Gender-Specific Rhabdomyolysis Risk in Alzheimer's Disease Patients Receiving Memantine: A Pharmacovigilance Study

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.)

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BRAC University
October 2023

Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing a 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 thesis titled "Gender-Specific Rhabdomyolysis Risk in Alzheimer's Disease Patients Receiving Memantine: A Pharmacovigilance Study" **s**ubmitted by Nadira Tabassum (19346012) of Summer, 2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on October 2023.

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Ethics Statement

In the whole study, no animal models were used nor did any human subjects take part in the study for clinical purposes, hence no sort of unethical occurrence happened.

Abstract

Alzheimer's disease is a neurodegenerative disease. Using FDA Adverse Event Reporting System database, a pharmacovigilance study for gender specific rhabdomyolysis risk in memantine users was conducted between January 2016-June 2023. "R" statistical tool was used to calculate the reporting odds ratio (95%CI), which serves as a signal index. Memantine showed a signal, when the whole dataset is used as a comparator, but not when AChEIs are used. ROR,95% CI value for male memantine consumers 5.68 (2.12 - 15.19), for female 7.98 (2.55-24.70) while using whole dataset as comparator. Again, male patients value is 1.40 (0.46 - 4.26), whereas 2.53 (0.65 - 9.83) for females, using AChEIs as comparator. Females have a higher risk of developing rhabdomyolysis than males as the ROR value was higher for them in both comparisons. Thus, data shows memantine has a safer, more acceptable profile than AChEIs & can be considered in comparison to other options.

Keywords: Pharmacovigilance; Alzheimer Disease; Dementia; Memantine; Rhabdomyolysis.

Dedication

Dedicated to my parents and my nanu, Engineer, Nazrul Islam Bhuiyan

Acknowledgement

Before everything, I want to thank the most merciful Allah for giving me the strength to go through the hardships and for everything in my life.

It is a great pleasure to acknowledge my sincere gratitude to my supervisor, the honorable Assistant Dean of the School of Pharmacy, BRAC University, Professor Dr. Hasina Yasmin for the support, enthusiasm, and encouragement she gave and how she showed us the right track, monitored us throughout the journey.

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List of Acronyms

PSEN1	Presenilin-1
PSEN2	Presenilin-2
Aph1	Anterior pharynx-defective 1
APP	Amyloid protein precursor
AChEI	Acetylcholinesterase inhibitor
ROR	Reporting Odds Ratio
CI	Confidence Interval
Aβ	Amyloid Beta
MedDRA	Medical Dictionary for Regulatory Activities
AD	Alzheimer's disease
FAERS	FDA Adverse Event Reporting System

Chapter 1

Introduction

1.1 Alzheimer’s Disease: Brief Summary

Alzheimer's disease (AD) which is an incurable developing neurodegenerative ailment due to intracellular neurofibrillary tangles which is a kind of beta amyloid accumulation, extracellular plaques which leads to inevitable neurodegeneration and dementia. and is perhaps a typical type of dementia in older patients mainly (Jeremic et al., 2021; Koola, 2020). Neuronal function becomes compromised, resulting in a slow worsening in cognition, learning and behavior that finally results in death. Alzheimer's disease involves language skills, reduction of thinking capability, memory skills, personality changes, including sort of changes to the brain which gradually worsen over time. The basic daily duties become gradually harder to perform due to AD. It can be diagnosed as a delayed outcome of AD, which is responsible in case of higher than 90% of cases, or a symptom that appear autosomal dominant type caused by known alteration in the presenilin as PSEN1, PSEN2, APP, ApoE-4. While there is little question that genes play a precious part in the occurrence during late-onset of AD, their heritability here ranges from 58 to 79%, and with up to 90% accuracy, nowadays polygenic risk scores can diagnose AD. As many as 81 million human beings worldwide will be suffering from dementia by 2040, and almost all of them will experience Alzheimer's disease. A growing elderly population is partially responsible for the rise in dementia cases. A report of the findings of the Alzheimer's Association (2017), each year's economic spending will be much higher than $270 billion, due in part to our unsuccessful efforts to prevent, delay, or slow down the advancement of this fatal condition. As the executive, the memory role deficits associated with AD invariably worsen regardless of

therapy, they can have a major impact on many aspects of everyday functioning. Even though AD makes up almost two thirds of the report coming from dementia and is the most established type of dementia, it can be hard to identify and diagnose AD in its early stages. Following cardiovascular and cerebrovascular disorders, malignant tumors, and AD, these conditions are now the third and third-leading causes of disability and death among the elderly (Chu, 2012).

Reports of the Alzheimer's Association suggested, usually seven phases are present in Alzheimer's Disease development. The very initial stage is "no impairment." stage 2 is distinguished by “very mild decline"; although there are memory lapses, neither others' views nor a medical examination reveals any other symptoms. Instead of AD, these symptoms could be caused by aging-related changes. In the third stage, known as "mild cognitive decline," people start to recognize that they have memory issues. Some patients with modest cognitive impairment may be diagnosed with AD, but not all of them. The person declines from medium to severe in phases 4–7. The development and course of AD differ greatly from person to person. Alzheimer's disease should be diagnosed by a qualified medical professional because various disorders require different approaches. Although there are a number of symptomatic drugs available with only minor benefits for cognition, there is currently no disease-modifying therapy. All phases of dementia may benefit from acetylcholinesterase inhibitors, nevertheless, their clinical efficacy for the patients having mild cognitive impairment and forwarding towards Alzheimer’s has not been substantiated. Memantine barely improves cognition overall and only in moderate to severe stages. When used alongside a cholinesterase inhibitor, memantine may be beneficial. Although there is little verification establishing the therapeutic benefits of vitamin E supplements and medicinal foods, they may be taken into account in terms of cost, accessibility, and patient safety. Recently, seemingly effective disease-modifying therapies that largely addressed the amyloid cascade concept of AD have

failed to show effectiveness, forcing the consideration of alternative approaches (Watwood, 2011).

1.2 Alzheimer Disease: Key Clinical Characteristics

Some clinical characteristics are defined to be known signs of AD as transformation of personality. More frequently things common in moderate stage AD as emotional symptoms and disruptive behaviors such as restlessness may worsen. Non-cognitive symptoms also known as behavioral and psychological symptoms of dementia (BPSD), are very frequently seen in AD patients. In 10-75% of Alzheimer patient tend to show dysphoria (sadness, depressed state of mind), irritability, hallucinations, anxiety, social withdrawal, euphoria, apathy, sunset, sleep disturbance, disinhibition, suspiciousness, delusions, disturbing behavior, pacing and stereotypic or repetitive behavior, aggression (physical or can be verbal). In addition to cognitive and behavioral symptoms, there may be early somatic symptoms. Progressive weight loss along with a low body mass index are early symptoms (Chu, 2012).

1.3 Pathophysiology Based on Alzheimer's Disease Hypothesis

Alzheimer's disease is a severe disease that has several relevant variables. The precise underlying reason for Alzheimer's disease is still unknown due to the complicated nature of the human brain and the shortage of rational animal models and research tools.

1.3.1 Aβ Cascade Hypothesis

The amyloid cascade hypothesis states that it triggers neurodegeneration in Alzheimer's patients' brains. are due to aberrant buildup of amyloid beta plaques in distinctive places of the brain. Due to the appropriate cleavage of APP, soluble ectodomains are released, which regulate cell survival, proliferation, and motility as well as neurite outgrowth and functions.

