A PHARMACOVIGILANCE STUDY ON MEMANTINE: SIGNAL DETECTION OF RHABDOMYOLYSIS AND DEATH

By

Osama Bin Abu Bakar
19146094

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
February 2023

Declaration

It is hereby declared that

1. The thesis submitted is my/our 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.

Student's Full Name & Signature:

Osama Bin Abu Bakar
19146094

Approval

The project titled "A pharmacovigilance study on Memantine: signal detection of rhabdomyolysis and death" submitted by Osama Bin Abu Bakar, (19146094) of Summer, 2022 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on February 2023.

Supervisor:

Professor Dr. Hasina Yasmin
Assistant Dean and Program Director
School of Pharmacy
BRAC University

Approved By:

Program Director:

Professor Dr. Hasina Yasmin
Assistant Dean and Program Director
School of Pharmacy
BRAC University

Dean:

Professor Dr. Eva Rahman Kabir
Professor and Dean, School of Pharmacy
BRAC University

Ethics Statement

This study does not involve any sought of human and animal trials.

Abstract

Alzheimer's Disease (AD) is a complex and common neurological disorder and dementia's leading cause. Memantine works to treat moderate to severe AD. This study focused on Food and Drug Administration Adverse Event Reporting System (FAERS) data with the purpose to determine its effect on adverse events of Death and Rhabdomyolysis based on two comparators; the whole database and drug class. To conduct this disproportionality analysis, we have incorporated ROR and 95% CI values. We figured out that memantine possesses a higher mortality benefits ratio than other drugs enlisting both the comparators; whole database and drug class with a value of (ROR = 0.68; CI 95% = 0.46–1.00; P = 0.0483) and (ROR = 0.19; CI 95% = 0.13–0.28; P <0.0001) respectively. In addition, in the cases of rhabdomyolysis, we also find out that memantine has a lower profile assigning both comparators 8.10 (4.48 to 14.67; p < 0.0001); whole database and 2.25 (1.11 to 4.54; P = 0.0241); drug class.

Keywords: Alzheimer’s disease; Dementia; FAERS Database; Memantine; Mortality Benefits; Rhabdomyolysis.

Dedication

Dedicated to my parents, for whom I'm here, my friends, and my teachers who have enlightened me till now. A special mention to my supervisor, Professor Dr. Hasina Yasmin.

Acknowledgement

To start with, all praises and thanks to Almighty Allah for His immense blessings. This project would have never seen the face of light without His benevolence and mercy.

I would also like to extend my gratitude to my supervisor Dr. Hasina Yasmin, PhD, Professor, Assistant Dean and Program Director, School of Pharmacy, Brac University, without whom the execution of this project was unimaginable. I will be immensely grateful for her guidance, encouragement, instructions and monitoring throughout my project work amidst her busy schedule. Likewise, my special thanks to Dr. Mesbah Talukder, PhD, Professor, School of Pharmacy, Brac University, for his support and guidance in the project. Moreover, I would like to thank Professor Dr. Eva Rahman Kabir, Chairperson, Department of Pharmacy, Brac University for always being willing to lend a hand.

Last but not the least, to my family and friends, who have helped me in whatever way possible throughout this journey, I would want to convey my profound gratitude to them.

Table of Contents

List of Tables

List of Figures

List of Acronyms

AD	Alzheimer’s Disease
ASRs	Age-standardized rates
DALYs	Disability-adjusted life years
SDI	Sociodemographic index
Aβ	Amyloid-β peptide
SP	Senile plaques
NFTs	Neurofibrillary tangles
EOAD	Early-onset Alzheimer’s disease
LOAD	Late-onset Alzheimer’s disease
APP	Aβ precursor protein
PHF	Paired helical filaments
NMDA	N-methyl-D-aspartate receptor
Ach	Acetylcholine
AChEIs	Acetylcholinesterase inhibitors
BBB	Blood Brain Barrier
APOE ε4	Apolipoprotein E 4
BuChE	Butyrylcholinesterase
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
MMSE	Mini-Mental State Examination

NMDAR	N-methyl-D-aspartate receptor
LTP	Long-term potentiation
PET	Positron emission tomography
GABA	Gamma-aminobutyric acid
ADR	Adverse drug reaction
MedDRA	Medical Dictionary for Regulatory Activities

Chapter 1: Introduction

1.1 Alzheimer's Disease

Alzheimer's Disease (AD) – a progressive and debilitating neurological disorder that is accountable for gradually demolishing the memory and cognitive abilities of an individual. According to the World Health Organization, AD is a neurodegenerative condition with an unknown etiology that is marked by a progressive decline in memory and cognitive abilities (Moreta et al., 2021). Alois Alzheimer, a psychiatrist, and neurologist, first described the symptoms of AD in 1906 after conducting an autopsy on a 51 years old patient named Auguste Deter who used to suffer from memory loss, disorientation, hallucinations, and difficulty speaking clearly from 1901 to 1906. By analyzing Auguste's brain, Alois Alzheimer identified intraneuronal neurofibrillary tangles (NFTs) as well as extracellular amyloid plaques along with substantial brain atrophy. He came to the conclusion that this was an entirely new type of dementia as a result of these findings. Nevertheless, the primary cause of dementia is the disease itself, which as it progresses results in a massive loss of cholinergic synapses (García-Morales et al., 2021). The development of senile plaques due to the buildup of amyloid-β as well as the appearance of neurofibrillary tangles made of hyperphosphorylated tau protein within the cells are two distinctive features that define the pathophysiology of this neurodegenerative disorder. In addition, up to 60–75% of dementia diagnoses around the world are due to this degenerative brain disorder, making it the most prevalent type of dementia (Pardo-Moreno et al., 2022).

Alzheimer's patients and their caregivers frequently list memory loss as one of the initial signs of their condition subsequently interfering with the development of memories from molecular scales to neural networks. Likewise, early on in the disease's progression, both the working

memory as well as the long-term declarative memory are impacted (Jahn, 2013). Moreover, it is anticipated that by 2050, 115.4 million people would be impacted by AD, which currently affects about 35.6 million people worldwide contributing to 7.7 million new instances of AD being identified each year (Pardo-Moreno et al., 2022). Also, at 65 years of age, the incidence is 0.5 percent every year; by the time an individual reaches 85 years of age, it is approximately 8 percent per year. Mutations in the two distinctive genes; the precursor protein of amyloid as well as the presenilin 1 and 2 are the sources of unusual, and dominant forms of this disease that manifest prior to the age of 60 whereas the sporadic type as well as some familial variants that manifest after the 60s are linked to the apolipoprotein E 4 variant (APOE ε4) (Mayeux & Sano, 1999).

It is considered that AD is influenced by both environmental as well as genetic factors. Although the majority of AD cases are sporadic, a minor percentage of inherited instances allow the identification of genes, which, along with neuropathology, provides crucial information on the disease's broader etiology. The progression and onset of Alzheimer's are often impacted by environmental and metabolic-related risk factors enlisting inflammations and vascular dysfunctions. Likewise, poor diet, diabetes, stress, cardiovascular diseases, and brain damage are connected to the increased risk of dementia (Sheppard & Coleman, 2020). AD is characterized by a wide range of clinical symptoms, including memory impairment that interferes with daily activities, challenges with routine tasks, confusion about time and location, and difficulties comprehending visual imagery and spatial relationships. In addition, the main risk factor for Alzheimer's is age, including smoking, hypertension, obesity, atherosclerosis, diabetes, and hypercholesterolemia as other risk factors. (Rahman et al., 2017). In this review, we discussed Alzheimer's in detail enlisting its prevalence, pathophysiology, etiology, and current and future treatment options and we deeply focused on the drug memantine and its effects on patient mortality rate and rhabdomyolysis.

1.2 Prevalence of Alzheimer's Disease

AD has grown to be a significant public health issue as the world's aging population continues to rise. "The age-standardized rates (ASRs) of mortality, prevalence, incidence as well as disability-adjusted life years (DALYs) from 1990 to 2019 associated with Alzheimer's and certain other dementias, were calculated employing data from the Global Burden of Disease (GBD) 2019 database." The study showed unequivocally that between the particular time frame, AD incidence and prevalence surged by 147.95 and 160.84%, correspondingly. In addition, women consistently had larger ASRs than men did, but men's increases were more noticeable, the ASRs of DALYs, prevalence, and incidence also showed a positive correlation with the sociodemographic index (SDI). Also indicated that, for men, smoking was a significant risk factor for dementia, whereas, for women, the main risk factor was obesity (Li et al., 2022).

Alzheimer's dementia affects 6.5 million Americans aged 65 and older, according to studies. If no medical advances are made to prevent, slow down, or cure AD, this figure might increase to 13.8 million in 2060. AD was officially classified as the sixth-leading reason for death in the US in 2019, with confirmed death certificates indicating 121,499 losses from AD in that year, and also ranked as seventh in 2020 and 2021. For Americans 65 and over, it continues to be the fifth-leading reason for death. Deaths from heart disease, HIV, and stroke all declined from 2000 to 2019, while recorded deaths from AD grew by more than 145%. In 2021, more than 11 million relatives and unpaid caregivers gave Alzheimer's patients and those with other dementias approximately 16 billion hours of care including its value of $271.6 billion ("2022 Alzheimer's Disease Facts and Figures," 2022).

The prevalence of AD patients in Bangladesh is quite sporadically documented due to no accurate epidemiological statistics on AD. On top of that, the majority of the country's

population is currently young. The amount of funding available for AD research is minimal, and AD awareness in this country is now in its early stages. Additionally, Bangladesh, a nation with a lower middle class, is not yet ready to manage AD. Nevertheless, as the vast majority of its population is set to turn 60, policymakers, health professionals, and related groups should step forward to consider Alzheimer's and its management in a constructive way and take the appropriate measures in this regard (Rahman et al., 2017). Alzheimer's or dementia mortality in Bangladesh amounted 9, 917 in 2017, accounting for 1.26% of all deaths, based on WHO data which places Bangladesh at 152 positions globally (Roy et al., 2020).

1.3 Etiology of Alzheimer's Disease

The cause of Alzheimer's disease is currently unknown, but it is thought to have multiple contributing factors. The etiopathogenesis of Alzheimer's is assumed to be influenced by both genetic as well as non-genetic variables. Mendelian inheritance determines the occurrence of the APP, PSEN1, and PSEN2 mutations, which cause Early-onset Alzheimer’s disease (EOAD) whereas numerous dangerous genes have been discovered recently by genome-wide association studies, which impact the vulnerability to Late-onset Alzheimer’s disease (LOAD) (Jiang et al., 2013). While LOAD appears after age 65 in over 95% of instances, EOAD manifests before that age. As a result of mutations in the genes APP, PSEN1, or PSEN2, almost all instances of EOAD are familial, whereas the majority of cases of LOAD remain sporadic (Sheppard and Coleman, 2020).

In the cases of familial AD, a small portion (less than 3 percent) that are of genetic origin among all subtypes of Alzheimer’s disease is distinguished by an earlier development (roughly 10–12 years ago) in comparison to Idiopathic AD, also termed as Sporadic AD. A pattern of dominant inheritance is often observed in familial AD and the primary mutations that take place on the gene include the APP gene, presenilin 1 and 2, and proteolytic enzymes that originate

the Aβ peptides. Furthermore, mutations in the APOE gene and APOE4 variant can also elevate the risk of the formation of this dementia. Regardless of the genetic factors, hypertension, sedentary lifestyle, use of tobacco, hypercholesterolemia, diabetes mellitus, overweight, all these factors can contribute to the development of 33.3% of cases of AD (García-Morales et al., 2021).

Moreover, by inducing inflammation, which could lead to brain damage that leads to AD, factors like diets, aluminum, and viruses may raise the prevalence of Alzheimer's disease. In a dozen nations, it was discovered that eating an acid-forming diet, consuming a lot of dietary fat, and consuming a lot of calories were significant contributors to the onset of AD, whereas eating fish was discovered to be a substantial risk factor for the disease's prevention. Numerous studies have associated aluminum with a greater likelihood of developing AD and the potential for neurological impairment (W.B. et al., 2002).

