SIGNAL DETECTION OF RHABDOMYOLYSIS AND DEATH FOR GALANTAMINE: A PHARMACOVIGILENCE 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 (B. Pharm)

School of Pharmacy
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The project titled "[Signal detection of of rhabdomyolysis and death for Galantamine: a pharmacovigilance study]" submitted by Swastika karmaker (18346089), of Summer 2022 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

No humans or animals of any kinds were involved as samples for this study.

Abstract

Galantamine is one of the common acetylcholinesterase inhibitors used to treat Alzheimer's disease, a neurodegenerative disorder. This study was conducted to determine the impact of galantamine on mortality rate and rhabdomyolysis using the FDA Event Reporting System(FAERS) database, which includes data from drug class and the whole database. Comparing the mortality rate of galantamine to that of other drugs and other class, it was found that 24 deaths were recorded on FAERS, compared to 456,120 and 680 deaths for other drugs and drug class, respectively. In this analysis, galantamine showed better mortality benefit than others. The ROR value of death cases for other drugs was 1.22(95%CI:0.81-1.83;p=0.3435) vs. drug class 0.31(95%CI:0.21-0.47;p<0.0001). Furthermore,8 rhabdomyolysis cases were recorded in FAERS, while 16379 and 19 cases were reported on other drugs and other class, respectively. It has been found that galantamine is more likely of causing rhabdomyolysis than other drugs. The Reporting Odds Ratio (ROR) value for rhabdomyolysis for other drugs was 11.35 (95%CI:5.65-22.80; p<0.0001) vs drug class 4.05(95%CI:1.77-9.29; p=0.0009).

Keywords: Alzheimer’s Disease; Dementia; Galantamine; Mortality; Rhabdomyolysis.

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List of Acronyms

AD Alzheimer Disease

ACh. Acetylcholine

AChE. Acetylcholine Esterase

AChEIs Acetylcholine Esterase Inhibitors

Aβ Amyloid beta

APP Amyloid Precursor Protein

BBB Blood Brain Barrier

CTE Chronic Traumatic Encephalopathy

CYP450 Cytochrome P450

FAERS FDA Adverse Event Reporting System

FDA Food and Drug Administration

LC Locus coeruleus

NMDA N-methyl-D-aspartate

PSEN1 Presenilin 1

SORT1 Sortilin 1

TBI Traumatic Brain Injury

WHO World Health Organization

Chapter 1

Introduction

1.1 Alzheimer’s Disease

Alzheimer's disease is a brain disorder, that generally affects older people. Patients are identified with having "Alzheimer's disease" when they exhibit the specific brain abnormalities that indicate the disorder. Inflammation, twisted fibers, protein clumps, and dysfunction brought on by the death of nerve cells and the connections between them are some of these brain adaptations (Ballard et al.,2011). Cortical neurons have pairs of helical filaments that have a distinctive appearance under an electron microscope. Proteins having unusual properties are present in these filaments. The number of cholinergic neurons in deep brain areas like the nucleus basalis of Meynert in the substantia innominata is significantly reduced when there is a trend toward decreased cholinergic activity in the cortex (KOKMEN, 1984). Alzheimer's disease symptoms include a decline in cognition, memory, and communication, as well as changes in personality and other brain impairments that progressively worsen. Even the most fundamental daily functions eventually become less effective as a result of AD. Alzheimer's disease has become the most frequent reason for dementia among elderly people (Ballard et al., 2011). When the central nervous system is afflicted with dementia, behavioral, intellectual, and memory capacities all decrease. The illness commonly worsens and causes serious problems with functional and social adaptability. The majority of clinical and pathologic research have shown that Alzheimer's disease is responsible for at least 50% of dementia cases (Scheltens et al., 2021).

The progression of the disorder affects symptoms of Alzheimer's. Alzheimer's disease is classified into three phases based on the degree of cognitive decline: preclinical or

presymptomatic, mild, and dementia-stage. These stages are separate from the Alzheimer's disease classification found in the DSM-5. Episodental short-term loss of memory with comparatively sparing long-term memory is the earliest as well as the most prevalent exhibiting symptom, and it may be evoked in the majority of patients even when it is not the presenting symptom. Short-term memory loss causes difficulties with multitasking and intellectual thoughts, as well as limitations in problem-solving, judgment, executive functioning, low motivation, and disorientation.