APP is made up of 770 amino acids among them amyloid beta has 28 residues and extra 14 residues originating out of the transmembrane area. The C-terminal fragment, termed C83 resides in the membrane where it gets degraded with the help of γ-secretase at residue 711 so that soluble P3 peptide can get released. Then in the place where cleavage occurs, γ-secretase cleaves releasing some massive soluble ectodomain APPs into the channel. In contrast, aberrant cleavage occurs due to β-secretase, releasing short length APPs at the time of disease condition and C-terminal fragment termed "C99" is maintained in the membrane and further cleaved via γ-secretase which forms insoluble Aβ peptides. Following C83 and C99 are degraded down via γ-secretase, the APP intracellular domain name flows into the cytoplasm, where it's made soluble and proceeds to nuclei to perform additional gene-expression tasks. APP is cut down distinctly in distressed states. BACE-1, a membrane-spanning aspartyl protease with a binding location in the lumen, as well as γ-secretase, an intramembrane aspartyl protease composed of four proteins: Nicastrin, presenilin also anterior pharynx-defective 1 (Aph1) PSEN2, split APP to release amyloid beta. This combination increases γ-secretase hustle and bustle, causing the formation of not soluble & potentially hazardous Aβ fragments. β -secretase cleavage is the first and critical step, requiring cutting off Aβ's N-terminus. The largest part of the protein's extracellular area disappears, exhibiting the APP C-terminus. This C terminal of Aβ then gets further cleaved, resulting in the creation of Aβoligomers, which afterwards polymerize to form aggregated plaques. A metabolic waste product called beta amyloid can be found in the space between brain cells. These group together to produce amyloid plaques in the case of AD, which ultimately trigger neuroinflammation and destruction of neural connectivity (Tiwari et al., 2019). In addition, mounting evidence shows that this fragile peptide is essential for the physiological mechanisms involved in memory formation. The report of the past 25 years illustrated that to cause neuronal death within a range of in vivo and in vitro, along with having synaptotoxic

effects, the reasons are mainly some of Aβ, including insoluble aggregates, oligomers and soluble dimers. Regarding the original premise, however, it is currently believed that the first and foremost reason of the neurodegenerative condition is due to soluble Aβ peptides more than insoluble fibrillar aggregates as they appear to more closely correlate with AD symptoms and severity. Hence, a primary target for therapy to manage AD is amyloid beta pathology considering Aβ mainstay for neurotic and synaptic degeneration. Additionally, inhibition of Aβ-production via β- or γ secretase inhibition and active and passive vaccination contrasting with Aβ appear to be promising ways (Ricciarelli & Fedele, 2017).

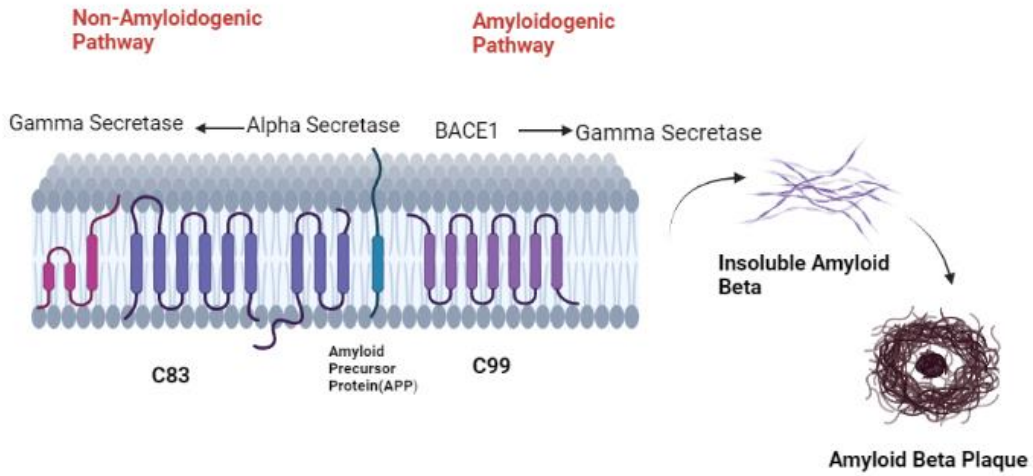

Figure 1: Aβ cascade hypothesis (Tiwari et al., 2019)

1.3.2 Tau Hypothesis

Tau protein encounters neurological changes, which leads to the generation of neurofibrillary tangles (NT) and paired helical filaments (PHF), two of the main distinguishing symbols of Alzheimer's disease and other tauopathies. Tau protein is an element of the microtubule-associated protein (MAP) family, which may disrupt development, axonal growth, neuronal polarization, and, subsequently, neuronal function and normal brain functions. Tau is a

component of the microtubule-related proteins that determines how stable tubulin polymerization processes. There is a human tau gene location on chromosome 17. Six tau isoforms arise in the adult human brain as the outcome of mRNA alternative splicing, whether or not they have exons 2, 3, and 10. It was proposed over a decade ago to suggest that since diverse tau isoforms operate differently within growing and aging brains, they might possess distinct functions. Alternative splicing has been identified varying between several kinds of neuronal cells as well as neurons develop. Exon 10 comprises the microtubule-binding region. Exon 10 is inserted to generate 4-repeat (4R) tau isoforms, however not to generate 3-repeat (3R) tau isoforms. The adult human brain generates either 3R and 4R tau isoforms, and these are primarily located in the axons of adult neurons during physiologically normal conditions. In accordance with the tau hypothesis, tau is the main contributory factor of Alzheimer's disease. 3R and 4R tau aggregates in a hyperphosphorylated state in the pathological acceptance of AD brains (Kametani & Hasegawa, 2018; Sinsky et al., 2021).

In addition, the four parts of tau are the microtubule-binding domain (MBD), C-terminal and region the proline-rich domain (PRD). Through alternative splicing of exons 2, 3, and 10 in the human tau gene (MAPT), which has 16 exons, causes formation of six isoforms. Ideally, phosphorylation assists in maintaining the cytoskeletal integrity and the tau protein has eighty-five possible threonine (T), serine (S), tyrosine (Y) phosphorylation sites. Generally, about 45 distinct tau phosphorylation sites are noticed in the brains of Alzheimer's disease patients. Also, it’s been recommended that abnormal tau phosphorylation contributes to the physiopathology of AD. Tau grows hyperphosphorylated which detached from microtubules under physiological conditions. Then, phosphorylated tau sticks together to form NFTs and paired helical filaments (PHFs) (Gong & Iqbal, n.d.).

In a mouse and cultured cell-based experimental paradigm, aberrant tau (fibril tau like amyloid) converts to abnormal condition. Thus, it has been speculated that in brain cells only

a small amount of tau is aggregated, before spreading to other locations and causing illness and neurodegeneration. Because it has been demonstrated that tau multiplies and spreads between cells, this concept has recently attracted attention. It has been hypothesized that various molecular conformers (or strains) of aggregating tau occur because of the development of numerous human tauopathies with distinctive fibril morphologies (Kametani & Hasegawa, 2018).

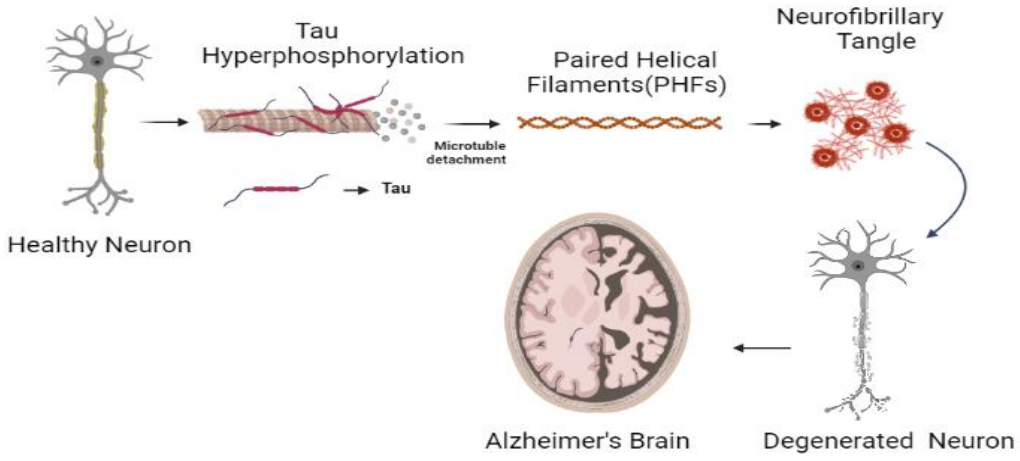

Figure 2: Tau Hypothesis modified (Gong & Iqbal, n.d.)