1.4 Pathophysiology of Alzheimer's Disease

Due to the complex nature of AD, the pathophysiology is dependent on a number of theories. A protein plaque of Aβ buildup and the development of neurofibrillary tangles associated with tau protein hyperphosphorylation are the two main hypotheses associated with AD. These anomalies in proteins, oxidative stress, inflammatory processes, loss of synaptic function, a decrease of neurotransmitters, and ultimately cell death all are associated with the pathophysiology of AD (Rahman et al., 2017).

Likewise, a significant deterioration of episodic memory; memory for particular events that an individual has experienced, is a hallmark of AD. This symptom is frequently accompanied by a broad spectrum of cognitive deficiencies in regions like decision-making, language, executive function, as well as visuospatial abilities. As of right now, there is no definitive premortem

diagnosis for this disorder; rather, it can only be identified histologically postmortem based on the appearance of neurofibrillary tangles, senile plaques (SP), also the loss of neurons and synapses. (Pardo-Moreno et al., 2022).

1.4.1 Pathology of Amyloid β

Amyloid β (Aβ) is a peptide of 39-43 amino acids acquired by the gradual processing of Aβ precursor protein (APP) via an amyloidogenic route using two complexes including β- and γ-secretase. Aβ in the parenchymal tissue gradually builds up to cause senile plaques. These SP come in a variety of morphological shapes, comprising diffuse, compact, dense-cored, neuritic, and classic (Breijyeh & Karaman, 2020). SP remains a plausible source of synaptic as well as neuronal degeneration and is a characteristic neuropathological hallmark in AD-affected brains (Figure: 01). Although most cases of AD are thought to be caused by mutations in the APP and β-secretase, dementia's causes are still poorly understood, given that most occurrences are spontaneous and that these people acquire Aβ without identified mutations. Consequently, it has been suggested that changes in Aβ destruction or clearance could also play a significant role in the pathophysiology of AD (Baranello et al., 2015). According to certain research, the buildup of Aβ, similar to SP, may be a factor in the degeneration of dendritic spines (Kartalou et al., 2020). Additionally, aberrant curvature of neighboring neurites has been linked to SP, which may affect cortical integration of the synapses (Ramos-Rodriguez et al., 2016). Aβ has a significant impact on both neurotoxicity and neuronal function. Hence, besides cognitive deficits, the buildup of thicker plaques in the cerebral cortex, amygdala, and hippocampus can stimulate microglia and astrocytes, destroy the axons, dendrites, and loss of synapses (Breijyeh & Karaman, 2020).

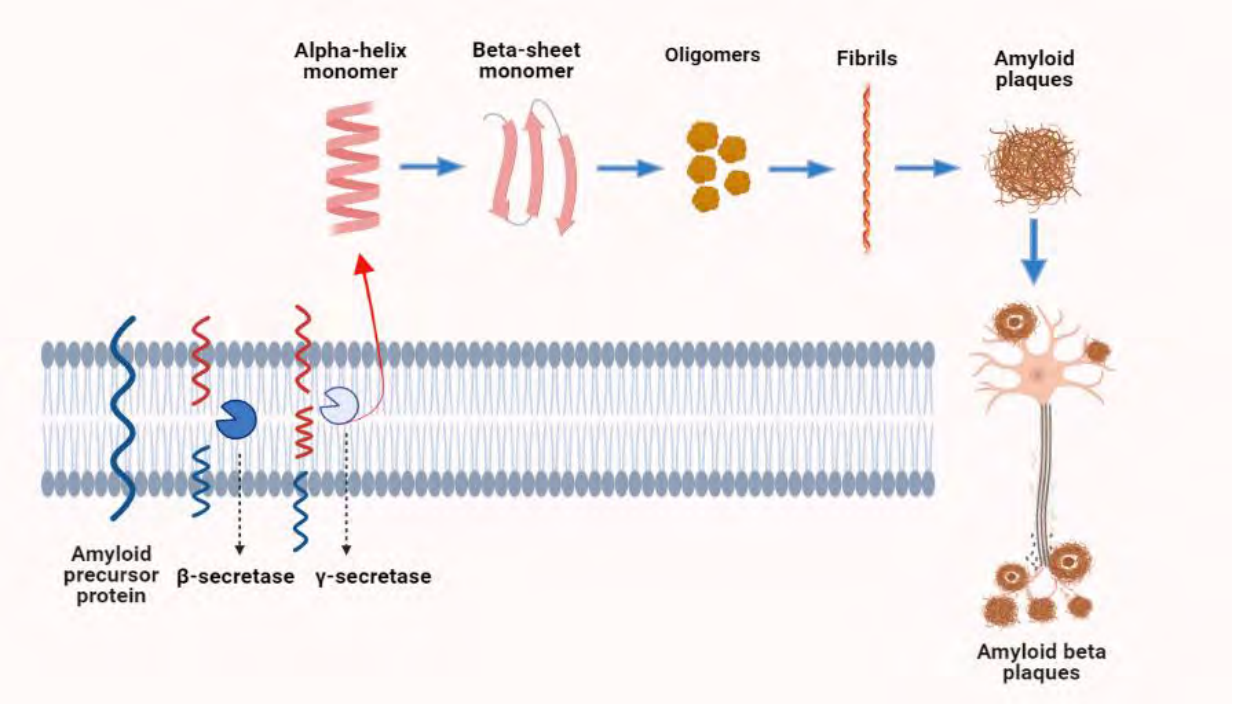

Figure 01: Illustration of Amyloid beta pathology (modified from: García-Morales et al., 2021)

1.4.2 Tau Pathology

Tau - a microtubule-associated protein, which binds to tubulin to facilitate microtubule assembly, is widely found in the brain. In addition to supporting other cytoskeletal components, it controls a number of crucial neuronal processes (Toombs & Zetterberg, 2021). NFTs are defective tau protein filaments that have been abnormally phosphorylated; at some stages, they can twist around one another to create paired helical filaments (PHF). In AD patients' brains, phosphorylated tau makes up the majority of NFTs, and its progression can be used to interpret the three different stages of NFT morphology: pre-tangle, mature, and ghost or extracellular tangles (Brion, 1998). It seems that as the disease progresses and becomes more severe, tau protein deposition rises in Alzheimer's patients (Figure: 02). Additionally, it is commonly recognized that tau malfunction is one of the primary proximal factors in the death of neurons

in AD, even while neurofibrillary tangles seem to be associated with subsequent pathogenic processes (García-Morales et al., 2021).

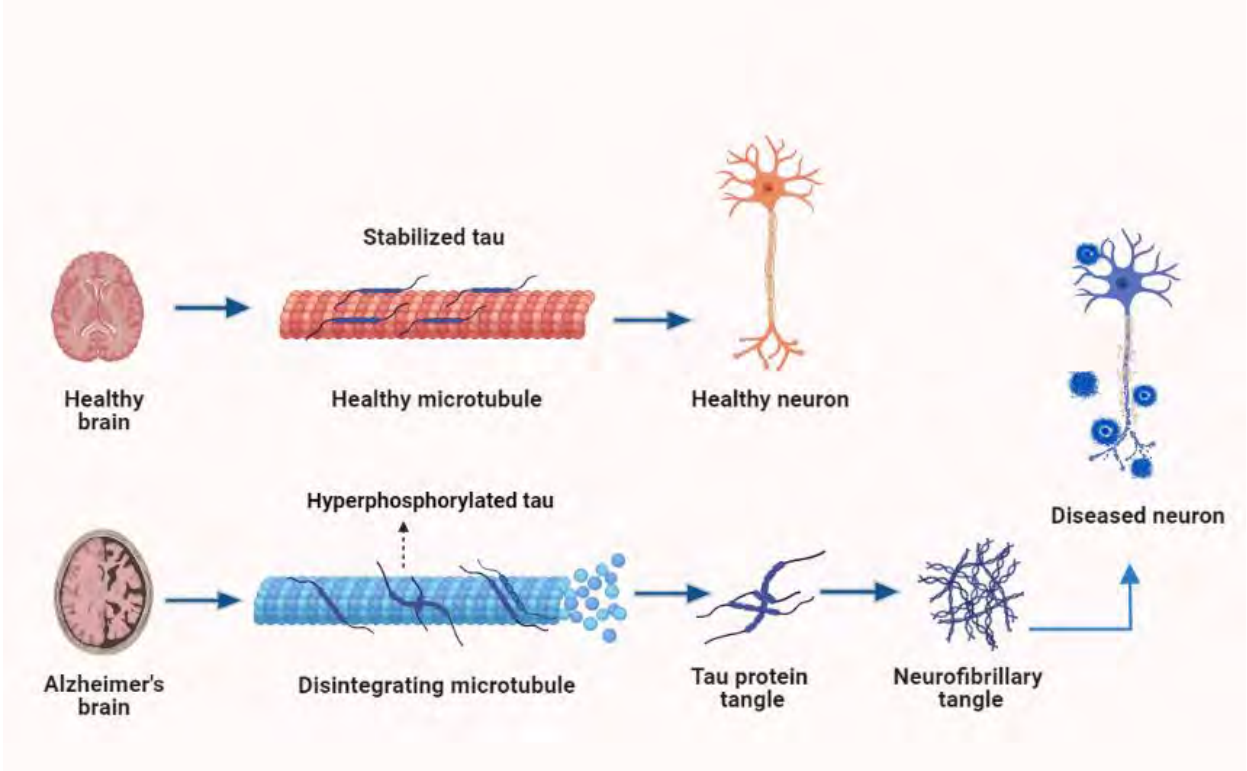

Figure 02: Illustration of tau pathology (modified from: Mah et al., 2021)

1.4.3 Neuronal Loss and Neuroinflammation

The histological characteristic of dementia that most closely correlates with its severity and longevity is neuronal loss. Additionally, it is the primary reason for the cortical atrophy seen in AD (García-Morales et al., 2021). The mechanisms of neuronal loss include oxidative stress, mitochondrial damage, and abnormalities in axonal transport. Pre-synaptic terminals, dendritic spines, and axonal dystrophy are finally lost as a consequence of these events (Overk & Masliah, 2014). Neuroinflammation and oxidative stress, in conjunction with SP and abnormally phosphorylated tau, are significant contributors to neurodegeneration. There are two aspects to inflammation. In one sense, it induces the release of inflammatory mediators

like cytokines, which increases cerebral circulation to the affected region and triggers the clearance of injured tissues by microglial cells. On the other side, an overactive inflammatory response may result in tissue damage, encourage chronic inflammation, and ultimately result in neuronal death (Sankar et al., 2020).

1.5 Current Treatment Options for Alzheimer's Disease

Although the cases and incidences of Alzheimer's disease have been gradually increasing in recent years, there is no effective treatment for halting or reversing the progression of this silent deadly disorder. As shown in the Table 01, to date, only six drugs have been authorized by the US FDA, among which aducanumab is utilized for the clearance of Aβ plaques, and the rest including donepezil, galantamine, rivastigmine, memantine, and a combination of memantine and donepezil all of which falls under symptomatic therapy with two levels of action either working as an antagonist of the N-methyl-D-aspartate receptor (NMDA-receptor) or through exerting agonistic effect at the cholinergic system (Pardo-Moreno et al., 2022).

1.5.1 Cholinesterase inhibitors

Acetylcholine (ACh) breakdown in the synapses is prevented by acetylcholinesterase inhibitors (AChEIs), leading to continual ACh buildup as well as cholinergic receptors activation. Cholinergic transmission is thought to be severely important for memory, learning, attentiveness, and other complex mental functions. Cholinesterase inhibitors are one of the few drug therapies that have been clinically proven to be effective in the treatment of AD dementia. They increase the availability of acetylcholine neurotransmitters on the brain's synapses thus increasing cognitive and neural cell activity (Hampel et al., 2018). Drugs like Tacrine, donepezil, rivastigmine, and galantamine work in this particular way. Another strategy is the elevation of choline reuptake which leads to an increase in the synthesis of acetylcholine at

presynaptic terminals, which may aid in the treatment of AD. The choline transporter, which provides choline for the generation of ACh, can be targeted in order to do this (Breijyeh & Karaman, 2020). Moreover, while the advantages of various cholinesterase inhibitors are identical, there are significant differences in the side effects brought on by these medications. Due to the limited efficacy of these cholinesterase inhibitors for people with mild or moderate Alzheimer's, these inhibitors can be started at any point following a diagnosis (Mayeux & Sano, 1999). Only one-third of patients exhibit a clinically discernible benefit from cholinesterase inhibitors. Another third exhibits a clinical deterioration within the initial six months of treatment, and 29% of patients discontinue treatment due to side effects (Waite, 2015).

