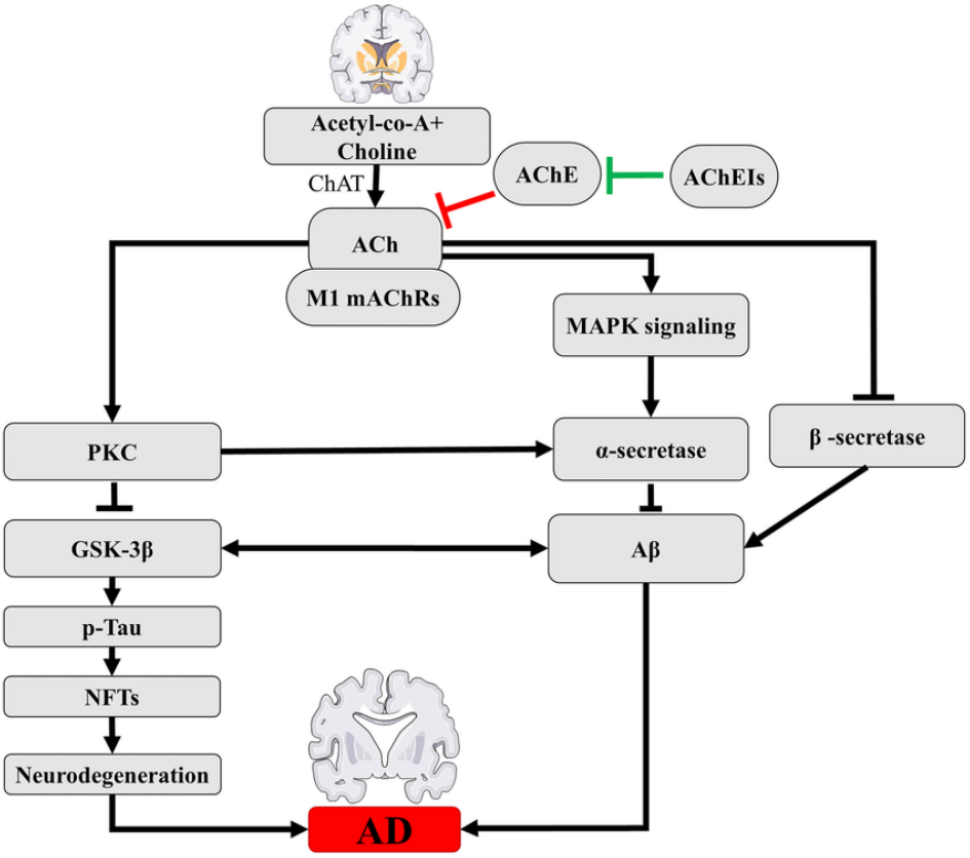


Figure 5: The role of ACh in the cholinergic pathway in AD (Grossberg et al., 2015).

1.5 Current Treatment Options of AD

1.5.1 Cholinesterase inhibitors

Tacrine is introduced as first generation cholinesterase inhibitor but had few hepatotoxic adverse effects. After that, Rivastigmine, Donepezil and Galantamine were introduced which are now the most extensively used medication. These agents show relatively similar efficacy for which

selection must be based on physicians experience, cost and patients tolerance (Briggs et al., 2016).

Rivastigmine

Rivastigmine therapy starts with an initial dose of 6 mg two times daily for 24 weeks. The maximum tolerated dose is 12 mg twice daily. Rivastigmine is administered as oral capsule, solution and transdermal patch. The most frequent side effects of Rivastigmine are abdominal pain, nausea, diarrhea, vomiting and loss of weight. Side effects limit the administration of Rivastigmine in highest tolerated dose in many patients. Rivastigmine is excreted through renal route (kidneys) that is indeed good for those patients who have liver disorder. It has central nervous system selectivity that binds in the esteratic site of enzyme. Rivastigmine forms a carbamoylated complex with the enzyme and can inhibit both acetyl-cholinesterase (AChE) and butyl-cholinesterase (BuChE) equally. FDA approved Rivastigmine in 1997. In addition to oral dosage form, FDA approved Rivastigmine transdermal patch (Exelon patch) in 2007 (Stepankova & Komers, 2008).

Donepezil

Donepezil therapy starts with an initial dose of 5 mg once a day during evening for 4 to 6 weeks. Consequently, dosage is increased to 10 mg once per day for 3 months and the maximum tolerated dose is 23 mg once daily. Donepezil can be administered as oral tablet. The most frequent side effects of Donepezil are headache, nausea, vomiting and felling dizzy at daytime. As a result it is assumed that about one-third of patients might not be able to tolerate Donepezil therapy due to its side effects. Donepezil is excreted through renal route (kidneys) that is indeed

good for those patients who have liver disorders. Donepezil binds and reversibly inhibits AChE enzyme. FDA approved Donepezil in 1996 (Briggs et al., 2016).

Galantamine

Galantamine therapy starts with an initial dose of 4 mg twice daily for 4 weeks and the dosage is increased to 8 mg two times daily for additional 4 weeks. If needed the dosage is increased to 12 mg two times a day and the maximum tolerated dose is 24 mg two times a day. Galantamine can be administered as oral tablet and solution. Patients tolerability is higher for Galantamine as it is a selective agent. However, there are few common side effects such as diarrhea, vomiting, nausea, headache, dizziness, loss of weight and loss of appetite is seen with Galantamine therapy. The routes of excretion for Galantamine are kidneys and liver where it excreted equally. Galantamine binds and reversibly inhibits AChE enzyme. FDA approved Galantamine in 2001 (Press, 2010).