1.3.3 Cholinergic and Oxidative Stress Hypothesis

One of the most prevalent theories about AD is the cholinergic hypothesis, as an absence of this neurotransmitter disrupts memory and learning. Attention, memory, learning, sensory information, additionally some more essential functions are only a few of the physiological parts in which ACh acts an important role in the brain. Degeneration of the cholinergic neurons leads to altered cognitive and memory functions, which occurs in AD. Experimental studies investigating AD diagnosed brains as subjects revealed distinct parts of the cerebral cortex showed decreased activity. It is feasible to mention choline acetyltransferase-related activities

in this context. It's interesting to note that an in vitro study indicates the A peptide inhibits cholinergic neurotransmission. Additionally, additional studies showed that cognitive function is decreased when the number of muscarinic, nicotinic acetylcholine (ACh) receptors in presynaptic cholinergic sections diminishes. It should be emphasized that the key therapeutic target for the cholinergic theory is the acetylcholinesterase (AChE) enzyme (Breijyeh & Karaman, 2020).

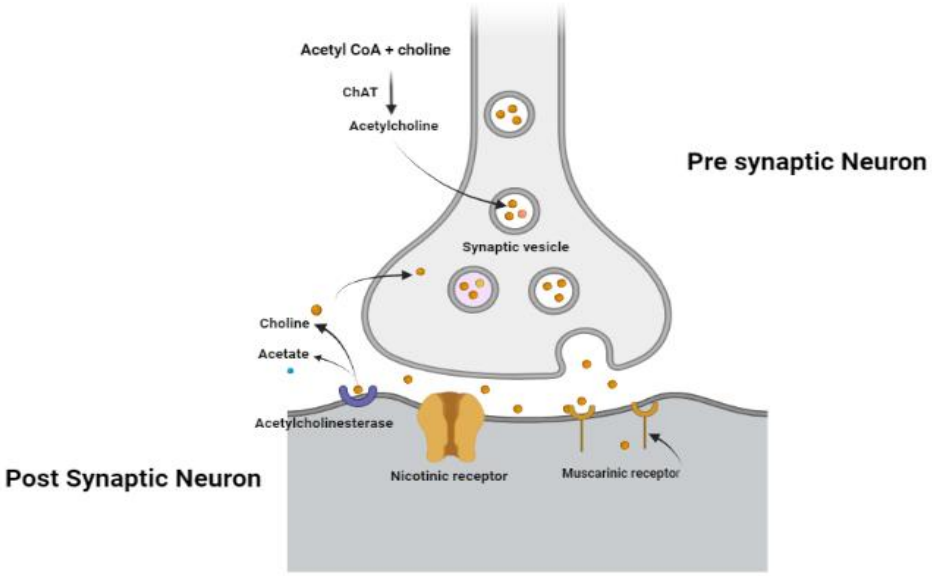

Figure 3: Cholinergic Hypothesis (Min et al., 2022)

1.4 Alzheimer's Disease: Prevalence and Impact

Approximately 8% of people over 65 and 30% of those over 85 have the condition, making age a significant risk factor. The prevalence of AD is predicted to quadruple over the next 50 years as the baby boomer population ages more rapidly in affluent nations. Age is considered to be a mainstay risk factor for AD. Symptoms typically appear after the age of 60 for unidentified reasons. About 1 in 8 adults, within the age 65-74, have Alzheimer's disease. The number of those affected doubles among patients who are at the age of near 70, and over half

of those over the age of 85 are impacted by AD. The risk of AD may also be increased by a person's genetic composition. A person's risk of acquiring Alzheimer's disease (AD) can be also due to the contribution of genetic inheritance, which is a typical form of the condition, that appears after the age of 60, but they cannot ensure that they will. For instance, those who carry one or two copies of the gene APOE e4 are more likely to get the condition. Between the ages of 30 and 60, an uncommon, early-onset variant of Alzheimer's disease (AD) manifests itself in family clusters. There are less than 5% occurrences of the earliest outbreak of AD, which is thought to be caused by genetic abnormalities. To add with, male is less likely to get AD compared to females, and there are gender disparities in sensitivity, age of onset, as well as clinical development. The findings of the most recent WHO study, females are more prone to have Alzheimer's disease and other kinds of dementia, account for approximately 65% of all dementia deaths worldwide. Nevertheless, the prevalence is not larger, implying that both appeared to be just as susceptible (Jeremic et al., 2021; Watwood, 2011).

1.5 Biomarkers of Alzheimer's Disease

A vast array of clinical trials over and over show that biomarkers convey scientifically relevant information, throughout the early stages of disease. Recent improvements in technology have made possible the evaluation of several of these biomarkers employing fully automated analyses with excellent accuracy, consistency. The aggregated form of hyper phosphorylated tau protein and the extracellular deposition of amyloid-β (Aβ) within the brain constitute the two key pathogenic characteristics related to Alzheimer's disease. The plasma Aβ42/Aβ40 ratio, Aβ-PET or CSF stand for Alzheimer disease in the brain. Tau-PET imaging and, to a lesser extent, CSR P tau and plasma demonstrate tau-tangle pathology in Alzheimer's disease. Nevertheless, plasma P-tau and CSF have the potential to reflect increased tau production and phosphorylation that happens due to AD (Hansson, 2021).

1.5.1. AD Pathology Biomarker: Positron Emission Tomography (PET)

A sort of molecular imaging termed Positron emission tomography (PET) can reveal the functional and structural changes in the brain that are actually occurring. Other than that, the stage of AD can be categorized by analyzing numerous pathophysiological changes with the help of PET. Applying the radioactive tracer 18F-fluorodeoxyglucose (FDG-PET), the technique can assess the metabolism of the brain across different portions (Hansson, 2021)

1.5.2. AD Pathology Specific CSF Biomarkers

Due to a lower dilution of the protein content or proximity towards the brain, makes CSF a great source of biomarkers. Additionally, the biochemical alteration occurs in the brain parenchymal tissue can be seen with this biomarker. Recent studies have proven that plasma and CSF protein biomarkers are useful diagnostic tools for Alzheimer's disease (Hansson, 2021)

1.6 Current Supervision of AD

At present FDA-approved symptomatic drugs for Alzheimer's disease are there in addition to a recently beneficial drug " Aducanumab" that has been approved. Yet, there are no preventive or therapies. Patients can also get advantages of non-pharmacologic approaches towards treatment, such as cognitively stimulating activities like physical exercise like walking, then reading and interpersonal skills like family gatherings. Despite research suggesting that nutritional status may play a role in Alzheimer's disease, it is unknown which dietary approach produces the best neuroprotective effects. Other actions include brain training, physical activity, social engagement is also noticed. A collaborative strategy may be far more successful than any individual approach (Folch et al., 2018)

1.6.1 Psychoeducation

Psychoeducation is something that helps to enhance their knowledge of mental health and good health. For a caregiver who is responsible towards an AD patient must have psychoeducation, it is a non-pharmaceutical way for dementia patients. In the initial stage of Alzheimer's this is an important tool for caregivers to enhance their knowledge. Multiple outcomes are observed due to these as psycho behavioral disorders are seen to be reduced, lessening in the rate of nursing home placement, most importantly a new door to caregivers as it aids in the well-being of patients of AD (Atri, 2019).

1.6.2 Behavioral Approaches and Strategies:

Some behavioral tactics can be advised, both in general and with regard to the patient-caregiver, for example creating a calm, safe environment with consistent care, pleasurable environment, maintained daily routines, and reassurance. Importantly, providing only necessary information at an appropriate time in a manner that the patient can go through (i.e., in brief and small chunks) (Atri, 2019).

1.6.3 Ketogenic Diet:

The ketogenic diet (KD) is considered a particular diet that has a correlation with neurodegenerative disease. Although, in the beginning this diet was mainly prescribed to the e treatment of epilepsy, currently it is also advised to AD patients. A normal diet and supplementing it with ketogenic agents for example, medium chain triglycerides (MCT) can also help to achieve results. Quality of life, daily activities of AD patients can be improved by this diet which was found in a newly recent, small, randomized, cross-over trial in New Zealand. Additionally, stress proteins such as GRP78 and HSP70 activated via low levels of

carbohydrates, which also partly reduces ROS and supports mitochondrial activity, (This dysfunction is an indication in the pathogenesis of AD (Hersant & Grossberg, 2022).