Table 01: List of FDA Approved drug for AD

Generic Name	Tacrine	**Generic Name**	Rivastigmine
Approval	1993 (Discontinued in 2013)	**Approval**	2000
Chemical formula	$C_{13}H_{14}N_2$	**Chemical formula**	$C_{14}H_{22}N_2O_2$
Mechanism ofAction		**Mechanism ofAction**	
It is a central acetylcholinesteraseinhibitor		Rivastigmine is a pseudo-irreversible acetylcholinesteraseinhibitor	
Generic Name	Donepezil	**Generic Name**	Memantine
Approval	1996	**Approval**	2003
Chemical formula	$C_{24}H_{29}NO_3$	**Chemical formula**	$C_{12}H_{21}N$
Mechanism ofAction		**Mechanism ofAction**	
Donepezilis a non-competitive acetylcholinesteraseinhibitor		It is a non-competitive voltage-dependent NMDAreceptor antagonist	
Generic Name	Galantamine	**Generic Name**	Aducanumab
Approval	2001	**Approval**	2021
Chemical formula	$C_{17}H_{21}NO_3$	**Weight**	47.70
Mechanism of Action		**Mechanism of Action**	
It is a competitive acetylcholinesteraseinhibitor		Aducanumab is a monoclonal antibody that is specific for soluble Aβ plaques	

Donepezil

Donepezil is a derivative of indanone benzylpiperidine that acts by reversibly tying up with acetylcholinesterase. This second-generation AChEIs is regarded as the most effective medication for treating Alzheimer's. This AChE inhibitor is non-competitive and got FDA approval in 1996. Donepezil works by reversibly attaching to acetylcholinesterase, blocking acetylcholine hydrolysis, and increasing the neurotransmitter's bioavailability at neural synapses. Its usage in AD patients has been demonstrated to reduce cognitive deterioration and enhance behavior. (Breijyeh & Karaman, 2020, García-Morales et al., 2021). The oral administration of donepezil comes in various forms including liquid, jelly, and tablet, and can also be applied as transdermal patches. The suggested starting dose for people with dementia of mild to moderate is 5 mg/day, while the dose may be adjusted to 23 mg/day for patients with dementia of moderate to severe (Kumar, 2022). A 10 mg/day dose of donepezil has been demonstrated to enhance cognitive function, and fundamental daily living activities, including clinical global impression ratings, but not behavior or life quality (Pardo-Moreno et al., 2022). Although, donepezil is a medication frequently used in individuals with Alzheimer's disease due to its once-daily regimen, good tolerability, and effective use. Nevertheless, the most prevalent side effects associated with donepezil were vomiting and diarrhea; and up to 14 percent of patients had sleeplessness (Mayeux & Sano, 1999).

Rivastigmine

Rivastigmine was launched in Switzerland in 1997 and later received FDA approval in 2000, is recommended for mild to moderate Alzheimer's in addition to Parkinson's dementia of mild to moderate stage. It works by attaching to the two distinctive sites of AChE (stearic and anionic sites) to inhibit both butyrylcholinesterase (BuChE) and AChE pseudo-irreversibly (Desai & Grossberg, 2005). Rivastigmine is known as a pseudo-irreversible because it

disperses in a slower manner in comparison to AChE and is often metabolized at the synapses by both AChE and BuChE (Breijyeh & Karaman, 2020). 26 weeks of ongoing treatment with daily doses of 6–12 mg taken orally or 9.5 mg daily applied topically, studies evaluating the administration of rivastigmine in the supervision of AD discovered improvements in the following; daily life activities, better cognitive function as measured by the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) and Mini-Mental State Examination (MMSE) and the clinician-rated global impression of change (Pardo-Moreno et al., 2022). Rivastigmine has a 0.355 oral bioavailability and a modest (40%) plasma protein binding rate. Its half-life for elimination is about two hours. Rivastigmine can be taken orally in the form of pills, liquid, or a newly created transdermal patch (Birks & Grimley Evans, 2015). Patients with AD who have trouble swallowing may benefit from rivastigmine transdermal patches while experiencing fewer adverse effects than with lower doses of the drug taken orally (Kandiah et al., 2017).

Galantamine

Galantamine, an alkaloid of tertiary isoquinoline that was approved in 2001, is regarded as a conventional first-line treatment for mild to moderate AD symptoms. It is a dual-action acetylcholinesterase inhibitor that is selective, competitive, as well as reversible. It increases the intrinsic action of neurotransmitter Ach on nicotinic receptors as well as inhibits acetylcholine esterase in a reversible manner, increasing the central nervous system's cholinergic neurotransmission. Galantamine has a high bioavailability, decreased plasma protein binding, as well as a high volume of clearance. The most effective dose appears to be between 16 and 24 mg/day, which is also the permitted maintenance dose level in the majority of regions (Razay & Wilcock, 2008). Galantamine, like other AChE inhibitors, has good efficacy and tolerance in improving behavioral symptoms, everyday activities, as well as

cognitive functioning (Breijyeh & Karaman, 2020). Galantamine has also been demonstrated to pass the BBB more quickly, having a longer-lasting impact on some brain regions including the hippocampus for 5 to 7 hours (Liu et al., 2018). Although this medication has demonstrated acceptable safety and tolerability, some side effects are associated with its usage, including convulsions, stomach cramps, erratic breathing, vomiting, confusion, and muscle weakness (Haake et al., 2020).

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

The use of drugs that block the NMDA subunit of glutamate receptors in Parkinson's disease has recently drawn attention. It is thought that NMDAR (N-methyl-D-aspartate receptor) plays a pivotal role in the pathophysiological state of AD. Ca2+ influx brought on by NMDAR stimulation promotes signal transduction, which in turn causes gene transcription required for the development of long-term potentiation (LTP), which is crucial for neuronal neurotransmission, plasticity, as well as the formation of memory. In addition, similar to dopaminergic agonists, antagonists of NMDA can alleviate the stiffness and akinesia caused by monoamine deficiency or catalepsy carried on by neuroleptics. Numerous uncompetitive NMDAR antagonists have been generated and studied in clinical settings, however, most of them were ineffective and had undesirable side effects. Memantine is the only medication in this class that has been authorized for the treatment of moderate to severe AD. On top of that, dopaminergic agonists' therapeutic benefits are greatly amplified by relatively low dosages of NMDA antagonists. To cure symptoms and slow the progression of the disease, NMDA antagonists may therefore be effective in the treatment of Parkinson's disease (Breijyeh & Karaman, 2020, Greenamyre & O’Brien, 1991).

Memantine

Memantine - a low-affinity, non-competitive inhibitor of the NMDAR, a subclass of glutamate receptor, which inhibits the glutaminergic system from being overactive and causing neurotoxicity in AD cases (Figure: 03). Memantine was the first medication authorized by the US FDA in 2003 for the treatment of moderate-to-severe AD. Both as a monotherapy and in conjunction with other therapies are options for its use. Treatment with memantine has been demonstrated to help AD patients with their general situation and cognitive impairment. This medication is safe and well-tolerated and as memantine has a low affinity for excitatory receptors, it blocks them without impairing normal synaptic transmission, where it is quickly removed from the NMDAR by high glutamate concentrations, preventing a persistent blockage (Breijyeh & Karaman, 2020, García-Morales et al., 2021). Following 6 months of the administration, a systemic analysis of double-blind, parallel-group, randomized trials of memantine revealed improvements in cognition, ADL, and behavior in individuals with moderate to severe AD (McShane et al. 2006). Memantine may lessen the psychological and behavioral signs of dementia, based on another comprehensive review that comprised six RCT studies (Maidment et al. 2008). In addition, memantine treatment led to a slight improvement in the overall clinical rating in individuals with moderate to severe AD: 0.21 points on the CIBIC-Plus, 3.11 for neuronal functioning on the Severe Impairment Battery (SIB), 1.09 on the ADCS-ADL scale for effectiveness in daily activities, and 1.84 on the neuropsychiatric inventory for mood and behavior (Pardo-Moreno et al., 2022). Dizziness, headaches, and disorientation were the side effects of memantine studies that were most commonly reported. Also, a minor number of patients might experience agitation (Alva and Cummings, 2008).

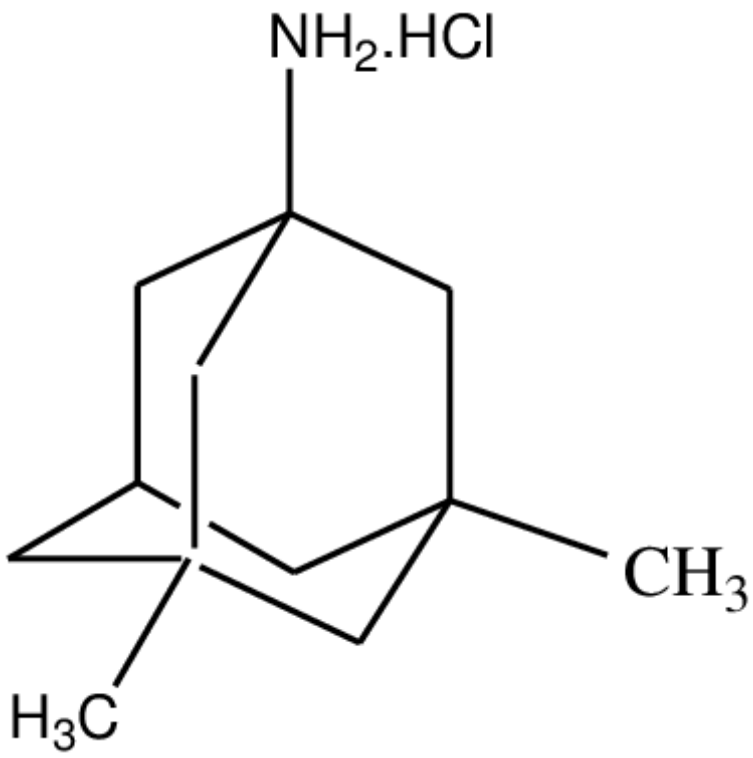

Figure 03: Structure of Memantine (modified from: PubChem)

1.6 Drugs Under Investigations

The quest for therapeutic alternatives has been sparked by the lack of efficient treatment options to halt and slow down the progression of AD, as well as the rising demand for novel medications intended to control the pathophysiological pathways underlying this disease (Hane et al., 2017). Two proteins, hyperphosphorylated tau, and amyloid-beta, which make up the majority of plaques, are deposited in the brains of people with AD. It is now feasible to quantify the amounts of these two proteins in the cerebrospinal fluid and brain using quantitative assessment as well as positron emission tomography (PET), which has become a crucial part of clinical studies (Waite, 2015). Now as of figure 04, here is a list of few drugs which are under investigation to treat AD.