1.5.2 N-methyl-D-aspartate (NMDA) Antagonist

Memantine

Memantine therapy starts with an initial dose of 5 mg once a day and the dosage is increased to 10 mg two times daily, 15 mg two times daily. The maximum tolerated dose is 20 mg two times a day. The minimum recommended interval between dose increments in one week. Memantine is administered as oral tablet, capsule and solution. The most common side effects of Memantine are headache, blurred vision and diarrhea. Memantine is excreted through renal route (kidneys). Memantine has ability of blocking NMDA receptor noncompetitively thus neuroprotective by preventing loss of neuron and reduce symptoms by restoring function of neurons that are

damaged. Additionally, it is usually well tolerated and shows fewer side effects than ChE-Is. However, somnolence, dizziness, hypertension as well as constipation can be observed. It can be beneficial in treating moderate to severe AD but less evidence found in using for milder AD. Patients who have mild AD or cognitive deterioration will be benefited using combination of Memantine to donepezil monotherapy. FDA approved Memantine in 2003 (Briggs et al., 2016).

1.6 Rivastigmine in the treatment of AD

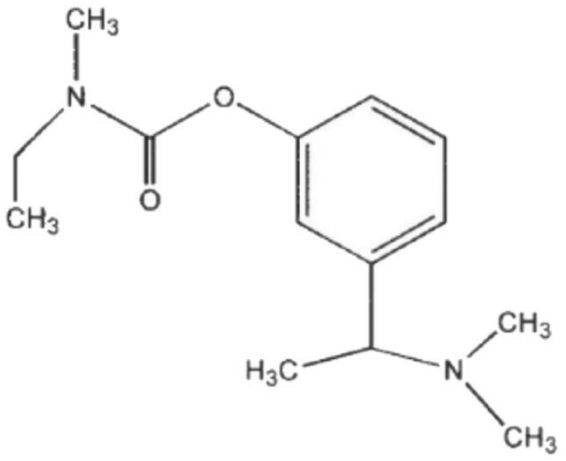


Figure 6 : Rivastigmine (Eldufani & Blaise, 2019).

Chemically Rivastigmine is (S)-N-Ethyl-N-methyl-3-[1-(dimethylamino) ethyl]-phenyl carbamate hydrogen-(2R, 3R)-tartrate. Its empirical formula is C14H22N2O2 • C4H6O6 and molecular weight is 400.43. Rivastigmine tartrate is highly soluble in water.

Acetylcholine is the first neurotransmitter that aids in improving attention and learning. Till now various drug types were used for modification of cholinergic neurotransmission. Cholinesterase inhibitors show a prominent way to treat mild to moderate AD. It inhibits released acetylcholine breakdown which results in enhancing the cholinergic neurotransmission. It is a dual inhibitor

(carbamate-type) of brain cholinesterase which can inhibit both AChE and BuChE. In brain mainly the hippocampus and cortex area, Rivastigmine targets both AChE as well as BuChE and also has ability to cross blood brain barrier. The drug Rivastigmine had proved its efficacy in treatment of enhancing or sustaining cognitive function, regular living activities, behaviors, and signs of dementia in mild to moderate AD patients (Hsieh et al., 2021).

1.7 Purpose of the study

AD is a long term neurological disorder which causes serious damage in brain results in decreased quality of life. However, only a few treatment options are available to treat this neurologic disorder. Among these Rivastigmine brought major advancement in treating AD. This study focused on the efficacy of Rivastigmine in Alzheimer's patients by reviewing data from several clinical trials.

Chapter 2

Methodology

A structured search on PubMed September 2022 by using several MeSH (Medical Subject Headings) terms and keywords for female and male AD, mechanism of action, pharmacokinetic, efficacy of Rivastigmine oral capsule and transdermal patch were performed. This search was identified 414 records. After initial screening and deduplication, the number came down to 293. In addition, selected articles bibliographies were hand searched to identify information. The report added the RCT investigating the efficacy of oral capsule and transdermal patch of Rivastigmine for AD. The exclusion criteria are the studies that investigated Parkinson disease other than male and female AD, RCT that did not include primary end point (ADAS-cog) and secondary end point (MMSE) as an outcome, studies that did not discuss on Rivastigmine oral capsule or patch, studies with insufficient data and studies that did not focus on RCT. The process of screening is shown in figure 7.