The deterioration in executive functioning in the early stages ranges from minimal to severe. The next two are language dysfunction and visual-spatial impairment. In the middle to late phases, it's also typical to have neuropsychiatric symptoms including apathy, social disengagement, impulsive behaviour, restlessness, psychosis, and wandering. Dyspraxia, olfactory dysfunction, sleep issues, and extrapyramidal motor symptoms including dystonia, akathisia, and parkinsonian indications occur later in the course of the condition in patients. The next stage is the loss of fundamental reflexes, incontinence, and total dependency on caregivers (Kumar et al., 2022).

1.2 Prevalence of AD

According to the Center for Disease Control, between 2000 and 2030, there will be 420 million more individuals over the age of 65 than there are now. The expanding elderly population has had a huge negative impact on the global economy as well as the families and carers of those with age-related illnesses. Given that AD is linked to aging, as the world's old population grows, this illness may become unsolvable on a worldwide scale. Within the year 2050, 13.8 million Americans alone will have been diagnosed with AD dementia, with more than half of them being older than 85, according to survey data. Currently, AD accounts for the majority of occurrences of dementia, which affect more than 36.5 million people globally. Every year,

approximately 5-7 million new cases of AD are diagnosed in the older population (Robinson et al., 2017). Prior to the COVID-19 epidemic, AD was the third most common reason of death in the US among seniors, just behind heart disease and cancer. The majority of developed nations consider AD as one of the largest financial threats. According to research, the cost of AD-related expenses in the United States alone in 2030 will be $7 billion USD, along with caregiver costs.

Based on the latest WHO statistics, 14,993 deaths in Bangladesh from Alzheimer's and dementia happened in 2020, accounting for 2.09% of all deaths. Bangladesh is ranked 142 worldwide due to its 13.89 per 100,000 population age-adjusted Death Rate.

1.3 Etiology

Factors affecting AD onset

Age: Age is among the most significant risk factors of having cognitive decline and AD among the different demographic characteristics, such as gender, race, and socioeconomic class, according to several epidemiological studies, including those cited by Henderson (Henderson, 1988). (Herrup, 2010). As people get older, the incidence rate of AD rises, reaching approximate 19% in those aged 75 to 84 and 30–35%, or even 50%, in those over 85 (Knopman, 2001). A person's brain loses synapses and dendrites as they age, as well as its volume and weight, and certain brain areas also undergo ventricle growth. (A. Armstrong, 2019).

Two additional age-related pathogenic mechanisms may be implicated in AD. While some evidence suggests that myelin loss occurs later in the disorder due to neurodegeneration, myelin degradation initially results in the death of white matter fiber tracts. The locus coeruleus (LC), which transports noradrenaline to the cortex through terminal varicosities and activates microglia to limit Aβ production, suffers from cell death. Because of aging and AD, NFT first

occur in the LC early on. Reduction of cells in the LC may thus cause an age-associated weakening of the blood-brain barrier (BBB), suggesting age-related vascular variables in AD(A. Armstrong, 2019).

Obesity: Diabetes, hypertension, and stroke are all known to be more common in those who are obese. These conditions could increase the likelihood of cognitive impairment, which would indirectly contribute to the emergence of AD. Overweight people will have white matter atrophy in their basal ganglia and corona radiata. Although there is a strong correlation with obesity, inflammation, and metabolic conditions like type 2 diabetes, it is not clear how obesity causes these white matter reductions (Shoelson et al., 2007).

Type 2 diabetes mellitus (T2DM): It is associated with obesity and is typically the result of insulin resistance. This is followed by insufficient insulin production, which results in a deficit of insulin and lowers the body's ability to metabolize glucose. There is evidence that T2DM increases the risk of AD and neurodegeneration. 2009 (Xu et al.) In research published by Talbot et al., brain insulin resistance among people with normal to mild cognitive impairment was compared to that in those with Alzheimer's disease. Their findings showed a consistent rise in brain insulin resistance in the hippocampal formations of AD patients in comparison to healthy individuals (Talbot et al., 2012). In the initial phases of AD, a decreased cerebral glucose metabolism rate may also be related to insulin resistance.