1.7 Pharmacological Interventions to Treat AD: FDA Approved

Since the specific processes and pathways of AD are still not fully understood, a significant number of treatment approaches have failed. At the moment, three medications are prescribed to manage the sign of AD and setbacks the development: N methyl D-aspartate receptor antagonists (NMDRAs), cholinesterase inhibitors and nowadays mostly prescribed combination therapy. The reduction of the neurotransmitter is considered to be the key contributing factor to AD, as cholinesterase inhibitors aid in the increase the amount of Ach. Cholinergic inhibitors including galantamine, tacrine donepezil, and rivastigmine are recommended to do this. These inhibitors constrain the brain's ability to produce less Ach. The NMDA receptor is supposed to enable calcium ions to enter to facilitate neurotransmission. Conversely, during AD, the receptor causes excess activity, which results in an excess of Ca2+, which causes excitotoxicity and cell death. Memantine, an anti-AD medication that links in the active form of the NMDA-receptor which plays as a non-competitive antagonist to regulate the elevated activity of the receptor. Donepezil and memantine (10 mg and 28 mg, respectively, once a day) have been administered as combination therapy with success to manage moderate-to-severe AD patients' language, behavioral and cognitive symptoms. Results were noticeably superior to placebo, which was a mixture of memantine along with placebo. Yet, for patients facing mild as well as moderate disease the combination was not that much beneficial (Chu, 2012).

Table 1: Potent Acetylcholinesterase Inhibitors (Chu, 2012)

Current Drug Therapy	**Mechanism of Action**	**Metabolism**
Donepezil	Reversibly binding to acetylcholinesterase acetylcholine hydrolysis is inhibited causing increase of the concentration of ACh at synapses.	CYP2D6 CYP3A4
Rivastigmine	Functions by linking to both active sites of AChE (anionic sites and stearic) causing a block of the metabolism of ACh	Non-hepatic
Galantamine (GAL)	Linking allosterically to the -subunit of nicotinic acetylcholine receptors, it can work as a competitive inhibitor of AChE.	CYP2D6 CYP3A4

1.8 Purpose of the Study

Approximately, 24 million people worldwide are considered to have dementia, among them the majority of them are thought to have Alzheimer's disease that makes Alzheimer's disease as a public alert, a major public health concern. Hence, more research should be conducted regarding this. Although there are several licensed treatments that can manage symptoms of Alzheimer's disease, still there is an emerging need to expand our vast wisdom regarding pathogenesis to build up effective disease-modifying treatments. Currently, memantine is considered as one of the five major drug therapies involved in slowing progression of AD. Memantine acts in different pathways rather than other commonly used treatments of AD. In our research, the focus is on the analysis based on FAERS data, the cases of adverse

event rhabdomyolysis association with our particular data Memantine compared to other drug classes such as AchEIs (donepezil, rivastigmine, galantamine).

1.9 Future Perspective on Therapies for AD

Evidently have been endless clinical trials using different medicines that have failed in the fifteen years prior. The most recent immunotherapy discoveries are motivating but there are still plenty of obstacles to overcome. Although several anti-Aβ medications have successfully reduced the load of Aβin clinical studies, only modest gains in minimizing cognitive decline are being observed. As an outcome, we've found that anti-amyloid therapy isn't the only option, but it should be paired with other medications which focus on various factors. These causes could include tau pathology, mitochondrial malfunction, inflammation, and many more, judging by experimental and medical research. Concentrating on aspects present in early and preclinical Alzheimer's disease stages, in particular, could be a more effective approach for combining treatment with anti-amyloid medications. In a comparable manner the substantial number of clinical studies against Aβ have brought attention to numerous major existing issues in AD clinical trials that must be overcome for potentially more effective disease-modifying medicines to lessen disease development. Additionally, some barriers are also considered for further research as the difficulty of objectively and quantitatively assessing the degree of cognitive impairment, timing of treatment, the lack of highly reliable biomarkers and specifically, early biomarkers, Aβ accumulation such as of APOE and familial history related to Alzheimer’s, the right targets and their brain penetration (Jeremic et al., 2021).

Table 2: Currently on trial drugs for Alzheimer's (Breijyeh & Karaman, 2020)

Drug	**Mechanism of action (In Phase III Clinical Trial)**
Aducanumab	a monoclonal antibody that targets Aβ-amyloid, then removing it
Thiethylperazine (TEP)	Turning on ABCC1 (ATP binding cassette subfamily C member 1 transport protein), then clears beta amyloid plaques. .
Gantenerumab	a monoclonal antibody which by attaching removes the Aβ-amyloid.
BHV4157 (tro riluzole)	A Glutamate modulator which decreases synaptic levels of glutamate, ultimately aiding in better synaptic functioning.
Daratumumab	a monoclonal antibody or immunomodulatory that targets CD38 along with balancing microglial activity.

Chapter 2

Drug Information

Memantine, expressed as mem' a teen, is considered as primary clinically available glutamate antagonist, with an antagonist action at the N-methyl-D-aspartate receptors in the brain, for correction of behavioral and cognitive functions associated with neurodegenerative disorders. Studies found glutamate to cause excitotoxic neuronal damage in Alzheimer's disease (AD), including in parkinsonism-related dementias. Hence, memantine represents a novel mode of action to hinder excitotoxicity of the glutamate

It is suggested by study that memantine plays a role as low-to-moderate affinity noncompetitive (open-channel) which is voltage dependent mainly an N-methyl-D-aspartate (NMDA) receptor antagonist, which binds preferentially to NMDA receptor that works with calcium channels. Furthermore, memantine blocks the excess, toxic levels of glutamate that are actually the culprit behind neuronal dysfunction. In addition, whenever a strong signal is initiated, memantine may also upregulate NMDA receptor expression. Nonetheless, the therapeutic benefits of memantine administration in patients with AD is worthy.

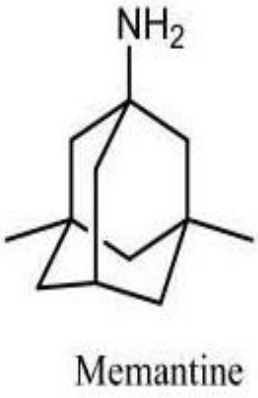

*Figure 4: Chemical structure of memantine(*Memantine Hydrochloride | LGC Standards, *n.d.)*

2.1 FDA Approval of Memantine for Alzheimer's Disease

On 16 October of 2003, The Food and Drug Administration (FDA) approved memantine, commercially named as “Namenda”. for treatment of moderate to severe Alzheimer's Disease. The previously available treatments as AChEIs for Alzheimer’s Disease have been studied among mild to moderate patients. Also, memantine’s mechanism of action is distinct from that of other drugs currently available for treating this disease. To add with, “Namenda” is in tablet form of memantine HCL (generic name) which is the first approved drug of memantine, manufactured by Forest Laboratories Inc.

2.1.1. Mechanism of Action of Memantine

Memantine, IUPAC name as 1-amino-3,5-dimethyladamantane, an amantadine derivative which is a non-competitive NMDA receptor antagonist which has a low to moderate affinity for NMDA receptors. NMDARs are a kind of ionotropic glutamate receptors that are situated in almost all vertebrate excitatory synapses. NMDARs are centrally involved in fundamental nervous system functions including memory, learning, cognitive behavior. These are also heteromeric ligand-gated ion channels composed of four subunits. NR1, NR2 and NR3 are the subunits of NMDAR. Functional glutamate-dependent NMDARs must contain NR1 and NR2 subunits for the activation. Usually, NR3 subunits do not imply any importance regarding NMDA properties. NMDARs require two types of agonists for channel activation, one is glutamate site agonist at NR2 subunits, another one is a glycine site agonist at NR1 subunits. Production of beta-amyloid proteins in the brain of an AD patient causes excessive levels of extra-synaptic glutamate levels by inhibiting glutamate uptake. Binding of the glutamate to the NMDA receptor causes influx of Ca, in addition monovalent cations as Na+, K+, these intracellular increase of calcium acts as secondary messenger causing intracellular signaling cascade which controls membrane excitability and synaptic transmission. NMDA receptors

work as calcium [II] ion (Ca2+) channels by binding to glycine and glutamate sites. However, the cell membrane needs to be depolarized for the magnesium [II] ion (Mg2+) to block the channel. As a consequence, when the neuron is at rest, there isn't any Ca2+ inflow. Mg2+ exits the channel in pathological circumstances, such as a membrane that is continuously depolarized, which inhibits neuronal metabolism. In this case for prolonged time the Ca2+ flow is uncontrolled than usual. This increase in Calcium 2+ concentration accelerate modifications in how cells function, which can cause them to stop functioning from free radicals or from being overloaded with mitochondria, resulting in the release of apoptosis-inducing proteins, the activation of caspases, and free radical production. Studies related to drug memantine shows only in the absence of Mg^{2+} the memantine can block the channel flow. Thus, correlation among memantine with Mg^{2+} should be further investigated. As it happens, Mg^{2+} and memantine cannot bind simultaneously, Mg^{2+} and memantine will have to compete for binding(Folch et al., 2018; Kishi et al., 2017; Matsunaga et al., 2018).