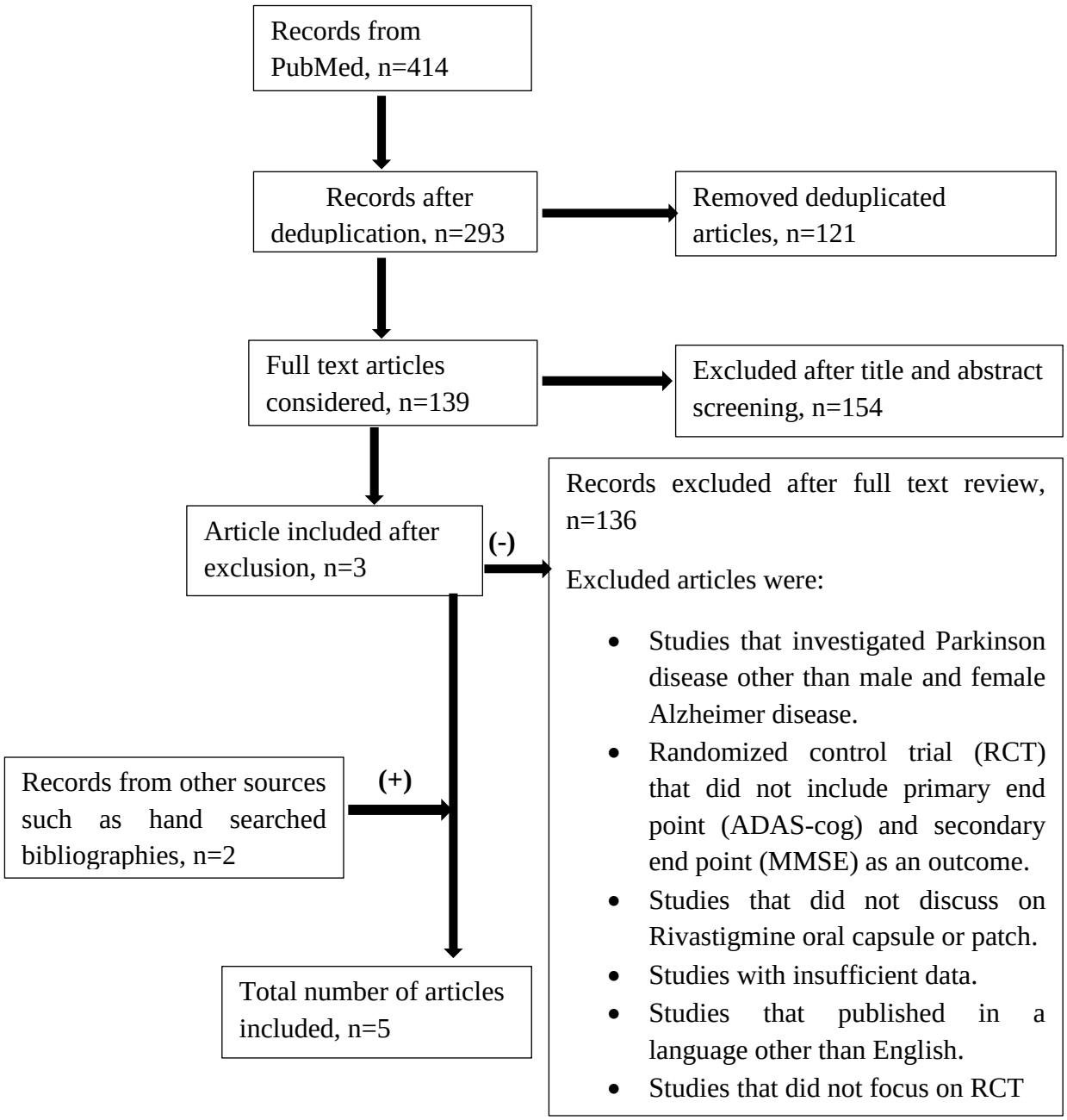


Figure 7: Sources, search strategy, and article exclusion criteria.

Chapter 3

Pharmacodynamics of Rivastigmine

3.1 Indications

Rivastigmine is used in the treatment of mild to moderate dementia (memory loss and mental changes) linked to AD or Parkinson's disease and also used to treat Lewy Body Dementia. Rivastigmine can facilitate some patients thinking ability. But it cannot be able to cure or stop AD or Parkinson's disease from getting worse.

3.2 Approved dosage form

Table 1: Rivastigmine brand name, dosage form, route of administration, dose and FDA approved year.

Dosage form	Brand Name	Route of Administration	Doses/ strengths	FDA Approval (year)
Capsule	Exelon Rivadem Rivamer Rivasmin Srivasmin	administered by oral route and swallowed capsule	1.5 mg 3 mg 4.5 mg 6 mg 12 mg	1997
Solution	Exelon Rivastoron Reminyl Rivast	administered by oral route and it directly swallowed from	1.5 mg/ml/d 2 mg/ml/d 3 mg/ml/d 4.5 mg/ml/d	2000

		the syringe	6 mg/ml/d	
Transdermal patch	Exelon Alzest Mylan Sinsin Prometax	applied to the skin	4.6 mg/d 9.5 mg/d 13.3 mg/d	2007
Tablet	Zeemine	administered by oral route	1.5 mg/d 3 mg/d	-

3.3 Dosage Regimen

Oral Capsule

- For mild to moderate AD: 6 - 12 mg two times a day is administered by oral route. Begin with 1.5 mg two times daily after that increase by 1.5 mg/dose in each two weeks per patient tolerated. 12 mg/d is the highest dose.
- Dose need to be taken with food. If interruption of treatment passes more than 3 days, physicians need to re-titrate starting at 1.5 mg.

Transdermal patch

- For mild to moderate AD: Primarily 4.6 mg patch once daily is applied for four weeks. If it fails to reduce AD then increases to 9.5 mg patch daily for four weeks.

- For severe AD: At first 4.6 mg patch once daily is applied for four weeks which increase to 9.5 mg patch daily for four weeks. Moreover, if necessary 13.3 mg Patch daily can be administered.
- 13.3 mg once daily is the maximum dose which is administered by Transdermal route. If necessary to convert from oral dose 6-12 mg/day, starting from 9.5 mg patch once daily. If interruption of treatment passes 3 days then start with 4.6 mg patch and titrate.