Physical activity and diet: They are crucial for ensuring general well-being. According to studies, regular exercise lowers the likelihood of dementia and delays the onset of AD. Walking has been associated with increased gray matter volume, which is thought to protect against cognitive impairment. Aerobic exercise training, in particular, has been shown to reverse hippocampus volume loss in late adulthood, improving cognitive performance and delaying subsequent decline (Erickson et al., 2011). Dietary research demonstrates that diets high in

sugar and saturated fats have negative effects on cognition, but the Mediterranean diet and diets high in seafood have received extensive praise for their favorable effects (Hardman et al., 2016).

Traumatic brain injury (TBI)

TBI might weaken the BBB, allowing plasma proteins to seep out and making the immune system more sensitive to brain antigens that are often kept apart from them. After then, other investigations revealed a correlation between head trauma and AD. Similar to AD, APP is present in neuronal cell bodies and dystrophic neurites around Aβ accumulation in those who have survived head injuries. Later studies revealed that TBI enhanced the number of APP-immunoreactive neurons in the medial temporal lobe (MTL) and that certain neurons in the MTL produced substantial quantities of APP.

As a result, increased APP expression in individuals who have suffered head trauma may indicate an acute-phase respond to neuronal injury, with APP overexpression leading to A buildup. Aβ deposits in AD contain a variety of acute-phase proteins, including as amyloid-P, complement elements, and -antichymotrypsin. Regland and Gottfries also suggested that APP supports neuronal survival and proliferation in order to sustain cell function. The finding that APP has structural characteristics with the precursors to the neurotrophic factor, epidermal growth factor, supports the idea that it may have neurotrophic effects. NFT may also have a role in how damaged neurons respond.

The identification of chronic traumatic encephalopathy (CTE), a neurodegenerative condition thought to be directly related to repeated brain damage, further emphasizes the association between TBI and AD. CTE has been related to contact sports like boxing, football, ice hockey, and wrestling as a consequence, in addition to veterans of the armed forces who have frequently

been exposed to explosion shock waves from explosive weapons. Clinically, the signs of CTE are similar to those of AD as well as include motor symptoms, behavioral changes, mood problems, and loss of memory and executive ability. There are similarities between the neuropathology of AD and CTE. As a result, CTE patients show decreased grey matter volume in a number of brain areas, most notably the frontal and anterior temporal lobes along with expansion of the lateral and third ventricles (A. Armstrong, 2019).

Stress: Glucocorticoids, which are frequently associated with cognitive impairment and the pathogenesis of AD, have an impact on the progression of many chronic disorders, including AD. The psychological well-being of people with moderate cognitive decline was worse than that of controls, and this has been linked to increased AD pathology as evaluated by self-reported vigor and activity (Chen et al., 2014).

1.4 Pathology

Neurofibrillary tangles and abnormal neuritic plaque accumulation are hallmarks of Alzheimer's disease.

Plaques: They are microscopic lesions that are circular in shape and have an extracellular amyloid beta-peptide core surrounded by enlarged axonal terminals. The beta-amyloid peptide is produced by a transmembrane protein called an amyloid precursor protein (APP), which is then degraded by the proteases alpha, beta, and gamma-secretase as shown in Figure 1. Both alpha and beta-secretases frequently cleave APP, and the tiny fragments that result do not injure neurons. Additionally, the 42 amino acid peptides are created as a result of the beta-secretase and gamma-secretase cleavages that occur in succession (beta-amyloid 42). Neurons are impacted by amyloid aggregation, which is brought on by an elevation in beta-amyloid 42.