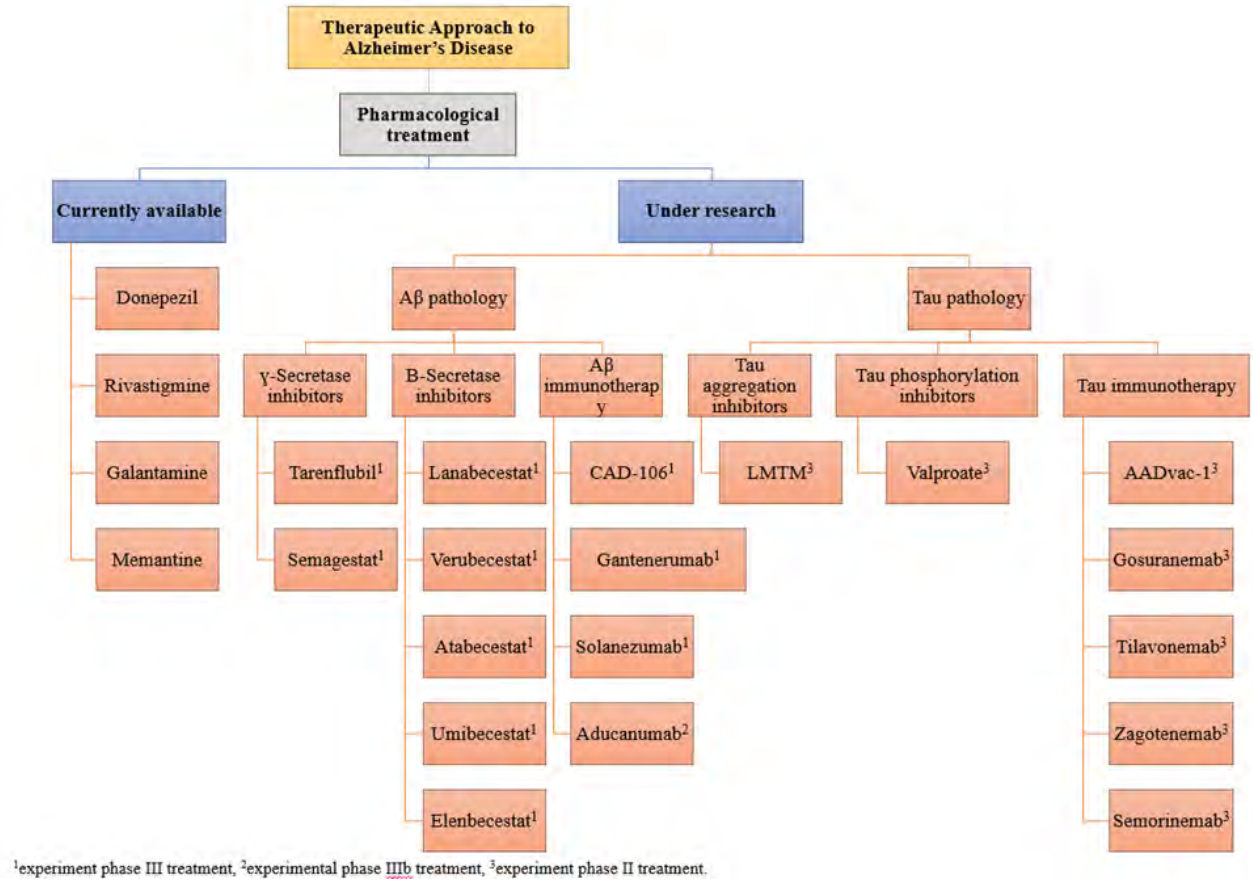

Figure 04: Overview of the drugs under investigations to treat AD

1.6.1 Aβ pathology

There are three main therapeutic options in the treatment of Aβ pathology. The first one focuses on the reduction of the excessive Aβ42 through various inhibitors including the α, β, and γ-secretase. The next therapeutic goal aims to decrease the Aβ load in SP by employing aggregation inhibitors or metal-interfering medications. The third treatment goal aims to increase Aβ clearance through immunotherapy (Yiannopoulou & Papageorgiou, 2020).

γ-secretase inhibitors

One of the potential therapeutic options in the management of AD can be obtained by inhibiting γ-secretase, which cleaves transmembrane proteins like the Notch 1 receptor and works on the

APP by successive cleavage (Yiannopoulou & Papageorgiou, 2012). In addition, the significance of Tarenflurbil and Semagacestat (LY-450139) must be emphasized. Both medications have been investigated in various phase II clinical trials, with results that show a notable slowdown of cognitive decline and a decrease in Aβ40 levels. The intranasal drug Tarenflurbil, which has limited brain penetration and efficacy, prevented it from continuing to Phase III (Saretz et al., 2021). Similarly, Semagacestat did not enhance cognitive capabilities and, in patients getting a greater dose, worsened functional capacity in addition to increasing the chance of developing infections and cancer of the skin (Doody et al., 2013).

β-secretase inhibitors

There are a number of β-secretase inhibitors that have been effective in lowering Aβ levels in CSF, including Lanabecestat, Umibecestat, Verubecestat Elenbecestat, and Atabecestat. Nevertheless, phase III of the trials was discontinued due to patients' cognitive and functional decline while taking these medications, as well as the emergence of side effects. Despite these events, it's important to note that every therapy considerably lowered CSF Aβ levels (Imbimbo & Watling, 2019).

α-secretase activators

Another potential therapeutic target is the regulation of α-secretase as it is responsible for cleaving APP and initiating the non-amyloidogenic pathway. The scientific literature states that phosphatidylinositol 3-kinase (PI3K)/Akt pathway via - Gamma-aminobutyric acid (GABA) receptor signaling mediates the activation of α-secretase. Etazolate is a receptor modulator of GABA, that has been examined in phase II clinical trials indicating its safety in patients who have mild to moderate AD. A phase III experiment, however, is still waiting (Vellas et al., 2011).

Aggregation inhibitors

This class of medicines aims to inhibit the development of the Aβ42 fibers that characterize Aβ pathology. (ELND005) belongs to this class and was the last one to be tested in phase II on humans. Due to a lack of evidence for its effectiveness and dose-dependent toxicity, it was stopped being used (Salloway et al., 2011b). At the moment, research is focused on the application of peptidomimetics, which can reverse or stop the aggregation of Aβ42. KLVFF and γ-AApeptides are two classes of peptidomimetics, where it's noted that γ-AApeptides are 100 times more potent than KLVFF (Nimmagadda et al., 2019).

Immunotherapy

One of the most recent therapeutic strategies being studied is Aβ clearing by immunotherapy. These medications improve Aβ clearance in immunotherapeutic approaches and can be used in active or passive immunotherapy, respectively (Wisniewski & Goñi, 2015). Active immunotherapy requires the administration of complete proteins or fragments of proteins that encourage B cells to produce antibodies, so enhancing the patient's immunological response. In passive immunotherapy, monoclonal or polyclonal antibodies that respond against Aβ peptides are passively inoculated (Folch et al., 2018). Various drugs of this group have reached phase III clinical trials including aducanumab, CAD106, gantenerumab, and solanezumab (Yiannopoulou & Papageorgiou, 2020). In patients with moderate AD, CAD106 has demonstrated safety and good tolerability while lowering Aβ buildup. In addition, two-phase IIIb clinical trials with aducanumab have been conducted, and owing to the dispute, the FDA in the US authorized aducanumab in mid-2021 for use in individuals with moderate AD. (Citation) It is significant to note that there are areas of study within this form of immunotherapy focused on acquiring human anti-Aβ via intravenous immunoglobulin (Sabbagh & Cummings, 2020). Plasma exchange using albumin is a treatment that is also being

researched. This procedure removes plasma Aβ and replaces it with albumin to eradicate the condition (Boada et al., 2017).

1.6.2 Tau Pathology

Recent research has emphasized the treatment strategy for tau pathology due to the inconsistent results of the numerous pharmacological trials addressing the Aβ pathology. The proposed treatments for tau pathology attempt to suppress abnormal tau hyperphosphorylation, decrease tau protein buildup, as well as help develop both active and passive immunotherapies (Chang et al., 2021). Since several different kinase subtypes encourage tau phosphorylation, its inhibition has been suggested as a potential pharmaceutical strategy in AD. In this regard, glycogen synthase kinase 3 beta (GSK3β) is one of the therapeutic targets to inhibit the hyperphosphorylation of tau protein. Lithium chloride is one of the most extensively researched GSK3 inhibitors, and research in cell culture has amply demonstrated that lithium therapy can successfully inhibit the enzyme and lower tau phosphorylation levels (Congdon & Sigurdsson, 2018). Leuco-methylthioninium bis(hydromethanesulfonate) (LMTM), a methylene blue compound, stands out among medications that aim to prevent the accumulation of phosphorylated tau because of its high levels of tolerance and absorption (Long & Holtzman, 2019).

Likewise, immunotherapy is the most recent therapeutic strategy used to treat tau pathology. There are two types of immunotherapies in this category: active and passive. A number of immunotherapy-based medications, including zagotenemab, semorinemab, tilavonemab, and gosuranemab have entered phase II, although haven't shown any outstanding results. Only AADvac-1 usage in individuals with mild to moderate AD has progressed to phase II, with results suggesting a decrease in abnormally phosphorylated tau in CSF as well as a delay of

cognitive loss (Soeda & Takashima, 2020). This group also includes ACI-35 as a therapeutic alternative.

1.7 Purpose of the Study

The behavior, functioning, and cognitive deterioration of AD patients appear to have been positively impacted by treatment, as per research, and as usual, like other medications, these treatment options are also associated with side effects. Now, in order to better understand how the NMDA antagonist, memantine affects death rates and the occurrence of rhabdomyolysis in patients who are taking it to manage AD dementia, the following study was planned to carried out. It's been claimed that in the treatment of AD, acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine) as well as memantine are the best choice by the physicians although all of them are associated with some sought of side effects or adverse events.

As a consequence, in this study, we tried to figure out the impact of memantine on patients' mortality benefit ratio and its connection in the onset of particular side effect rhabdomyolysis through evaluating the adverse drug reactions data collected from FDA's special adverse events reporting system the FAERS database.

Chapter 2: Memantine

2.1 Pharmacodynamics

Indications

Memantine is a prescription medication used to treat Alzheimer's-related dementia that ranges from moderate to severe. This NMDA receptor antagonist was first authorized by the FDA in 2013 and functions differently from cholinesterase inhibitors. It may enhance memory, consciousness, and the capacity to carry out daily tasks, however, it does not treat Alzheimer's disease. Memantine lessens the effects of brain chemicals that may be involved in developing Alzheimer's disease symptoms. More specifically, it inhibits the actions of glutamate, the neurotransmitter in Alzheimer's disease that causes excessive excitation and neuronal excitability in the brain.

Additionally, it is used to alleviate the signs and symptoms of

- Alzheimer's disease
- Corticobasal degeneration (CBD)
- Lewy body dementia
- Mixed dementia – when an individual has multiple forms of dementia

These are the several brand names that memantine is offered under: Namenda XR, and Namenda (USA), and Ebixa, Nemdatine, Valios (UK & EMA). NAMENDA, a product of the abbvie, is the most popular memantine brand that is frequently prescribed.

Dosage forms and strengths

Memantine is available in a range of dosages and strengths. The list that follows provides an overview of the dosage forms and strengths that are offered.

- Tablets - (5 mg and 10 mg)
- Capsules; extended-release - (7 mg, 14 mg, 21 mg, and 28 mg)
- Oral solutions - (2 mg/mL)
- Oral kit (extended-release and immediate-release)

The marketed dosages of NAMENDA are 5 mg and 10 mg. 5 mg of NAMENDA once daily is the initial dose that is advised. To reach 10 mg/day, the dosage can be raised in 5 mg increments (5 mg twice per day), 15 mg/day (separate doses of 5 and 10 mg), as well as 20 mg/day (10 mg twice each day). One week is the bare minimum suggested time between dose increases. In controlled trials, a daily dose of 20 mg has been demonstrated to be effective.

Dosage Considerations and Modifications

Memantine is not recommended for usage in children. For tablets, the initial dose is 5 mg taken once a day; increased by 5 mg/day in weekly increments. The target dosage for maintenance is greater than five weeks. For extended-release capsules, an initial daily oral dose of 7 mg, the dosage may be raised by 7 mg per day every week in increments, The daily oral target dose for maintenance is 28 mg.

Renal impairment

- No dosage change is necessary for mild or moderate conditions.
- In patients who suffer from severe renal impairment, a targeted dose of 5 mg twice per day is advised in the case of NAMENDA.