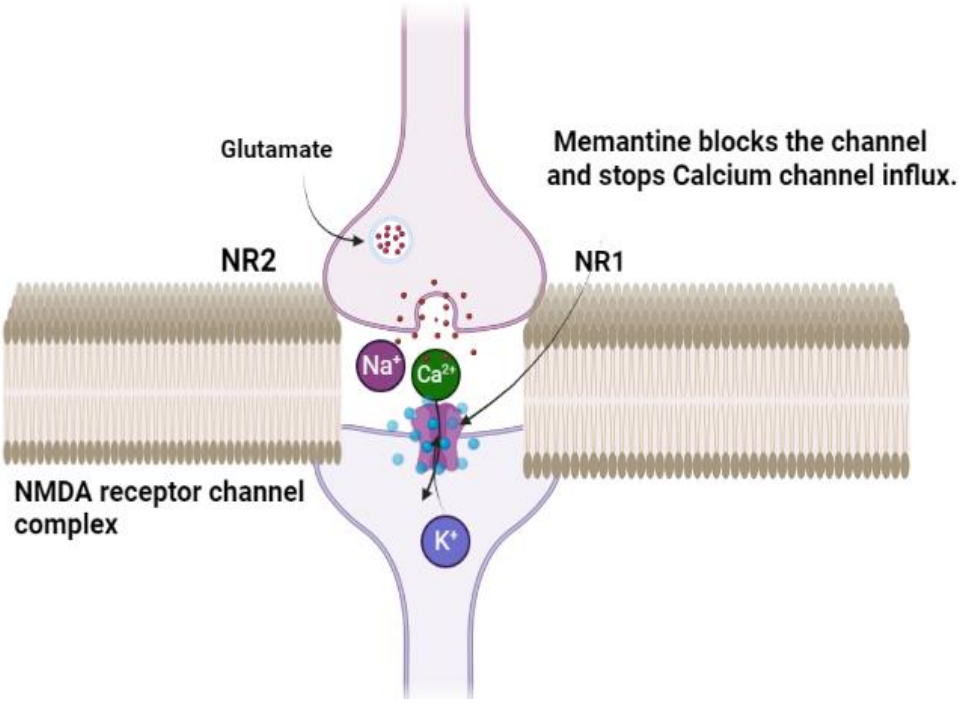

Figure 5:Mechanism of action of Memantine, modified from (Witt et al., 2004)

2.2 Dosage and Administration

NAMENDA is the first brand name drug of this class. Initially, daily 5 mg for once is the suggested starting dose. Usually with 5mg increments the doses administrations should be as 10 mg/day (5 mg twice daily), 15 mg/day (5 mg and 10 mg as separate doses), and 20 mg/day (10 mg twice daily), keeping in mind that there should be minimum one week gap among dose increments. In controlled clinical trials, the effective dose was found to be 20 mg/day. It can be given with or without food. If any patient misses a single dose, then the following dose should not be doubled. Hence, the following dose should be taken on time. Also, if a patient forgets to take medicine many times, then dosing may need to be resumed at reduced levels and re-titrated accordingly as mentioned. Moreover, any liquid as water cannot be mixed with the oral solution. The oral solution is administered using dosage equipment that is given with the medication package such as tubing, a syringe, syringe adaptor cap, tubing, and also many other supplies needed to administer the drug. The supplied syringe should be used to withdraw the administered volume of oral solution of drug, which should then be slowly squirted into the patient's mouth corner. Starting and target doses for memantine in immediate-release form are 5- 20 mg/day, which subsequently should be increased by 5 mg increments.

Memantine is available in an extended-release version which is legalized only in the United States, an FDA approved medicine, the starting and target doses of 7 mg/day and 28 mg/day, The dose should be sequentially raised up-to 7 mg range increments(Kuns et al., 2023).

2.2.1 Dosage Form and Strength:

Usually, two dosage 10 mg tablets, and another one 5mg tablets are on the market and both are capsule shaped. Also, an oral solution 2 mg/mL is found, which does not consist of alcohol and sugar. and have a slight smell of peppermint (Williams & Buvanendran, 2022).

2.2.2 Side Effect Profile:

The more common side effects that can occur with memantine include headache and drowsiness, dizziness. To add, constipation, dyspnea, hypersensitivity, balance disorders, hypertension, dyspnea, elevated liver function test are also observed as adverse events.

2.3 Pharmacokinetic Profile

2.3.1 Absorption of Memantine

About around 100% absolute bioavailability with a T-max of 3- 7 hours is seen in the absorption profile of memantine. There is no evidence that food can cause any alteration in memantine absorption. Memantine is a non-competitive low-affinity NMDA receptor antagonist with a t (1/2) of 70 h. A peak concentration is attained within 3-7 hours due to memantine oral treatment. Additionally, over a therapeutic drug range linear pharmacokinetics can be observed. Food has no effect on memantine absorption (fda & cder, n.d.).

2.3.2 Distribution of Memantine

20 mg of memantine for mild to moderate Alzheimer's disease have significantly improved mood, cognition including capacity to do regular tasks. A steady-state plasma concentration ranging from 70-150 ng/ml (0.5 to 1 mol) can be achieved by a daily dose of 20 mg but with a significant interindividual variation. Daily dosages ranging from 5-30 mg shows approximately

a CSF/serum ratio of 0.52 within cerebrospinal fluid. Memantine has a volume of distribution largely in the kidney, brain and lung ranging 9-11 L/kg, including 45% of memantine is linked to plasma proteins (fda & cder, n.d.).

2.3.3 Biotransformation of Memantine

In some data, no association of the hepatic microsomal CYP450 enzyme system has been seen in the metabolism of memantine. Also, the parent compound accounts for approximately 80% of the circulating memantine-related material in humans. In humans, the primary metabolites due to memantine are isomeric combinations of 4- and 6-hydroxy-memantine, and 1-nitroso-3,5-dimethyl-adamantane and N-3,5-dimethyl-gludantan which does not consist of NMDA-antagonistic activity. In vitro studies showed no cytochrome P450-catalyzed metabolism. In one trial, 84% of the dosage of orally administered memantine was recovered within 20 days where more than 99% was eliminated. Usually, it is partially metabolized in the liver.

2.3.4 Elimination of Memantine

Memantine is excreted mono exponentially, with a terminal ½ life of 60-100 hours also remains unaltered in urine after elimination. Total clearance was about 170 ml/min/1.73 m found in a healthy kidney individual, with tubular secretion accounting for a portion of total renal clearance. Cation transport protein medicates tubular reabsorption that is perhaps included in renal clearance. The remaining is converted to three polar metabolites with low NMDA receptor antagonistic activity, which are 1-nitroso deaminated memantine N-glucuronide conjugate, 6-hydroxy memantine. The parent medication and the N-glucuronide conjugate combinedly excretes about 74% of the administered dose of memantine. Moreover, renal clearance is brought via active tubular secretion, which is regulated by pH-dependent tubular reabsorption. (fda & cder, n.d.)

2.4 Pharmacodynamic Profile

Memantine demonstrated minimal to marginal affinity for voltage-dependent Ca2+, k+, or Na+ channels along with GABA, benzodiazepine, adrenergic, dopamine, glycine receptor and histamine. Memantine additionally demonstrated antagonistic effects for the 5HT3 receptor likewise the same for NMDA receptors and blocks nicotinic acetylcholine receptors with potencies ranging from one-sixth to one-tenth. Moreover, drug memantine doesn't interfere with the reversible inhibition of acetylcholinesterase with the help of tacrine, galantamine, or donepezil based on some in vitro investigations (fda & cder, n.d.)