Oral Solution

- For mild to moderate AD: 2 mg/ml two times a day is administered by oral route and it swallowed directly from the syringe Begin with 1.5 mg two times daily after that increase by 1.5 mg/dose in each two weeks per patient tolerated. 6 mg/ml/d is the highest dose.
- Dose need to be taken with food.

3.4 Side effects

Common side effects of Rivastigmine

Diarrhea

Abdominal pain

Nausea

Vomiting

Loss of weight

Headache

Dizziness

Anorexia

Other side effects of Rivastigmine

Severe skin redness, itching, or irritation, Seizure (convulsions), Painful urination, Anxiety, Asthenia, Depression, Drowsiness, Dyspepsia, Fatigue, Tremor (uncontrolled shaking), Diaphoresis, Flatulence and Malaise.

3.5 Drug – Drug interactions

Since Rivastigmine is metabolized by hydrolysis and not by the major cytochrome P450 isozymes, no drug interactions related to cytochrome P450 have been identified in humans. However, few study reported interactions of Rivastigmine with atenolol and similar beta-blockers. Those drugs should be avoided or alternate drug should be used.

3.6 Mechanism of Action of Rivastigmine

Two different cholinesterase enzymes AChE and BuChE hydrolyze ACh in the brain. AChE is mostly found at the synaptic nerve junctions and areas that have more function in the cerebral cortex. Moreover, BuChE is present in the glial cells (Astrocyte) of the brain as well as facilitates cholinergic function. By aging of humans, the function of both of the cholinesterase enzymes elevates. In AD, the overexpression of cholinesterase enzymes is much greater than normal level. Like the other ChE-Is, Rivastigmine is one of them which has been showed reversibly bind to as well as block both of these enzymes which causes an overall elevation of ACh (Moghul & Wilkinson, 2016).

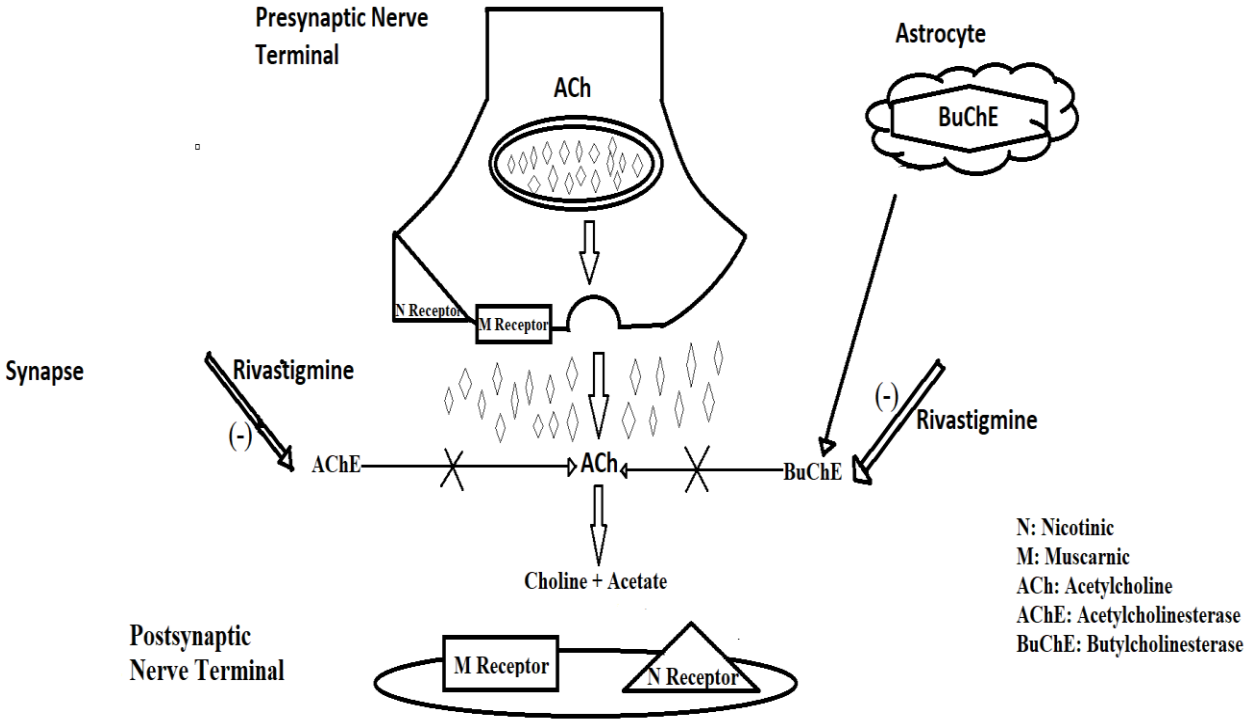


Figure 8: Mechanisms of Action of Rivastigmine (Moghul & Wilkinson, 2016).

Chapter 4

Pharmacokinetics of Rivastigmine

4.1 Absorption

Rivastigmine capsule is quickly and totally absorbed along with a bioavailability of approximately 40% and represents linear pharmacokinetics up to 3 mg two times a day while at higher dose represents non-linear pharmacokinetics. Additionally, doubling the dose from 3 to 6 mg two times daily results in a 3-fold rise in area under curve (AUC). Within approximately an hour peak plasma concentration (Cmax) is reached. Administration of Rivastigmine in presence of food delays absorption (tmax) by 90 minutes decreases Cmax by about 30% (6.8 ng.h/ml) as well as increases AUC by approximately 30% (166 ng.h/ml).