- In the cases of other drugs in renal impairment (5-29 mL/min of creatinine clearance), for extended-release dosage form, not more than 14 mg each day, and for tablets, 2 times a day of 5 mg.

Hepatic Impairment

- There is no need of changing the dosage for mild or moderate conditions with Child-Paugh A or B.
- Patients with severe liver impairment should use caution when taking NAMENDA.
- In the case of other drugs for hepatic impairment with Child-Pugh C, the drug needs to be taken cautiously.

Pregnancy and Lactation

- Administration of memantine during pregnancy can be allowed. Memantine use during pregnancy has not been studied, so you can stop it if you want to be cautious. Likewise, it is uncertain if memantine can be secreted in breast milk; if breastfeeding is significant then needs to be done cautiously. In both cases, have a conversation with the physician or pharmacist to be on the safe side.
- Data regarding NAMENDA's impact on milk production or its effects on breastfed infants are sparse. There is insufficient evidence on the developmental risk connected with NAMENDA use when discussing its impact on pregnant mothers.

Administration Considerations

Memantine can be consumed anyway with or without food. Memantine should not be taken more than the recommended dosage or for a longer period. Talking of capsules, it's not an appropriate approach to split the dose; rather needs o consume the complete contents of the capsule. Likewise, a capsule for extended-release must not be opened, chewed, crushed, or

broken. Must need to take it in totality. To facilitate the swallowing procedure, the extended-release capsule can be intake by sprinkling with a full of a spoon of applesauce. In the case of oral solution, you can use the dosing syringe that comes with the medication or a medicine cup if you prefer to measure the oral liquid medicine. In addition, it's not suitable for the oral solution to be combined with another liquid. A melt-in-mouth tablet version of memantine is also available (orodispersible tablet). The tablet should be placed in your mouth and allowed to dissolve until it is completely disappeared.

When it comes to storage, Memantine should be kept in a cool, dry place at room temperature along with its precise distance from heat and moisture. The included cap should be used to properly seal the oral solution of this medication. The oral syringe-filled bottle should not be kept in storage. Regarding the missed dose, the missed dose should be only taken if you remember that right away. If your next scheduled or planned dose is soon due, skip the missing dose. In such a context, do not double up on your medication to make up for a missing dosage. It might be necessary to restart the dosage at lower amounts and re-titrate if it is skipped for a few days.

Side effects or Adverse Reactions of Memantine

Like all other medications, patients taking memantine can experience a few common side effects, nevertheless, everyone encounters them. If your physician adjusts your dose slowly over at least one month, then the possibility of having side effects is much less likely to occur. And over 1 in 100 individuals experience these typical side effects from memantine and they are

- Headaches,
- Constipation,

- Diarrhea,
- Feeling dizzy, and
- Confusion.

Serious side effects or adverse effects with memantine are possible. Even while not all of these adverse effects are likely to happen, once they do, medical attention or a call to your physician may be required.

- Unusually gaining or losing weight
- Seizure or convulsions
- Irrational alterations in mood and behavior
- Development of real-feeling but false sensory hallucinations in hearing, tasting, and seeing - This can be an indication of psychosis.
- Memantine can, in very rare circumstances, cause a severe allergic reaction (anaphylaxis).

Another part of the side effects related to memantine is associated with clinical trials, case studies, as well as post-marketing monitoring. These are uncommon and deserve a doctor's attention if they develop.

- Neurological disorders - Intracranial hemorrhage, Cerebral infarction, Tardive dyskinesia, Abnormal gait
- Dermatological disorders - Rash, Stevens-Johnson syndrome
- Cardiovascular disorders - Myocardial infarction, tachycardia, bradyarrhythmia, syncope
- Psychiatric - suicidal ideation
- Musculoskeletal – Arthralgia

Drug-Drug Interactions

With Cholinesterase Inhibitors - The pharmacokinetics of memantine weren't impacted by being administered alongside the donepezil hydrochloride (AChE inhibitor). Additionally, donepezil's ability to inhibit AChE was unaffected by memantine. In a 24-week of a controlled clinical trial, for patients with mild to moderate AD, it was found that donepezil alone had a similar adverse events profile to that seen with NAMENDA combined with it.

Impact of memantine (NAMENDA) on Other Drug Metabolism - Investigations carried out in vitro using cytochrome 450 enzyme marker substrates (CYP1A2, -2D6, -2A6, - 2E1, -2C9, -3A4) revealed memantine only slightly inhibited these enzymes. Additionally, in vitro research has found that memantine does not stimulate the CYP450 (CYP1A2, -2E1, and -2C9) isozymes at concentrations higher than those linked to efficacy. It is anticipated that medications metabolized by CYP enzymes won't have any pharmacokinetic complications with them.

Memantine's potential for interactions with warfarin and bupropion were assessed in pharmacokinetic investigations. Bupropion, a CYP2B6 substrate, and hydroxy-bupropion, its metabolite, were not affected by memantine's pharmacokinetic properties. Memantine also had no impact on the prothrombin INR, which was used to measure warfarin's pharmacokinetics and pharmacodynamics properties.

Effects of Other Drugs on Memantine (NAMENDA) - Memantine is primarily eliminated through the renal pathway, and medications that impede or are substrates of the CYP450 isoenzyme are not anticipated to affect the memantine's metabolism. Memantine's mode of action as an antagonist makes it plausible that it might increase the effects of anti-parkinsonian medicines (levodopa, and dopamine), even though barbiturates and neuroleptics' effects might

be lessened. Memantine coadministration may have an impact on the anti-spasmodic drugs dantrolene and baclofen as well.

Removed Through Renal Route - Memantine is partly excreted through tubular secretion, so taking it with other medications that also impact the renal cationic system, such as hydrochlorothiazide (HCTZ), metformin, triamterene (TA), quinidine, cimetidine, and ranitidine may alter the plasma concentration of both medications. The bioavailability of memantine or TA was unaffected by the concurrent administration of NAMENDA and HCTZ/TA, although the bioavailability of HCTZ was 20% lower. Additionally, the pharmacokinetic profile of memantine, glyburide, and metformin, were unaffected by co-administration of the antihyperglycemic medication Glucovance (metformin and glibenclamide) and memantine.

Highly Plasma Protein-Bound Drugs - Memantine only binds to plasma proteins at a modest rate (45%), It is unusual that medications like warfarin and digoxin, which are strongly linked to plasma proteins, will interact.

Mechanism of Action of Memantine

Long-term potentiation (LTP) is a crucial memory and learning mechanism. Glutamate neurotransmitter mediates LTP through the NMDA receptor. The NMDA receptors are widely distributed in the brain. Also, these receptors are widely dispersed in the dendrites of the pyramidal cells of the cortex and hippocampus (regions of the brain known to play a role in cognition, memory, and learning). Along with the association between learning and LTP, increased glutamate levels are linked to excitotoxicity (Thomas & Grossberg, 2009). Moreover, AB plaques, a pathogenic aspect of AD, were discovered to cause astrocyte depolarization,

extracellular glutamate buildup, and intracellular Ca2+ deposition. As a result, the route of glutamate-induced excitotoxicity is a great target for the treatment of AD (Figure: 05)

In order for NMDA receptors to work, they must bind to a calcium ion channel, which can be opened by the binding of glutamate, glycine, or NMDA. On the other hand, the channel is blocked by the magnesium ion, hence it only works whenever the cell is depolarized. This stops calcium from entering the neuron when it is in a resting state. Magnesium exits the channel in pathological conditions, like in a chronic depolarized membrane, which inhibits neuronal metabolism and results in cell death (Zeevalk & Nicklas, 1992). When this occurs, the calcium flow is unrestrained for a prolonged duration than usual. This increased ingress of Ca2+ causes a change in cell functions, subsequently resulting in cell death either from free radicals or from the overstimulation of the mitochondria.

Now, memantine is a non-competitive antagonist of the CNS's NMDA subtype glutamate receptors that reduce the channel's permeability to stop calcium entry. Therefore, by blocking the action of glutamate and subsequently reducing the post-synaptic stimulation, memantine improves the symptoms of AD in patients by decreasing neurotoxicity. Additionally, memantine displays its antagonistic activity at the nicotinic acetylcholine as well as serotonergic type 3 (5-HT3) receptors. It is inactive at the voltage-dependent channels including sodium, potassium, and calcium. Likewise, it doesn't exert its effect on the GABA, dopamine, glycine, adrenergic, benzodiazepine, or histamine receptors (Kuns, 2022).

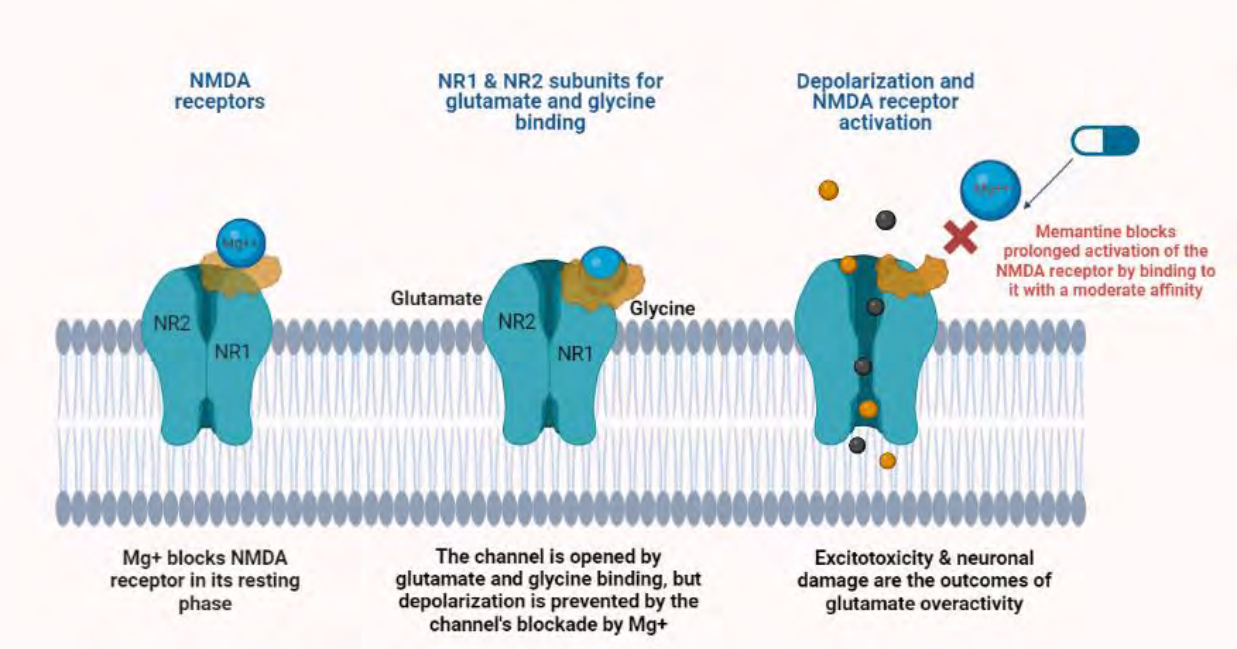

Figure 05: Mechanism of Action of Memantine (modified from: Rege, 2023)

2.2 Pharmacokinetics

Absorption

Memantine is rapidly absorbed after it is administered orally and reaches its peak levels in 3 to 7 hours. The pharmacokinetics of memantine is linear over the therapeutic range of dose. Food has no impact on how well memantine is absorbed.