2.4.1 Symptomatic Effects

It is speculated that in Alzheimer's the glutamate excitotoxicity brought by NMDA receptors is a key factor in the pathophysiology, also the symptoms observed in the disorder. A clinically successful healthcare for managing Alzheimer's disease symptoms is memantine. In the radial maze for testing the spatial learning of rats, following entorhinal cortex lesions with quinolinic acid, 20 mg/kg/day of memantine 7–13 days after abrasion and 4 days before training showed a symptomatic effectiveness. Memantine had no impacts on choline acetyltransferase (ChAT) activity or brain NGF levels that were linked with memory improvement. Whereas, while doing the Morris water maze test in AA23 mice for cognition, memantine at low dosages (2 mg/kg, i.p. daily for 1 week) showed mildly symptomatic effects, particularly at the probe phase. Also, studies showed no effective result for 10 mg/kg, higher doses of the drug (Rammes et al., 2008).

2.4.2 Potential Abuse

The vast majority of research conclusively shows that memantine did not represent any potential abuse signal at therapeutic levels, although it could in fact avoid overuse of addictive substances notably morphine or ethanol. Memantine induces rate "decreasing" effects in rats when cocaine is self-administered in a progressive ratio. As a result of this, although it cannot be fully considered that memantine misuse could occur in individual with a history of abusing medications with the same kind of pharmacology, such as the cases of ketamine, it is generally of little significance to AD patients who are the target of treatment (Rammes et al., 2008).

2.4.3 Monitoring Efficacy

Usually, to observe any noticeable efficacy in a patient it may take months. But regular activities, cognitive functioning improvements, decreasing in the progression of decline in cognitive function and memory impairment is observed. (*Memantine - StatPearls - NCBI Bookshelf*, n.d.)

2.5 Drug Interaction

2.5.1 Memantine Association with pH of Urine

Usually in alkaline urine (pH 8), the elimination rate of urine drops to 80%, therefore manifesting more adverse events to associate with drugs. This pH can be affected by sodium bicarbonate, other drugs, and diet plans. Urine and renin related diseases also have a likelihood to affect the pH. Hence, usage of memantine should be prescribed checking these factors.

2.5.2 Combination with Another NMDA Antagonists

Ketamine, dextromethorphan and amantadine are some other authorized NMDA antagonists. Systemically investigation of consumption of memantine with these drugs still are under investigation, hence precaution should be taken.

2.6 Drug Contradiction

Patients having allergy to memantine or anything with the compound associated with the drug should be careful about taking this drug.

2.6.1 Renal Impairment

According to the Cockroft- Gault equation, those who have creatinine elimination rate about 5-29 mL/min tend to have renal diseases. Hence, patients of these diseases are advised to take a regular dose 10mg each day and a target dose of memantine (five milligram), two times a day. A study based on the pK profile of memantine was analyzed by administration of 20 mg dosage among mild, moderate and several renal diseases patients, where elimination half-life was about 18%, 41% and 95%, by comparing them with healthy individuals.

2.6.2 Hepatic Impairment:

Patients those having severe hepatic disease are advised to take memantine cautiously. Study showed an increase of elimination half-life of about sixteen % among severe hepatic disease patients compared with healthy patients. Nevertheless, there was no requirement to change doses for patients having mild & moderate hepatic impairment. As there are less studies regarding these, hence precaution should be taken always.

2.10 Potential Combination Therapy with Memantine

Combination of memantine with 6-cholorotacrine, a new combinational drug, has twofold action in case of hindering action of both AChE and NMDARs. Donepezil, a AchEIs drug, represented the most significance in cognitive behavior. One evident case showed significant outcomes in improving learning, memory, cognitive behavior due to combination use of galantamine along with memantine. But not much research was not conducted regarding this combination so the result cannot be completely assumed to be significant (Kishi et al., 2017).

Chapter 3

Methodology

3.1 Data Source

Our research is reflective data investigation of adverse event reports that depend on the FAERS database. The Adverse Event Reporting System (FAERS), which is the part of United States Food and Drug Administration (FDA) is a database established to aid FDA's pharmacovigilance of therapeutic biologics and medicinal products. Any shortcoming in medication, the FDA’s adverse events (AEs) reports, quantitative investigation of the cases that are reported about drugs, also aiding in signal identification, all of these are arranged in this database. To add with FAERS consist certain information such as drug info by case reports, administrative and demographic details, drug information from case reports, outcomes of patients via reported case, also reaction information from the reports, drug therapy starts and end dates from the reports, and all "Medical Dictionary for Regulatory Activities" (MedDRA) idiom used in the reports. The adverse events are usually voluntarily reported by healthcare workers and consumers (Sakaeda et al., 2013).Usually, clinical researchers, healthcare professionals, and pharmaceutical industries widely use FAERS databases to investigate pharmacovigilance of any medical products (Tian et al., 2022).

In our study, FDA-approved “Acetylcholinesterase inhibitors” drug classes (rivastigmine, donepezil, galantamine), including our particular "NMDA receptor antagonist" (memantine) drugs adverse events from FAERS are analyzed. The Adverse event was termed as Rhabdomyolysis following MedDRA (Medical Directory of Regulatory Activities) preferer terminology. In the latest update taken on August 30, there are 27,096,432 reports in the database. The analysis was conducted in June 2023, and the information for this study has

been collected from January 2016 to June 2023 time frame. For this study, the generic name "memantine" was mainly the sole drug that was suspected for the desired adverse event.

3.2 Inclusion and Exclusion Criteria

The FAERS Public Dashboard was searched to look for cases and non-cases data, which are arranged from "January 2016" to "June 2023" and memantine is suspected as the sole medicinal product responsible for predicted adverse events ``rhabdomyolysis" as according to MedDRA terminology. Also, reported odds ratio (ROR) along with June95% of confidence interval 95% were done to detect signals to identify the association of our particular drug memantine with the adverse effect "rhabdomyolysis". The duplicated report considering the age, sex, event date was excluded by the case number and cross-referencing them.

3.3 Statistical Analysis

For this study, June 2023 FAERS databases were analyzed. Case and non-case analysis was done to interpret the relation among Memantine and the adverse event, Rhabdomyolysis in the FAERS. Only the ADR of cases are taken, overlooking the non-case ADR reports. The disproportionality is then determined by generating a 95% confidence interval (CI) and a reported odds ratio (ROR). Using a 2 by 2 contingency table, the ROR value was determined with help of R 4.3.1 version. Mainly it follows the formula where ROR is calculated by dividing the AE reports of the specific drug by the AE reports of all other drugs, where the specific drug is not included. In pharmacovigilance research, this strategy, the reported odds ratio (ROR) and lower bound of confidence interval 95%, acts as a signal detection index. A signal can be figured whenever ROR's lower bound limit, 95% confidence interval (CI) is more than one (>1). And, if it has a lower value than one, the signal is regarded as rejected (Ali et al., 2015; Jedlowski et al., 2021). Nonetheless, calculating the ROR in spontaneous

report databases has merits in that it facilitates the evaluation of the relative risk while emphasizing on categorizing which reports or people should be added or overlooked from the control sequences, providing more conscious bias cutback (Rothman et al., 2004).

In our research, The ROR with 95% confidence interval was subsequently calculated to observe the signal, for the corresponding adverse event (rhabdomyolysis) to report cases of memantine against other drug cases, when the whole database was used as a comparator. Again, another calculation was done but here as the comparator AChEIs (donepezil, rivastigmine, galantamine) drug cases were considered. Overall, the analysis helped to predict the relationship between the desired medication (memantine) and undesirable adverse consequences (rhabdomyolysis) cases against other drugs cases. Adding to that, this ROR value is used to observe signals to view the likelihood of Adverse event (rhabdomyolysis) with our particular drug Memantine among female and male memantine consumers. Lastly, a forest plot was also added to graphically represent the outcomes.

Chapter 4

Results & Discussions

4.1 Rhabdomyolysis

From FAERS database using R statistical software, data of Adverse effects from January 2016 to July 2023, we incorporated the reported odds ratio (ROR) as well as its related 95% confidence interval (CI) to conduct a disproportionality analysis, which gave signal meaning there were certain cases of rhabdomyolysis, results were analyzed categorizing female and male cases. The whole database drug cases comprise the desired adverse events (rhabdomyolysis) data, along with our study specific Drug, 'Memantine', whereas Class is considered as other classes drug (AChEIs: donepezil, rivastigmine, galantamine) to treat Alzheimer's Disease having the adverse event (rhabdomyolysis).