Rivastigmine patch is also quickly and totally absorbed with a bioavailability of approximately 50%. Administration of Rivastigmine patch in presence of food didn't cause any effect on absorption. After that Concentrations gradually increase, often reaching a maximum after 8 hours (tmax) which decreases Cmax by about 30% (3.3 ng.h/ml) as well as increases AUC by approximately 30% (207 ng.h/ml) (Focus, 2009).

4.2 Distribution

Both Rivastigmine capsule and patch are broadly distributed all over the body along with a volume of distribution (Vd) value ranges of 1.8 to 2.7 L/kg. Rivastigmine is able to penetrate the blood brain barrier (BBB) and reaching cerebrospinal fluid (CSF) peak concentrations in 1.4-2.6 hours. At 1-400 ng/mL concentration, Rivastigmine is almost 40% bound to plasma proteins that

falls under therapeutic range. Moreover Rivastigmine distributes equally between plasma as well as blood together with blood-to-plasma partition ratio of 0.9 at concentrations ranging from 1-400 ng/mL.

4.3 Metabolism

Both Rivastigmine capsule and patch are quickly and considerably metabolized, principally by cholinesterase-mediated hydrolysis to the decarbamylated metabolite. According to proof from in vitro and animal studies, the major cytochrome P450 isoenzymes are barely responsible for metabolism of Rivastigmine. Moreover, for Rivastigmine patch, less decarbamylated metabolite is founded subsequent to patch application, apparently cause of the deficit of pre-systemic (hepatic first pass) metabolism. According to *in vitro* studies, no specific metabolic pathways were identified in human skin.

4.4 Elimination

The main route of elimination of Rivastigmine is kidney. After administration of 14C-rivastigmine to six healthy volunteers, total recovery of radioactivity over 120 hours was 97% in urine and 0.4% in feces. In addition, none of the parent drug was identified in urine. The sulfate conjugate of the decarbamylated metabolite is the main component excreted in urine and indicates 40% of the dose. Moreover mean renal clearance of Rivastigmine is 1.8±0.6 L/min after 6 mg BID. The elimination half-life (t½) is almost 1.5 hours along with maximum elimination as metabolites through the urine. Renal clearance ranges between almost 2.1 and 2.8 L/hr (Emre et al., 2010).

Table 2: Pharmacokinetics of oral and transdermal dosage forms of Rivastigmine.

Pharmacokinetic parameters		Oral Rivastigmine	Transdermal Rivastigmine
Absorption	Bioavailability	~ 40% absorbed from the GIT	~50% absorbed from skin
	Cmax	6.8 ng.h/ml	3.3 ng.h/ml
	T max	90 minutes	8 hour
	AUC	166 ng.h/ml	207 ng.h/ml
	Bioavailability-effect of food	Food delays absorption	No effect
Distribution	Vd	1.8-2.7 L/kg	1.8-2.7 L/kg
	Plasma protein binding	40%	40%
	Blood brain barrier crossing	Yes	Yes
Metabolism	-	Metabolised by Cholinesterase enzyme	Metabolised by Cholinesterase enzyme
Excretion	Clearance	1.8±6 L/min	2.1-2.8 L/hr
	half-life (t½)	~1.5hr	~3.4 h
	Excretion of the drugs and it's metabolites	Urine (~ 97%) Faces (~ 0.4%)	Urine (>90%) Faces (<1%)

Cmax- peak plasma concentration, Tmax- time to reach Cmax, AUC- area under curve, Vd- volume of distribution, t½- half-life, ng.h/ml- nanogram hour per milliliter.

Chapter 5

Results and Discussion

5.1 Assessment of Dementia in AD

Rivastigmine moderately improves the cognitive function of AD patients and delays the cognitive deterioration in comparison to placebo like other ChE-Is. Rivastigmine has been applied in the evaluation of mild to moderate AD. The response to treatment of AD is primarily determined by the Alzheimer's Disease Assessment Scale–Cognitive section (ADAS-Cog) test, which measures cognitive ability. Secondary measures of clinical efficacy of the drug is the Mini Mental State Examination (MMSE). High scores above 26 on the MMSE which has a maximum score of 30 indicate mild cognitive damage. Clinical trials report the changes relative to baseline.

ADAS–Cog test is one of the most commonly used tests to measure cognition for new drugs and other interventions in clinical trials and researches. The ADAS-Cog was developed as a two-part scale: one measures cognitive abilities and the other measures non-cognitive abilities like behavior and mood. Most recent researches use the ADAS-Cog subscale that measures cognitive ability. It mainly determines memory and language consisting of 11 parts (Table 2) and takes about 30 minutes to run. Points are added for the errors in each part of the test for a total value ranging from 0 to 70. The more the impairment of the cognitive ability (language, memory, orientation as well as executive ability) the more the score. The highest score 70 represents the most severe dysfunction and the lowest score 0 represents the least dysfunction. Usually, it is a paper and pencil test, however, it also has the electronic version.

The ADAS-Cog helps in evaluating level of cognition and differentiating normal and damaged cognitive functions. It is helpful in measuring the degree of cognitive damage; hence, determines the stage of AD of a patient depend on the answer and the value. Therefore, ADAS-Cog is frequently used in the clinical trials (Kueper et al., 2018).