Distribution

Memantine has an average volume of distribution of 9–11 L/kg, with minimal binding with plasma protein (45%)

Table 02: Pharmacokinetic Parameters of Immediate-release and Extended-release Memantine

Pk Parameters		Immediate-release Memantine	Extended-release Memantine
Absorption	Bioavailability	100%	100%
	C_{max}	60 to 80 ng/mL for a dose of 20 mg.	31 to 65 ng/mL for a dose of 28 mg
	T_{max}	3-7 hours	9 to 12 hours
	AUC	It's approximately 650 to 900 ng*h/mL; 20 mg of a single dose	It's approximately 365 to 875 ng*h/mL; for a single dose of 28 mg
	Effect of food	No effect	Shown to decrease Tmax by 7 hours with no effect on AUC or Cmax
Distribution	Vd	9-11 L/kg	10 L/kg
	Protein binding	45%	-
	BBB permeability	Yes	Good permeability
Metabolism	Metabolizing enzymes	Hepatic CYP450 enzyme system	Hepatic CYP450 enzyme system
	First pass metabolism	To some extent	To minor extent
Elimination	Clearance	170 ml/min/1.73 m^2	170 to 195 mL/min
	$T_{1/2}$	60 to 80 hours	70 hours
	Excretion route	Urine - 48%	Urine - 57% to 82%

C_{max} - peak plasma concentration, T_{max} - time to reach C_{max}, AUC- area under curve, Vd- volume of distribution, $t_{1/2}$- drug half-life, V_{max}- maximum velocity, ng*h/ml- nanogram hour per milliliter

Metabolism

Memantine is partially metabolized in the liver. Memantine is not significantly metabolized by the liver's microsomal CYP450 enzyme system.

Elimination

Memantine is primarily eliminated unaltered in the urine (about 48%) and possesses a terminal elimination half-life of 60 to 80 hours. The remaining substance is mainly transformed into three polar metabolites with negligible NMDA receptor antagonistic action and the three parts are 1-nitroso-deaminated memantine, N-glucuronide conjugate and 6-hydroxy memantine. The parent medication plus the N-glucuronide conjugate is excreted together in amounts totaling 74% of the administered dose. A point to note is that, active tubular secretion, which is regulated by pH-dependent tubular reabsorption, is a component of renal clearance.

Chapter 3: Methodology

3.1 Data Source

This pharmacovigilance and observational analysis were carried out using data from the FAERS database. FAERS is the most effective and remarkable adverse event reporting system run by the US Food and Drug Administration and it receives approximately 1.5 million cases or reports of adverse incidents related to drugs, devices, and vaccinations every year. The US FDA receives reports of various adverse events spontaneously from consumers, companies, and healthcare providers, which are then included in the FAERS database. This database contains data on demographics, findings, reporting nations, suspected drugs, and on interacting pharmaceuticals (Vestergaard Kvist et al., 2021). Then, these instances are recorded into the FAERS database using relevant MedDRA (Medical Dictionary for Regulatory Activities) keywords. The Adverse drug reactions (ADRs) that have been documented in the FAERS, are increasing public awareness as well as helping in identifying safety related to different drugs (Mazhar et al., 2021). Data or stats on all adverse events documented by the FDA are accessible to the general folks on a quarterly basis (Vestergaard Kvist et al., 2021). As a consequence, we could see a substantial quantity of adverse events recorded by patients, pharmaceutical manufacturers, and healthcare professionals concerning the FDA-authorized "Acetylcholinesterase inhibitors" that are prescribed to treat Alzheimer's Disease by browsing through FAERS. There are 26,004,135 reports in the database as of now. The search was conducted on January 2023, and the stats or data were gathered between January 2015 and September 2022 for this study. The generic name "Memantine" was selected as the search

phrase. Additionally, The Medical Dictionary for Regulatory Activities (MedDRA) chosen terminology was used to select terminology for the adverse events classes.

3.2 Inclusion and Exclusion Criteria

Between January 2015 and September 2022, data for this study were gathered from the FAERS database. MedDRA recommended phrases were used to select the documented adverse occurrences for this investigation and the (PTs) were - “death”, “sudden cardiac death”, “brain death”, “apparent death”; “sudden death”, “cardiac death”, and “accidental death”; all of these terms were combined to find out data regarding the term’s "death" and "Rhabdomyolysis”. The database included all of the side effects or adverse events associated with the medication known by the generic name "Memantine." We incorporated all of the results for these medicines and omitted the information on which additional medications were thought to be contributing to the adverse effects. Consequently, "Memantine" was the sole medicine suspected of causing the intended adverse events. Additionally, we deleted all similar reports by finding them using the case number and cross-referencing the age, sex, as well as event date.

3.3 Statistical Analysis

In January 2023, using the FAERS database, the extraction of data as well as its analysis were carried out. In our paper, we incorporated the reported odds ratio (ROR) as well as its related 95% Confidence Interval (CI) to conduct a disproportionality analysis. This analysis aided us in detecting signals that indicate a reported connection between the desired medicine (Memantine) and undesirable side effects (Death and Rhabdomyolysis). ROR was used since it is an established case and non-case method for detecting medication safety signals (Bene et al., 2014). When calculating the disproportionality measures, ROR is regarded to be one of the techniques used most frequently. By employing a 2 by 2 contingency table with drug cases

(desired side effects) as well as non-cases (undesired side effects), the ROR was determined (van Puijenbroek et al., 2003). Therefore, the ROR was utilized to evaluate the level of disproportionality, whereas the CI established the statistical validity of the finding. If the confidence interval's cutoff point is greater than 1, it signals that there have been substantially more reports of adverse effects in comparison to those caused by other medicines. Nevertheless, if the confidence interval's cutoff value is equal to 1 or less than 1, then indicates that there is no evidence of a side effect or adverse effect, indicating that in comparison to other medications, the side effect is recorded less frequently (Sato et al., 2020).

In this study, ROR and the associated 95% confidence interval (CI) were determined to assess the reporting connection between the adverse events (Death and Rhabdomyolysis) and the relevant drug (Memantine), where the comparison was conducted employing the entire database (Sato et al., 2020). As an outcome, we were able to figure out the statistical importance in relevance with the adverse events and the drug in consideration when compared to all other pharmaceuticals in the database. The ROR with 95% CI was then determined for the respective medications, which had the same side effects, however, the comparator was a different class of drugs recommended for the identical treatment. It helped us pinpoint the treatments with the highest reporting relationship of the side effect or adverse events. A medication with a higher ROR rating has a higher reporting connection in comparison to other drugs. R, version 4.2.1, was employed to analyze all of the data in our study.

Chapter 4: Results & Discussions

4.1 Results

4.1.1 Mortality Rate

In terms of mortality rate in patients with AD, our concerned drug memantine doesn't showed any clinically significant ROR values (ROR<1).

To begin with, we used the whole database as a comparator where reports from January 2015 to September 2022 were collected. It was observed that 26 cases were related to patients' morality or death for memantine. In contrast, 456144 death cases were associated with other drugs. The ROR (95% Cl) of memantine was then measured to be 0.68 (0.46 to 1.00; p = 0.0483) which compares the death cases for specific drugs, in this regard, memantine, to other drugs cases obtained in the entire database (Table: 03).

Subsequently, by taking the class (Acetylcholinesterase inhibitors) as a comparator we measured the ROR value again where reports were gathered from January to September of 2025-2022. We observed 26 death cases related to memantine whereas 704 cases were related to other drugs. The reporting odds ratio (ROR) we found was 0.19 (CI = 0.13 to 0.28; p <0.0001). This indicates the comparison of death cases for specific drugs (memantine) to other drug cases in the drug class alone (Table: 03).

Table 03: Results for cases of death

FEARS database values from 2015-2022			
	Cases of death	**ROR (CI)**	***p* Value**
Memantine	26		
Other drugs (whole database as a comparator)	456144	0.68 (0.46 - 1.00)	P = 0.0483
Other drugs (class as comparator)	704	0.19 (0.13 - 0.28)	P < 0.0001

4.2.2 Rhabdomyolysis

Talking of rhabdomyolysis, our concerned drug memantine showed clinically significant ROR values (ROR>1).

We also looked for data/stats for rhabdomyolysis in the FAERS database and the reports we collected from 2015 to 2022. While employing the whole database as a comparator, we observed that in 11 cases of rhabdomyolysis, memantine was associated. On the other hand, 16379 cases of rhabdomyolysis were related to other drugs. This time, the ROR (95% Cl) was measured to be 8.10 (4.48 to 14.67; p < 0.0001) which indicates the comparison of rhabdomyolysis cases for our particular drug to other drugs cases gathered from the whole database (Table: 04).

In addition, considering the class (AChEIs) as a comparator and the same data as earlier we figured out 11 rhabdomyolysis cases with memantine whereas 27 cases with other drugs. The ROR obtained was 2.25 (CI = 1.11 to 4.54 with a p-value of P = 0.0241) which indicates the relationship of rhabdomyolysis cases of our particular drug with other drugs class (Table: 04).

Table 04: Results for cases of rhabdomyolysis

FEARS database values from 2015-2022			
	Cases of Rhabdomyolysis	**ROR (CI)**	***p* Value**
Memantine	11		
Other drugs (whole database as a comparator)	16379	8.10 (4.48 - 14.67)	P < 0.0001
Other drugs (class as comparator)	27	2.25 (1.11 - 4.54)	P = 0.0241