In our first analysis, the whole database was used as a comparator. In Table 3 cases of rhabdomyolysis of male memantine consumers are compared against all other drug cases. There were 3 cases of memantine while other drugs showed 8787 cases, having ROR (95% Cl) value 5.68 (2.12 - 15.19). In case of female memantine consumers in Table 4, 4 cases were due to memantine, and 5464 cases found for other drug cases. And ROI (95% CI) value was found 7.98 (2.55-24.70). Here, in both male and female cases, the lower bound of confidence interval value was >1, so a signal was detected. And the ROR value of female memantine consumers was higher than the male indicating female to be more prone to rhabdomyolysis.

Table 3: Whole database as a comparator in year (male) (2016-2023)

	Cases	ROR (CI)
Memantine	4	5.68 (2.12 - 15.19)
Other drugs	8787	

Table 4: Whole database as a comparator (female) (2016-2023)

	Cases	ROR (CI)
Memantine	3	7.94 (2.55 - 24.70)
Other drugs	5464	

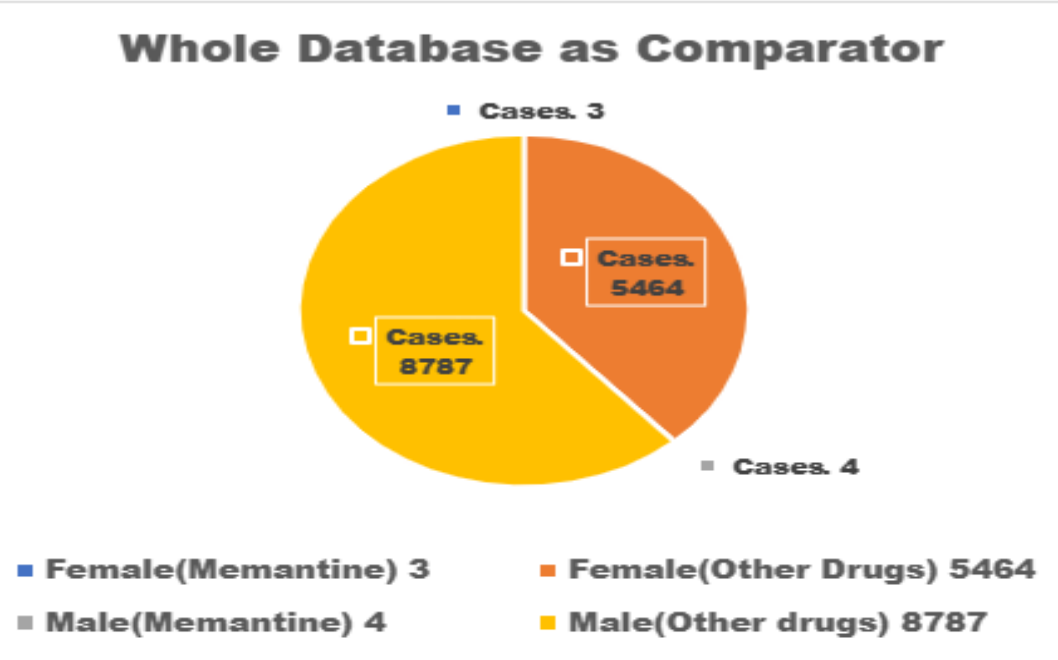

Figure 6: Gender specific cases of rhabdomyolysis (memantine against whole database)

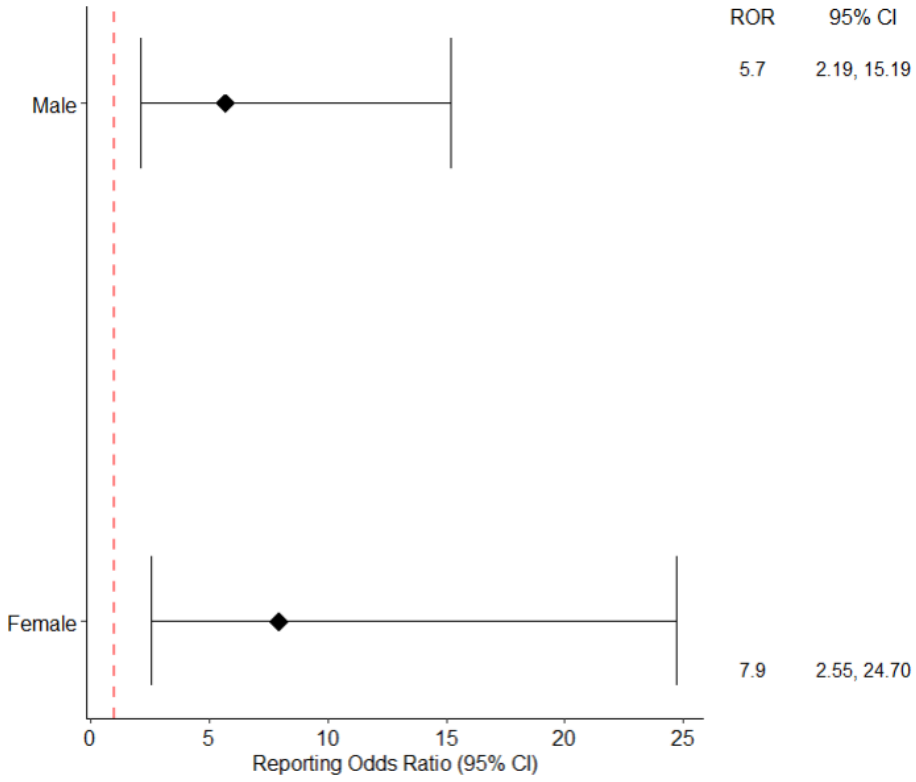

Figure 7: Forest plot for whole dataset

This forest plot provided a graphical representation of ROR values with the lower bound of confidence interval, the signal detection to show the chances of link of drug memantine with AEs (rhabdomyolysis)for the female and male memantine.

In the second analysis, the AChEIs (donepezil, rivastigmine, galantamine) class is considered as a comparator. In Table 5, 4 male memantine consumer cases were reported, whereas 14 cases were reported for other drugs cases with ROR of 1.40, lower bound of confidence interval (0.46 - 4.26). On the contrary, in Table 6 in case of female memantine consumers, 3 cases and 7 cases for other drugs cases, had a ROR of 2.53 for AEs (95% CI 0.65 - 9.83). Except, the lower bound confidence interval was less than 1 in both male and female cases so no signal was found but the ROR value was higher in female cases here too.

Table 5: Class as a comparator (males) (2016-2023)

	Cases	ROR (CI)
Memantine	4	1.40 (0.46 - 4.26)
Other drugs	14	

Table 6: Class as a comparator (females) (2016-2023)