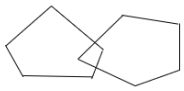
MMSE is a simple test of cognitive function using pen-and-paper and a total possible score is 30 points which includes tests of orientation, verbal memory, concentration, attention, naming and visuospatial skills (Table 3). The relation between the MMSE scores and level of dementia is shown in Table 4. A value ranges from 20 to 25 shows mild dementia, value ranges from 10 to 20 shows moderate dementia, and <10 shows severe dementia. Usually, the MMSE score of an AD patient declines about 2 to 4 points every year (*STATE "*, 1975).

Table 3: Items Assessed by the 11-Item ADAS-cog.

Domain	**Item**	**Score range**
Memory	Word recall	0-10
	Object naming	0-5
	Orientation	0-8
	Word recognition	0-12
	Remembering test recognition	0-5
Language	Commands	0-5
	Language (clarity of speech)	0-5
	Comprehension	0-5
	Word finding	0-5
Praxis	Constructional praxis	0-5
	Ideational praxis	0-5
	Total score	0-70

ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale (Schmitt et al., 2010).

Table 4: Analysis of AD severity using the MMSE.

Variables	**Questions**	**Max. Score**
Orientation	What is the year? Season? Date? Day? Month?	5
	Where are we now? State? Country? Town/city? Hospital? Floor?	5
Registration	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.	3
Attention and Calculation	"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)	5
Recall	"Earlier I told you the names of three things. Can you tell me what those were?“	3
Language	Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.	2
	"Repeat the phrase: 'No ifs, ands, or buts.'"	1
	"Take the paper in your hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)	3
	"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 bellow. All ten angles must be present and two must intersect.) 	1
	Total Score	30

Mini-Mental State Examination (Eftychios et al., 2021).

Table 5: Interpretation of MMSE score results.

Score	Degree of Impairment	Formal Psychometric Assessment	Day-to-Day Functioning
25-30	Questionably significant	If clinical signs of cognitive impairment are present, formal assessment of cognition may be valuable.	May have clinically significant but mild deficits. Likely to affect only most demanding activities of daily living.
20-25	Mild	Formal assessment may be helpful to better determine pattern and extent of deficits	Significant effect. May require some supervision, support and assistance.
10-20	Moderate	Formal assessment may be helpful if there are specific clinical indications.	Clear impairment. May require 24- hour supervision
0-10	Severe	Patient not likely to be testable.	Marked impairment. Likely to require 24-hour supervision and assistance with ADL.

MMSE: Mini-Mental State Examination (Eftychios et al., 2021).

Majority of the studies showed that ChE-Is augment of the cognitive functions in AD. This improvement was found in mild to moderate stages of the disease and some studies (Grossberg et al., 2015) showed improvement of cognitive function in the severe stage of AD. The improvement was observed mainly at 24 weeks of treatment. The drug stimulates the cognitive functions and behavioral symptoms in AD patients. Among the ChE-Is, Rivastigmine inhibits AChE both *in-vitro* and *in-vivo*. It preferentially inhibits AChE of the hippocampus and cortex and shows longer duration of action in comparison to other clinically useful carbamates. It is a pseudo-irreversible noncompetitive inhibitor of both BuChE and AChE. Both of these enzymes

are responsible for the catabolism of ACh and play an important role in the generation of neurofibrillary tangles and neurotic plaques, which are the hallmarks in the pathophysiology of AD. This property makes Rivastigmine an exciting candidate to be studied more in the treatment of AD. Various clinical trials of Rivastigmine are going on aiming to determine the safety, efficacy and tolerability.

Both Rivastigmine capsule and patch have shown many adverse events as well. The trials are still going on to reduce the presence of its adverse events (AE) like gastrointestinal problems, nausea and vomiting etc. For this review, articles of the last fifteen years (2007-2022) were considered. Table 6-8 summarizes the clinical trials conducted on Rivastigmine capsule and patch (Park et al., 2017; Zhang et al., 2016; Feldman & Lane, 2007).

5.2 Efficacy of Rivastigmine patch

The effectiveness of Rivastigmine transdermal patch (10 cm^2) is determined in mild to moderate AD patients using 9.5mg/d once daily ranging from 24 weeks in duration (Park et al, 2017; Zhang et al, 2016). The effectiveness was assessed by using ADAS-cog and MMSE. ADAS-cog value ranges from 0–70 along with greater values (≥ 18) showing more cognitive deterioration. For Group 01 (minimal WMH) ADAS-cog value represent -0.62±5.70 (ITT-LOCF population) and -0.58±5.57 (PP population) also for Group 02(maximum WMH) ADAS-cog value represent -0.23±5.98 (ITT-LOCF population) and -0.13±6.17 (PP population) from baseline through 24 week that is slight change from baseline, suggesting that cognitive activity slightly improved.

For Group 01(minimal WMH) MMSE value represented 0.70±2.70 (ITT-LOCF population) and 0.66±2.81 (PP population). Also for Group 02 (maximum WMH), MMSE value represented 0.26±2.87 (ITT-LOCF population) and 0.17±2.99 (PP population) from baseline through 24

week that is slight change from the baseline, suggesting that cognitive activity slightly improved. But no statistical change from baseline through 24 weeks on the ADAS-Cog and MMSE between group 1 and group 2 were determined.