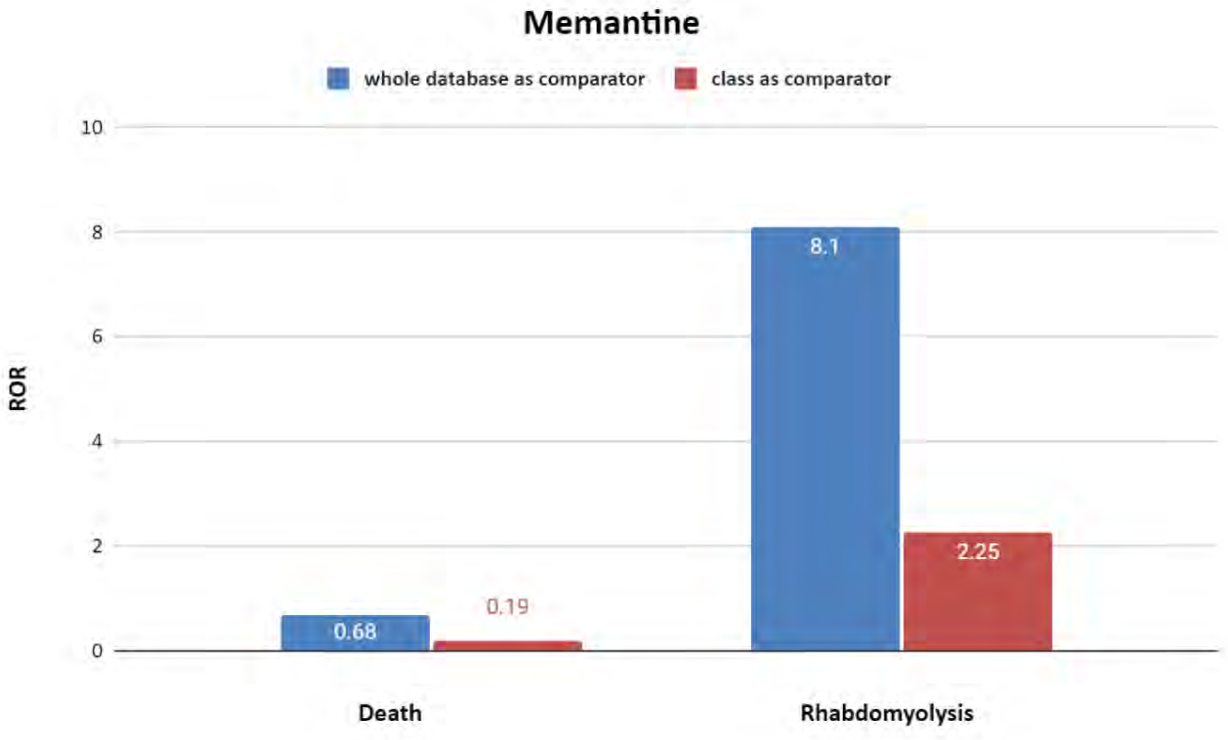

Figure 06: Comparison of the ROR values for cases of Death and Rhabdomyolysis

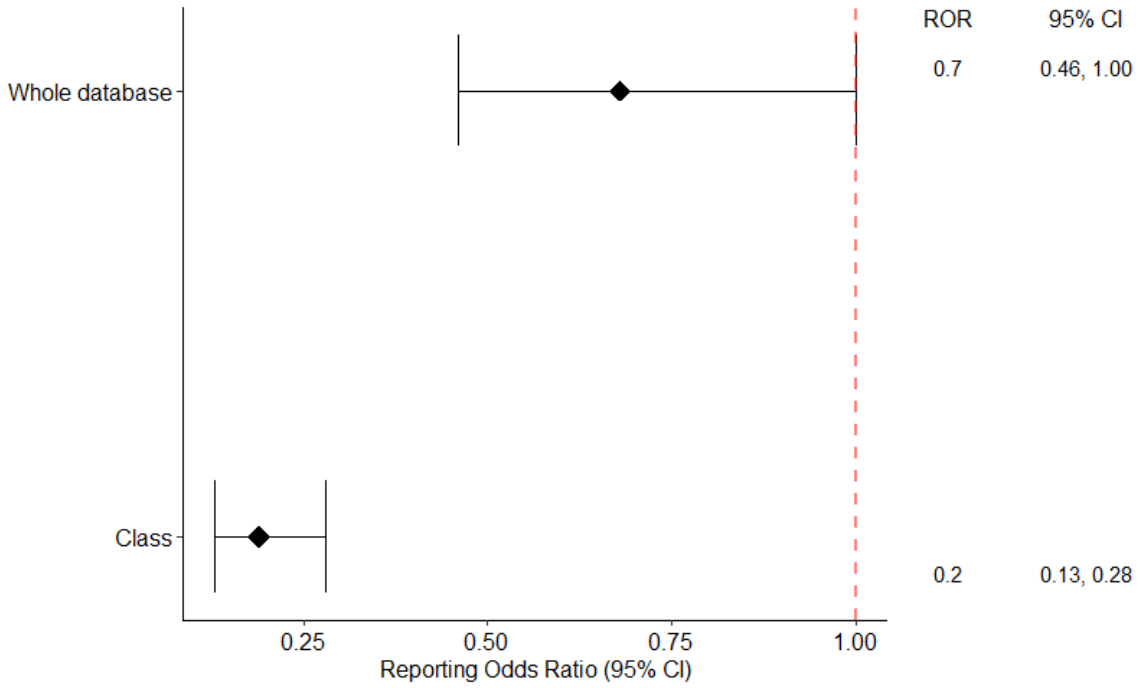

Figure 07: Forest plot of association between death and Memantine

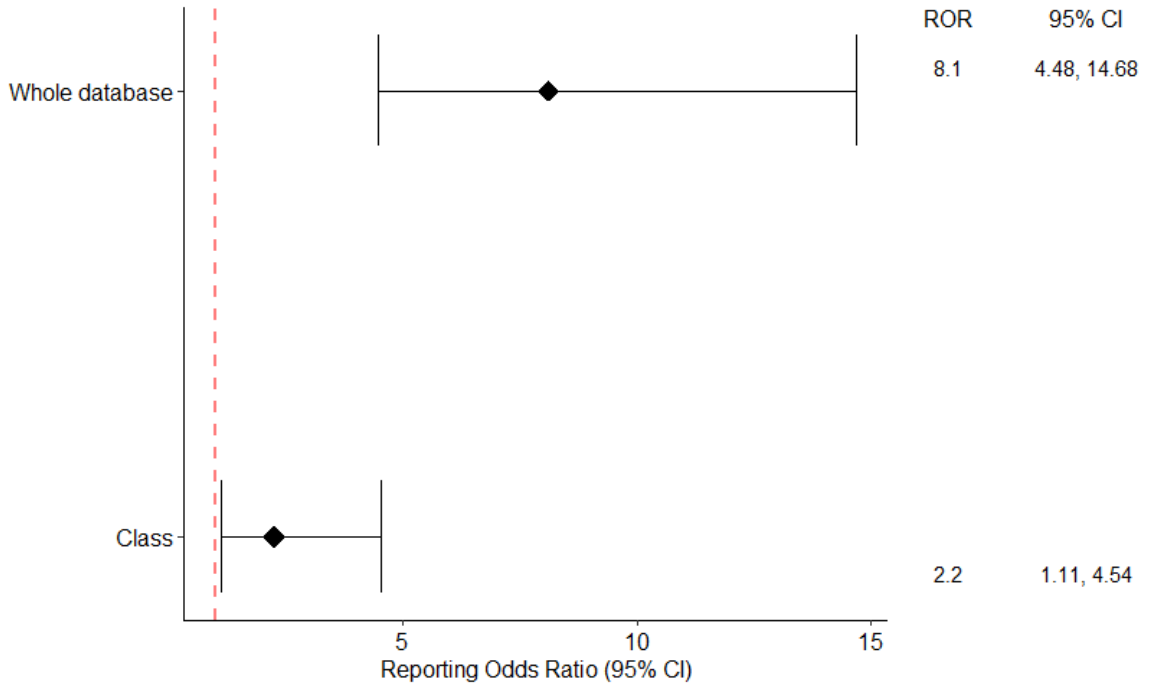

Figure 08: Forest plot of association between rhabdomyolysis and Memantine

4.2 Discussion

By conducting this systematic analysis based on FAERS database for memantine we have gathered a few unprecedented findings. We observed that memantine has an outstanding mortality benefit profile causing only 26 death cases in comparison to other drug classes of AchEIs (Donepezil, Rivastigmine, and Galantamine); which have 704 cases of death. As a consequence, it's fairly observable that memantine has a better mortality profile subsequently increasing life expectancy in AD patients. So, Alzheimer's patients can rely on memantine as a prime therapeutic option to alleviate or prolong the symptom of moderate to severe AD.

Besides, talking of rhabdomyolysis, memantine's association with rhabdomyolysis was fair as per the analysis of FAERS data rather than being the standard. However, it showed that memantine has fewer cases of rhabdomyolysis than the AchEIs. We observed only 11 cases of rhabdomyolysis related to memantine whereas the AchEIs showed a total number of 27

rhabdomyolysis cases analyzing the data of FEARS data between 2015-2022. As a consequence, we have concluded that memantine will not be a great choice to treat patients with AD having major issues related to the muscle or muscular system. Hence, individuals with muscular injuries may consider additional alternatives cause the administration of memantine has the potential to make the scenario worst and more severe.

When administered alone or in conjunction with other medications, memantine was discovered to have a favorable tolerability profile. Memantine had less drug-drug interactions, cautions, as well as contraindications in comparison to AChEIs (Jones et al., 2009). To sum up, our drug of concern, memantine owns a better mortality benefit rate along with fewer cases of rhabdomyolysis than other medication of concern.

Chapter 5: Conclusion

Elderly adults are more likely to develop AD, who may also suffer from other comorbid conditions along with prescribed on several medicines. Acetylcholinesterase inhibitors (AChEIs) as well as the NMDA-receptor antagonist, memantine are the two main medication classes used to treat Alzheimer's. All of the drugs have limitations of their own although, from our statistical analysis, we can state that memantine has the potential to be the prime option to treat AD as it has a better mortality-benefit ratio along with Donepezil. Hence, physicians can put their trust in these drugs to treat their patients who are suffering from AD. Nevertheless, memantine’s evidence on rhabdomyolysis is a topic of concern. In this regard, Rivastigmine has been observed to find null cases. Memantine will be a great choice to treat patients with AD unless the patient doesn't have any major issues related to the muscle or muscular system.

We believed that this study might come into action for the physicians to treat patients of AD and will serve as a focal source to select drugs considering the maximum efficacy, safety, and

tolerability. In a similar way, we anticipate that these results would be helpful for upcoming research on dementia and AD treatments.

Chapter 6: References

Alzheimer's disease facts and figures. (2022). *Alzheimer's and Dementia*, *18*(4), 700–789. https://doi.org/10.1002/alz.12638

Baranello, R., Bharani, K., Padmaraju, V., Chopra, N., Lahiri, D., Greig, N., Pappolla, M., & Sambamurti, K. (2015). Amyloid-Beta Protein Clearance and Degradation (ABCD) Pathways and their Role in Alzheimer's Disease. Current Alzheimer Research, 12(1), 32–46. https://doi.org/10.2174/1567205012666141218140953

Bene, J., Moulis, G., Auffret, M., Lefevre, G., Coquerelle, P., Coupe, P., Pere, P., & Gautier, S. (2014). Alopecia induced by tumor necrosis factor-alpha antagonists: description of 52 cases and disproportionality analysis in a nationwide pharmacovigilance database. Rheumatology (Oxford), 53(8), 1465-1469. https://doi.org/10.1093/rheumatology/keu145

Birks, J. S., & Grimley Evans, J. (2015). Rivastigmine for Alzheimer's disease. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.cd001191.pub3

Boada, M., Anaya, F., Ortiz, P., Olazarán, J., Shua-Haim, J. R., Obisesan, T. O., Hernández, I., Muñoz, J., Buendia, M., Alegret, M., Lafuente, A., Tárraga, L., Núñez, L., Torres, M., Grifols, J. R., Ferrer, I., Lopez, O. L., & Páez, A. (2017). Efficacy and Safety of Plasma Exchange with 5% Albumin to Modify Cerebrospinal Fluid and Plasma Amyloid-β Concentrations and Cognition Outcomes in Alzheimer's Disease Patients: A Multicenter, Randomized, Controlled Clinical Trial. Journal of Alzheimer's Disease, 56(1), 129–143. https://doi.org/10.3233/jad-160565

Brion, J. P. (1998). Neurofibrillary Tangles and Alzheimer's Disease. European Neurology, 40(3), 130–140. https://doi.org/10.1159/000007969

Chang, C. W., Shao, E., & Mucke, L. (2021). Tau: Enabler of diverse brain disorders and target of rapidly evolving therapeutic strategies. Science, 371(6532). https://doi.org/10.1126/science.abb8255

Congdon, E. E., & Sigurdsson, E. M. (2018). Tau-targeting therapies for Alzheimer's disease. Nature Reviews Neurology, 14(7), 399–415. https://doi.org/10.1038/s41582-018-0013-z

Desai, A. K., & Grossberg, G. T. (2005). Rivastigmine for Alzheimer's disease. *Expert Review of Neurotherapeutics*, *5*(5), 563–580. https://doi.org/10.1586/14737175.5.5.563

Doody, R. S., Raman, R., Farlow, M., Iwatsubo, T., Vellas, B., Joffe, S., Kieburtz, K., He, F., Sun, X., Thomas, R. G., Aisen, P. S., Siemers, E., Sethuraman, G., & Mohs, R. (2013). A Phase 3 Trial of Semagacestat for Treatment of Alzheimer's Disease. New England Journal of Medicine, 369(4), 341–350. https://doi.org/10.1056/nejmoa1210951

Folch, J., Ettcheto, M., Petrov, D., Abad, S., Pedrós, I., Marin, M., Olloquequi, J., & Camins, A. (2018). Una revisión de los avances en la terapéutica de la enfermedad de Alzheimer: estrategia frente a la proteína β-amiloide. Neurología, 33(1), 47–58. https://doi.org/10.1016/j.nrl.2015.03.012

García-Morales, V., González-Acedo, A., Melguizo-Rodríguez, L., Pardo-Moreno, T., Costela-Ruiz, V. J., Montiel-Troya, M., & Ramos-Rodríguez, J. J. (2021). Current understanding of the physiopathology, diagnosis, and therapeutic approach to Alzheimer's disease. *Biomedicines*, *9*(12), 1–16. https://doi.org/10.3390/biomedicines9121910

Greenamyre, J. T., & O'Brien, C. F. (1991). N-Methyl-d-Aspartate Antagonists in the Treatment of Parkinson's Disease. *Archives of Neurology*, *48*(9), 977–981. https://doi.org/10.1001/archneur.1991.00530210109030

Haake, A., Nguyen, K., Friedman, L., Chakkamparambil, B., & Grossberg, G. T. (2020). An update on the utility and safety of cholinesterase inhibitors for the treatment of Alzheimer's disease. *Expert Opinion on Drug Safety*, *19*(2), 147–157. https://doi.org/10.1080/14740338.2020.1721456

Hane, F. T., Robinson, M., Lee, B. Y., Bai, O., Leonenko, Z., & Albert, M. S. (2017). Recent Progress in Alzheimer's Disease Research, Part 3: Diagnosis and Treatment. Journal of Alzheimer's Disease, 57(3), 645–665. https://doi.org/10.3233/jad-160907

Imbimbo, B. P., & Watling, M. (2019). Investigational BACE inhibitors for the treatment of Alzheimer's disease. Expert Opinion on Investigational Drugs, 28(11), 967–975. https://doi.org/10.1080/13543784.2019.1683160

Jahn, H. (2013). Memory loss in Alzheimer's disease. *Dialogues in Clinical Neuroscience*, *15*(4), 445–454. https://doi.org/10.31887/dcns.2013.15.4/hjahn

Jiang, T., Yu, J. T., Tian, Y., & Tan, L. (2013). Epidemiology and etiology of Alzheimer's disease: from genetic to non-genetic factors. Current Alzheimer Research, 10(8), 852–867. https://doi.org/10.2174/15672050113109990155

Kandiah, N., Pai, M. C., Senanarong, V., Looi, I., Ampil, E., Park, K. W., Karanam, A. K., & Christopher, S. (2017). Rivastigmine: the advantages of dual inhibition of acetylcholinesterase and butyrylcholinesterase and its role in subcortical vascular dementia and Parkinson's disease dementia. Clinical interventions in aging, 12, 697–707. https://doi.org/10.2147/CIA.S129145

Kartalou, G. I., Endres, T., Lessmann, V., & Gottmann, K. (2020). Golgi-Cox impregnation combined with fluorescence staining of amyloid plaques reveals local spine loss in an Alzheimer's mouse model. Journal of Neuroscience Methods, 341, 108797. https://doi.org/10.1016/j.jneumeth.2020.108797

Kumar, A.; Gupta, V.; Sharma, S. Donepezil. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2022.