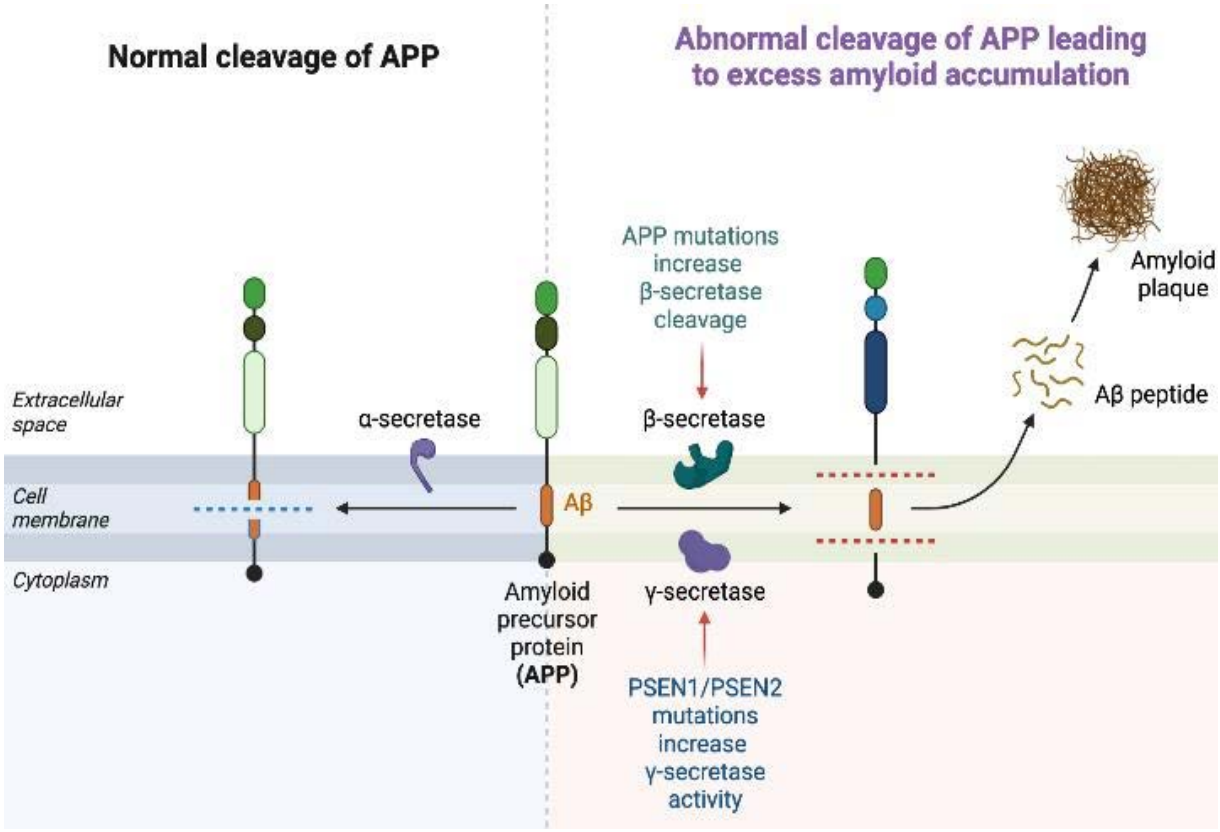

Figure 1: Plaque Formation

Beta-amyloid 42 promotes the growth of accumulated fibrillary amyloid protein instead of the usual APP degradation. The APP gene is located on chromosome 21, which has been linked to familial Alzheimer's disease. Amyloid plaque surrounds gray matter, meningeal arteries, and cerebral arteries in Alzheimer's disease. Plaques are milliary structures formed when multifocal gray matter accumulations combine. But despite having dementia, some individuals with brain scans were found to contain amyloid plaques, and others did not.

Neurofibrillary tangles: A protein named tau forms neurofibrillary tangles, which are fibrillary intracytoplasmic structures, in neurons. The stabilization of axonal microtubules is the tau protein's main objective. During intracellular transport, microtubules are crucial, and they are present on neuronal axons. Tau protein maintains the integrity of the microtubule

assembly. Figure 2 illustrates the development of tangles in the AD brain.