5.3 Efficacy of Rivastigmine Capsule

The effectiveness of Rivastigmine capsule is determined in mild to moderate AD patients using 12 mg/d twice daily ranging from 24-26 weeks in duration (Feldman & Lane, 2007; Zhang et el, 2016). Rivastigmine Capsule ADAS-cog value represented -0.9 (PP (OC)), -0.7 (ITT (OC)) and -0.9 (ITT (LOFC)). Rivastigmine Capsule MMSE value represented 0.7 (PP (OC)), 0.7 (ITT (OC)) and 0.7 (ITT (LOFC)). Also, MMSE value represented 0.8 (PP (OC)), 0.8 (ITT (OC)) and 0.7 (ITT (LOFC)) from baseline through to week 24 that is slight significantly different from baseline, suggesting that cognitive activity slightly improved (Zhang et el, 2016).

According to Feldman & Lane, 2007, Rivastigmine capsule ADAS-cog value represented -0.2±7.3 (ITT population) and -0.7±6.9 (LOCF population) from baseline through to week 26 that is slight significantly different from the baseline, suggesting that cognitive function slightly improved. Rivastigmine Capsule MMSE value represented 0.3±3.6 (ITT population) and 0.4±3.4 (LOCF population) from baseline through to week 26 that is slight significantly different from the baseline, suggesting that cognitive function slightly improved. There is also statistical change from baseline through 26 weeks on the ADAS-Cog were determined in ITT ($p = 0.03$) as well as LOCF population ($p=0.02$). There is also statistical changes from baseline through 26 week on MMSE were determined in ITT ($p=0.01$) as well as LOCF population ($p=0.07$).

Table 6: Efficacy of Rivastigmine in clinical studies.

Dosage form	Study	Study Type	Dosage Regimen		Result		
				N	Primary Endpoint (ADAS-cog)	Secondary Endpoint (MMSE)	Comments/ Discussion
Rivastigmine patch	(Park et al., 2017)	Open-label multicentre trial	9.5mg/d once daily for 24 weeks.	136 (Group 1) minimal WMH 62 (Group 2) maximum WMH	Group 1: baseline- 22.73 ± 7.84 p value- 0.037 at 24 weeks(ITT-LOCF population) -0.62 ± 5.70 P value- 0.378 at 24 weeks(PP population) -0.58 ± 5.57 P value-0.442 Group 2: baseline- 23.40 ± 7.27 p value- 0.037 at 24 weeks(ITT-LOCF population) -0.23 ± 5.98 P value- 0.378 at 24 weeks(PP population) -0.13 ± 6.17 P value- 0.442	Group 1: baseline- 19.63 ± 4.03 p value- 0.037 at 24 weeks(ITT-LOCF population) 0.70 ± 2.70 P value- 0.298 at 24 weeks(PP population) 0.66 ± 2.81 P value- 0.290 Group 2: baseline- 19.95 ± 4.10 p value- 0.037 at 24 weeks(ITT-LOCF population) 0.26 ± 2.87 P value- 0.298 at 24 weeks(PP population) 0.17 ± 2.99 P value-0.290	ADAS-Cog- Slight change from baseline through 24 week on the ADAS-Cog between group1 as well as group2 were determined in the both ITT-LOCF as well as PP populations, suggesting that cognitive activity slightly improved. But no statistical change from baseline through 24 week on the ADAS-Cog between both group were observed in the ITT-LOCF (p=0.378) as well as PP populations (p=0.442). MMSE- Slight change from baseline through 24 week on the MMSE between group 1 and group 2 were observed in the both ITT-LOCF as well as PP populations, suggesting that cognitive activity slightly improved. But no statistical change from baseline through 24 week on the MMSE between both group were determined in ITT-LOCF (p=0.298) as well as PP populations (p=0.290).

ADAS-cog value range is 0–70 along with greater values (≥ 18) indicating more cognitive damage. Moreover, MMSE normal cognition value 25 to 30 points, mild dementia value 21 to 24 points, moderate dementia value 10 to 20 points as well as severe dementia score 9 points or lower. A negative change from baseline in ADAS-Cog value represents cognitive damage. Additionally, standard p value= ≥0.05. Finally, the values are given as mean±standard deviation. WMH=white matter hyperintensities, ITT= intent-to-treat, LOCF = last observation carried forward, PP = per protocol, OC=observes cases, ADAS-Cog = alzheimer's disease assessment Scale-Cognitive subscale as well as MMSE=mini-mental state examination.

Table 7: Efficacy of Rivastigmine in clinical studies.

Dosage form	Study	Study type	Dosage regimen		Result		
				N	Primary endpoint (ADAS-cog)	Secondary Endpoint (MMSE)	Comments/ Discussion
Rivastigmine capsule Rivastigmine patch	(Zhang et al., 2016)	24-week, prospective, two-arm, randomized, parallel-group, double-blind, double-dummy, and multicentre trial	Rivastigmine capsule- 12 mg/d (twice daily)for 24weeks. Rivastigmine patch ($10cm^2$)-9.5mg/d (Once daily) for 24weeks.	232 234	Capsule baseline 28.2 Change from baseline at 24 weeks PP(OC)=-0.9 ITT(OC)=-0.7 ITT(LOFC)=-0.9 Patch baseline 29.4 Change from baseline at 24 weeks PP(OC)=-0.7 ITT(OC)=-0.7 ITT(LOFC)=-0.7	Capsule baseline= 16.6 Change from baseline at 24 weeks PP(OC)=0.7 ITT(OC)=0.7 ITT(LOFC)=0.7 Patch baseline 16.0 Change from baseline at 24 weeks PP(OC)=0.8 ITT(OC)=0.8 ITT(LOFC)=0.7	ADAS-cog- Slight change from baseline through 24 week on the ADAS-Cog were determined. MMSE- Slight change from baseline through 24 week on the MMSE were observed. Both suggesting that cognitive activity slightly improved.