Kuns, B. (2022, July 11). Memantine. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK500025/

Li, X., Feng, X., Sun, X., Hou, N., Han, F., & Liu, Y. (2022). Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2019. *Frontiers in Aging Neuroscience*, *14*. https://doi.org/10.3389/fnagi.2022.937486

Liu, Y., Zhang, Y., Zheng, X., Fang, T., Yang, X., Luo, X., Guo, A., Newell, K. A., Huang, X. F., & Yu, Y. (2018). Galantamine improves cognition, hippocampal inflammation, and synaptic plasticity impairments induced by lipopolysaccharide in mice. *Journal of Neuroinflammation*, *15*(1). https://doi.org/10.1186/s12974-018-1141-5

Long, J. M., & Holtzman, D. M. (2019). Alzheimer Disease: An Update on Pathobiology and Treatment Strategies. Cell, 179(2), 312–339. https://doi.org/10.1016/j.cell.2019.09.001

Mah, D., Zhao, J., Liu, X., Zhang, F., Liu, J., Wang, L., Linhardt, R. J., & Wang, C. (2021). The Sulfation Code of Tauopathies: Heparan Sulfate Proteoglycans in the Prion Like Spread of Tau Pathology. Frontiers in Molecular Biosciences, 8. https://doi.org/10.3389/fmolb.2021.671458

Mayeux, R., & Sano, M. (1999). Treatment of Alzheimer's Disease. *New England Journal of Medicine*, *341*(22), 1670–1679. https://doi.org/10.1056/nejm199911253412207

Mazhar, F., Battini, V., Gringeri, M., Pozzi, M., Mosini, G., Marran, A. M. N., Akram, S., van Manen, R. P., Radice, S., Clementi, E., & Carnovale, C. (2021). The impact of anti-TNFalpha agents on weight-related changes: new insights from a real-world pharmacovigilance study using the FDA adverse event reporting system (FAERS) database. Expert Opin Biol Ther, 21(9), 1281-1290. https://doi.org/10.1080/14712598.2021.1948529

Moreta, M. P. G., Burgos-Alonso, N., Torrecilla, M., Marco-Contelles, J., & Bruzos-Cidón, C. (2021). Efficacy of acetylcholinesterase inhibitors on cognitive function in Alzheimer's disease. Review of reviews. *Biomedicines*, *9*(11). https://doi.org/10.3390/biomedicines9111689

Nimmagadda, A., Shi, Y., & Cai, J. (2019). γ-AApeptides as a New Strategy for Therapeutic Development. Current Medicinal Chemistry, 26(13), 2313–2329. https://doi.org/10.2174/0929867324666171107095913

Overk, C. R., & Masliah, E. (2014). Pathogenesis of synaptic degeneration in Alzheimer's disease and Lewy body disease. Biochemical Pharmacology, 88(4), 508–516. https://doi.org/10.1016/j.bcp.2014.01.015

Pardo-Moreno, T., González-Acedo, A., Rivas-Domínguez, A., García-Morales, V., García-Cozar, F. J., Ramos-Rodríguez, J. J., & Melguizo-Rodríguez, L. (2022). Therapeutic Approach to Alzheimer's Disease: Current Treatments and New Perspectives. *Pharmaceutics*, *14*(6), 1–20. https://doi.org/10.3390/pharmaceutics140611172022

Rahman, M. R., Tajmim, A., Ali, M., & Sharif, M. (2017). Overview and Current Status of Alzheimer's Disease in Bangladesh. *Journal of Alzheimer's Disease Reports*, *1*(1), 27–42. https://doi.org/10.3233/adr-170012

Ramos-Rodriguez, J. J., Spires-Jones, T., Pooler, A. M., Lechuga-Sancho, A. M., Bacskai, B. J., & Garcia-Alloza, M. (2016). Progressive Neuronal Pathology and Synaptic Loss Induced by Prediabetes and Type 2 Diabetes in a Mouse Model of Alzheimer's Disease. Molecular Neurobiology, 54(5), 3428–3438. https://doi.org/10.1007/s12035-016-9921-3

Razay, G., & Wilcock, G. K. (2008). Galantamine in Alzheimer's disease. *Expert Review of Neurotherapeutics*, *8*(1), 9–17. https://doi.org/10.1586/14737175.8.1.9

Roy, N., Hassan, A.-M., Alom, R., Rajib, M. H. R., & Al-Mamun, K. A. (2020). The Situation of Alzheimer's Disease in Bangladesh: Facilities, Expertise, and Awareness among General People. *Journal of Neurological Disorders*, *8*(7), 1–7.

Sabbagh, M. N., & Cummings, J. (2020). Open Peer Commentary to "Failure to demonstrate efficacy of aducanumab: An analysis of the EMERGE and ENGAGE Trials as reported by Biogen December 2019." Alzheimer's &Amp; Dementia, 17(4), 702–703. https://doi.org/10.1002/alz.12235

Salloway, S., Sperling, R., Keren, R., Porsteinsson, A. P., Van Dyck, C. H., Tariot, P. N., Gilman, S., Arnold, D., Abushakra, S., Hernandez, C., Crans, G., Liang, E., Quinn, G., Bairu, M., Pastrak, A., & Cedarbaum, J. M. (2011b). A phase 2 randomized trial of ELND005, Scylla-inositol, in mild to moderate Alzheimer's disease. Neurology, 77(13), 1253–1262. https://doi.org/10.1212/wnl.0b013e3182309fa5

Sankar, S. B., Infante-Garcia, C., Weinstock, L. D., Ramos-Rodriguez, J. J., Hierro-Bujalance, C., Fernandez-Ponce, C., Wood, L. B., & Garcia-Alloza, M. (2020). Amyloid beta and diabetic pathology cooperatively stimulate cytokine expression in an Alzheimer's mouse model. Journal of Neuroinflammation, 17(1). https://doi.org/10.1186/s12974-020-1707-x

Saretz, S., Basset, G., Useini, L., Laube, M., Pietzsch, J., Drača, D., Maksimović-Ivanić, D., Trambauer, J., Steiner, H., & Hey-Hawkins, E. (2021). Modulation of γ-Secretase

Activity by a Carborane-Based Flurbiprofen Analogue. Molecules, 26(10), 2843. https://doi.org/10.3390/molecules26102843

Sato, K., Mano, T., Iwata, A., & Toda, T. (2020). Neuropsychiatric adverse events of chloroquine: a real-world pharmacovigilance study using the FDA Adverse Event Reporting System (FAERS) database. Biosci Trends, 14(2), 139-143. https://doi.org/10.5582/bst.2020.03082

Sheppard and Coleman, O. and M. (2020). Alzheimer's Disease: Etiology, Neuropathology, and Pathogenesis. https://www.ncbi.nlm.nih.gov/books/NBK566126/

Sheppard, O., & Coleman, M. (2020). Alzheimer's Disease: Etiology, Neuropathology, and Pathogenesis. *Alzheimer's Disease: Drug Discovery*, 1–22. https://doi.org/10.36255/exonpublications.alzheimersdisease.2020.ch1

Soeda, Y., & Takashima, A. (2020). New Insights into Drug Discovery Targeting Tau Protein. Frontiers in Molecular Neuroscience, 13. https://doi.org/10.3389/fnmol.2020.590896

Thomas, S. J., & Grossberg, G. T. (2009). Memantine: A review of studies into its safety and efficacy in treating Alzheimer's disease and other dementias. Clinical Interventions in Aging, 4, 367-377. https://doi.org/10.2147/cia.s6666

Toombs, J., & Zetterberg, H. (2021). Untangling the tau microtubule-binding region. Brain, 144(2), 359–362. https://doi.org/10.1093/brain/awaa468

Van Puijenbroek, E., Diemont, W., & van Grootheest, K. (2003). Application of quantitative signal detection in the Dutch spontaneous reporting system for adverse drug reactions. Drug Saf, 26(5), 293-301. https://doi.org/10.2165/00002018-200326050-00001

Vellas, B., Sol, O., J. Snyder, P., Ousset, P. J., Haddad, R., Maurin, M., Lemarie, J. C., Desire, L., & P. Pando, M. (2011). EHT0202 in Alzheimer's Disease: A 3-Month, Randomized, Placebo-Controlled, Double-Blind Study. Current Alzheimer Research, 8(2), 203–212. https://doi.org/10.2174/156720511795256053

Vestergaard Kvist, A., Faruque, J., Vallejo-Yague, E., Weiler, S., Winter, E. M., & Burden, A. M. (2021). Cardiovascular Safety Profile of Romosozumab: A

Pharmacovigilance Analysis of the US Food and Drug Administration Adverse Event Reporting System (FAERS). J Clin Med, 10(8). https://doi.org/10.3390/jcm10081660

W.B., G., A., C., R.F., I., & J., S. (2002). The significance of environmental factors in the etiology of Alzheimer's disease. Journal of Alzheimer's Disease, 4, 179–189. http://www.scopus.com/inward/record.url?eid=2-s2.00036592523&partnerID=40&md5=b551d6859628b75fe28e3fc7b2371e7b

Waite, L. M. (2015). Treatment for Alzheimer's disease: Has anything changed? *Australian Prescriber*, *38*(2), 60–63. https://doi.org/10.18773/austprescr.2015.018

Wisniewski, T., & Goñi, F. (2015). Immunotherapeutic Approaches for Alzheimer's Disease. Neuron, 85(6), 1162–1176. https://doi.org/10.1016/j.neuron.2014.12.064

Yiannopoulou, K. G., & Papageorgiou, S. G. (2012). Current and future treatments for Alzheimer's disease. Therapeutic Advances in Neurological Disorders. https://doi.org/10.1177/1756285612461679

Yiannopoulou, K. G., & Papageorgiou, S. G. (2020). Current and Future Treatments in Alzheimer Disease: An Update. Journal of Central Nervous System Disease, 12, 117957352090739. https://doi.org/10.1177/1179573520907397

Zeevalk, G. D., & Nicklas, W. J. (1992). Evidence that the Loss of the Voltage-Dependent Mg2+Block at the N-Methyl-D-Aspartate Receptor Underlies Receptor Activation During Inhibition of Neuronal Metabolism. Journal of Neurochemistry, 59(4), 1211–1220. https://doi.org/10.1111/j.1471-4159.1992.tb08430.x