	Cases	ROR (CI)
Memantine	3	2.53 (0.65 - 9.83)
Other drugs	7	

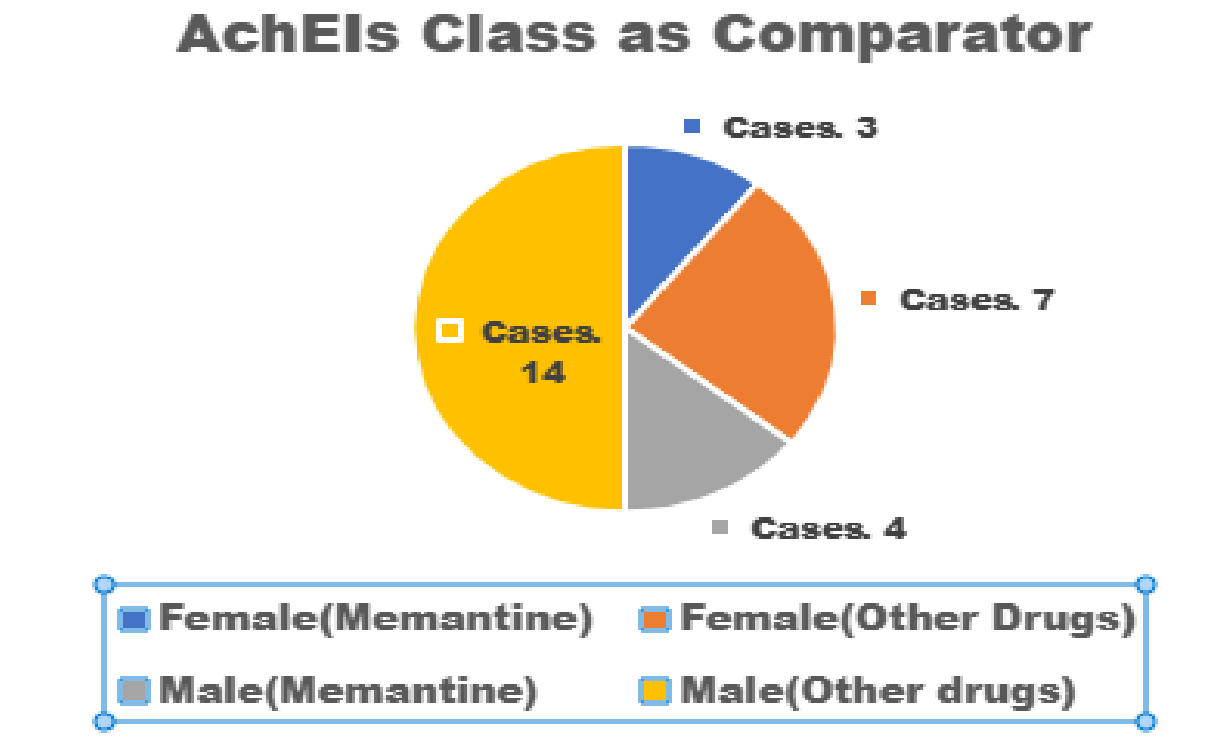

Figure 8: Gender specific cases of rhabdomyolysis (memantine against AChEIs drugs class)

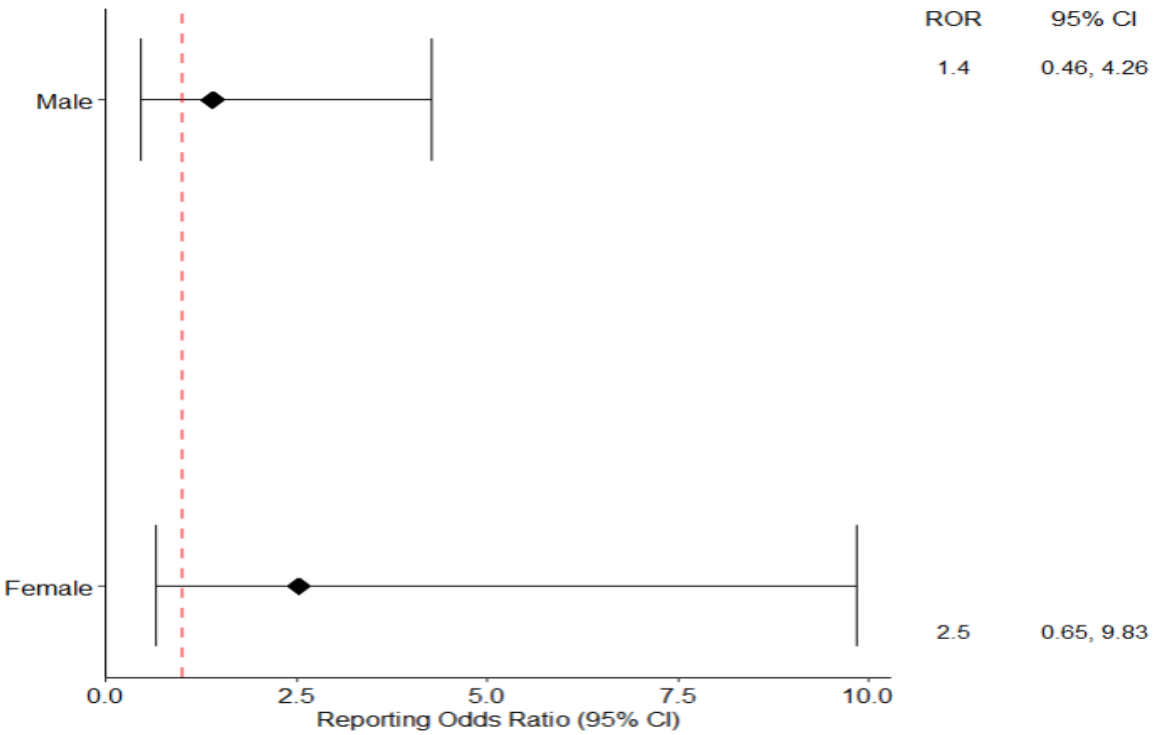

Figure 9: Forest plot for class comparator

This forest plot provided a visual representation of ROR values with the lower bound of confidence interval is conducted, where no signal is detected, indicating less case of rhabdomyolysis of memantine than AChEIs class for both male and female.

4.2 Discussion

In our pharmacovigilance study, FAERS database data within the January 2016-June2023 time frame, the ROR (95%CI) was calculated using the R 4.2.1 version tool. Case and non-cases report of AEs rhabdomyolysis) were taken for the ROR calculation. Later on, finding out the ROR values, only case reports were analyzed. These ROR values along with lower bounds of confidence interval helped to find out the signal to check the association between our particular drug (memantine) with AE, rhabdomyolysis termed in accordance with MedDRA. Only in whole datasets as comparator cases, signal was detected as 95% CI was greater than 1, indicating cases of memantine of rhabdomyolysis compared to other drugs cases. This signal shows the likelihood of association of memantine with rhabdomyolysis. As, lower bound value was less than 1 hence no signal found compared with AChEIs class as comparator, but as memantine had lower case of rhabdomyolysis rather than AChEIs, it can be suggested memantine as one of the most efficient therapies for Alzheimer's disease having a low likelihood of rhabdomyolysis. Based on one study, memantine displays a favorable and contrasting safety and tolerability rating when in comparison with AChEIs (Jones, 2010). In addition, the combined effect of memantine and donepezil was less favorable to patients rather than sole use of memantine. While memantine was deemed the most satisfactory medicine (Guo et al., 2020).

Rhabdomyolysis is a condition where breakdown of skeletal muscle happens. While comparing the male and female memantine consumers, for both other drug cases and AChEIs drug cases, the females had more cases of rhabdomyolysis than males. Certain issues may

trigger this issue. Usually, male muscles are thought to have more energy for anabolic metabolism, also skeletal muscles are faster, and also have more muscle mass which helps them to gain more power output rather than female. Nonetheless, women are more prone to Alzheimer's diseases, so these things may adhere to the reason for females having more rhabdomyolysis cases than male (Glenmark et al., 2004).

Also, not only physical, chemical factors but also some diseases may cause rhabdomyolysis. Metabolic disorders such as in hypothyroidism, thyroid level drops to a lower level than usual and it is considered as 2nd most common endocrine disorder in female(*Why Women Are More Susceptible to Thyroid Disease* , n.d.). This makes female Alzheimer's patients to be at more risk of rhabdomyolysis as hypothyroidism is also an issue to cause this adverse event (Torres et al., n.d.).

To add to that, another disease termed autoimmune disorder, where the host's immune system attacks its own system. Now in this disease, the greater proportion of genes originating from the X chromosome (women have 2, males have 1) doubles the odds of a wider range of mutations happening, putting women at an elevated risk of suffering from autoimmune illnesses and some studies also suggest that 80% of this disease are among women (Angum et al., 2020). This issue is concerning as this makes females more prone to rhabdomyolysis.

Along with drugs such as statins, AChEIs being the reason to cause rhabdomyolysis, issues mentioned above may trigger rhabdomyolysis and as females are in the risk position of having these diseases more, so it may adhere to the rising issue of this study where female memantine consumers cases were more compared to males.

Chapter 5

Conclusion

Alzheimer's disease (AD) is a serious alarming issue to public health throughout the world. For our research purpose, the pharmacovigilance reports of FAERS about memantine association with rhabdomyolysis in comparison with other AChEIs were analyzed. The study got some arguable results which indicated females are more prone to have rhabdomyolysis than to male. Females being more prone to autoimmune disorder, hypothyroidism may be the reason for this outcome. This data analysis found the likelihood of rhabdomyolysis more in case of AChEIs. Hence, memantine can be one of the most preferred prescription choices in case of tolerability or patient preference to treat Alzheimer patients having a risk profile of rhabdomyolysis. Nevertheless, clinical trials and longer period of thorough research on memantine should be conducted further to enhance clinical outcomes and to get more clear view of events associated with the drug.

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