ADAS-cog value range is 0–70 along with greater values (≥ 18) indicating more cognitive damage. Moreover, MMSE normal cognition value 25 to 30 points, mild dementia value 21 to 24 points, moderate dementia value 10 to 20 points as well as severe dementia score 9 points or lower. A negative change from baseline in ADAS-Cog value represents cognitive damage. Additionally, standard p value= ≥0.05. Finally, the values are given as mean±standard deviation. WMH=white matter hyperintensities, ITT= intent-to-treat, LOCF = last observation carried forward, PP = per protocol, OC=observes cases, ADAS-Cog = alzheimer's disease assessment Scale-Cognitive subscale as well as MMSE=mini-mental state examination.

Table 8: Efficacy of Rivastigmine in clinical studies.

Dosage form	Study	Study type	Dosage regime n		Result		Comments/ Discussion
				N	Primary endpoint (ADAS-cog)	Secondary Endpoint (MMSE)	
Rivastigmine capsule	(Feldman & Lane, 2007)	26 week internation al, randomised , double blind, placebo controlled study.	12 mg/d (twice daily) for 26weeks .	277 209	ITT population Baseline score 28.1±12.5 Week 26 change -0.2±7.3 P=0.03 LOCF population Baseline score 28.3±12.2 Week 26 change -0.7±6.9 P=0.02	ITT population Baseline score 18.1±4.7 Week 26 change 0.3±3.6 P=0.01 LOCF population Baseline score 18.1±4.5 Week 26 change 0.4±3.4 P=0.07	ADAS-cog-Slight change from baseline through 26 week on the ADAS-Cog were determined. There is also statistical from baseline through 26 week on the ADAS-Cog were determined in the ITT(p=0.03) as well as LOCF population(p=0.02) MMSE-Slight change from baseline through 26 week on the MMSE were determined. There is also statistical change from baseline through 26 week on MMSE were determined in ITT (p=0.01) as well as LOCF population (p=0.07) Both suggesting that cognitive activity slightly improved. Also showing statistical changes.

ADAS-cog value range is 0–70 along with greater values (≥ 18) indicating more cognitive damage. Moreover, MMSE normal cognition value 25 to 30 points, mild dementia value 21 to 24 points, moderate dementia value 10 to 20 points as well as severe dementia score 9 points or lower. A negative change from baseline in ADAS-Cog value represents cognitive damage. Additionally, standard p value= ≥0.05. Finally, the values are given as mean±standard deviation. WMH=white matter hyperintensities, ITT= intent-to-treat, LOCF = last observation carried forward, PP = per protocol, OC=observes cases, ADAS-Cog = alzheimer's disease assessment Scale-Cognitive subscale as well as MMSE=mini-mental state examination.

The primary enzyme AChE and BuChE that is responsible for breaking down acetylcholine in nervous system and both enzymes are actively inhibited by ChE-Is. This enables to lengthen the

action due to lack of neurotransmitter in the brain. ChE-Is was first approved medicine for symptomatic treatment of Alzheimer. Among other three available compounds of ChE-Is, Rivastigmine is on clinical trials in several countries worldwide. (Marucci et al., 2021). Based on few clinical experience of Rivastigmine in Alzheimer's patients it was suggested that Rivastigmine capsule 12 mg/d (twice daily) for 24 weeks and Rivastigmine patch ($10cm^2$) 9.5mg/d (Once daily) for 24 weeks is the optimal dose with 24 weeks. Some studies assume that dose adjustment with Rivastigmine capsule and patch can improve the patients and caregiver's acceptability and compliance thus decrease medical discontinue rate (Js et al., 2015). Rivastigmine which has high tolerability and effectiveness, it improves cognition, daily living activity as well as worldwide evaluation ratings with mild to moderately severe AD patients. Moreover, in a predominantly European population, Rivastigmine first shows engrossing evidence of efficacy (Rösler et al., n.d.). Rivastigmine patch-treated patients was mostly mild in severity condition of AD. Most AD patients belong to an older age group and are prone to higher risk of developing heart disorders such as high blood pressure and cardiac rhythm disturbances. However, data with the Rivastigmine patch do not point out an increased risk of cardiac AEs. Despite of the little function of ChE-Is while waiting for more successful approaches, these drugs still considered a Pharmacotherapeutic resource for treating AD (Zhang et al., 2016).

Chapter 6

Conclusion

The clinical trial of Rivastigmine patch therapy for 24 weeks, no major differences was observed in general cognitive ability between AD patients with minimal vs. moderate white matter hyper intensities (WMH). However, an important improvement was found in frontal function in AD patients with minimal WMHs when compared to patients with moderate WMHs. Rivastigmine capsule administered twice or thrice daily notably benefited cognitive ability in patients with AD. The trice daily dose showed a tendency for superior tolerability and permitted titration to higher doses which could be a therapeutic option for patients who face tolerability difficulties to Rivastigmine treatment. Similar efficacy was observed between once-daily transdermal Rivastigmine patch and oral bid Rivastigmine capsules in patients with mild to moderate AD. Further study is required to confirm the appropriate treatment of AD patients.

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