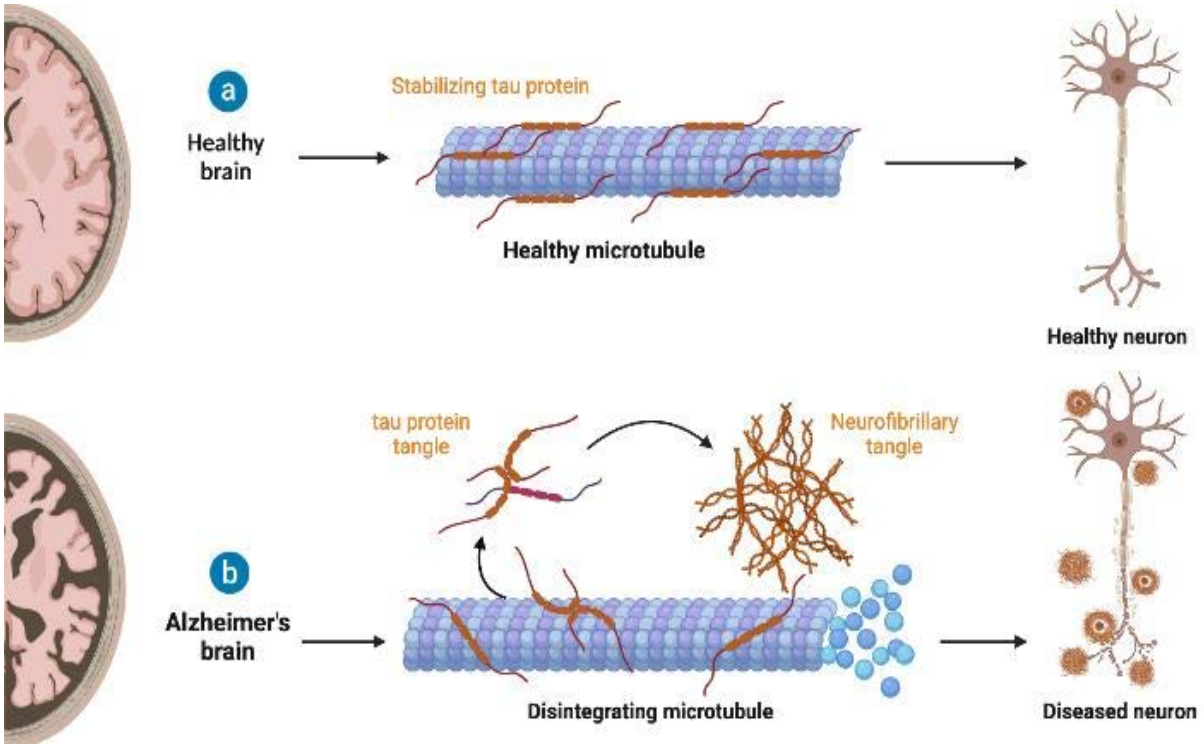

Figure 2: Neurofibrillary tangles

In Alzheimer's disease, extracellular beta-amyloid aggregation leads to tau hyperphosphorylation, which develops tau clumps. Tau aggregation results in the formation of neurofibrillary tangles, which are made up of twisted pairs of helical strands. Before moving on to other regions of the cerebral cortex, they first manifest in the hippocampus. Neurons contain an accumulation of tau-aggregates.

Genetic Basis of Alzheimer Disease

An autosomal dominant disorder with a nearly 100% penetrance rate is Alzheimer's disease. The autosomal dominant variant of the disease has been linked to three genes: the AAP gene on chromosome 21, Presenilin 1 (PSEN1) on chromosome 14, and Presenilin 2 (PSEN2) on chromosome 1. APP mutations may have an adverse effect on beta-amyloid peptide synthesis and aggregation. PSEN1 and PSEN2 mutations that inhibit gamma-secretase processing cause

beta-amyloid aggregates. Mutations in these three genes account for the majority of instances of early-onset Alzheimer's disease and 5% to 10% of all cases.

Apolipoprotein E, a lipid metabolism mediator with a strong affinity for beta-amyloid protein, is a further genetic component that increases the risk of developing Alzheimer's disease. Alzheimer's disease that manifests later in life and is more sporadic and familial has been related to the APOE isoform e4 gene (located on chromosome 19). Even while having one APOEe4 allele does not guarantee that a person would get Alzheimer's disease, about 50% of people who get only one allele and 90% of those who have two alleles do. Furthermore, the disease's onset age is lowered by each APOE e4 allele. Carrying the APOE e4 allele is a substantial risk factor for Alzheimer's disease. Variations in the sortilin receptor gene, SORT1, have been related to both familial and sporadic forms of Alzheimer's disease. APP must be carried from the cell surface to the Golgi-endoplasmic reticulum complex (Kumar et al., 2022).

1.5 Current treatment options

There are currently just two pharmacologic treatment options for Alzheimer's disease. The cholinesterase inhibitors donepezil, rivastigmine, and galantamine are administered as a course of treatment for people with mild, moderate, or chronic Parkinson's disease dementia as well as mild, moderate, or severe AD dementia. Memantine, which acts as both a non-competitive N-methyl-D-aspartate receptor antagonist and a dopamine agonist, may be helpful for people with moderate-to-severe AD (mini-mental state examination [MMSE] 15) who struggle with attention and mental clarity (Grossberg et al., 2013).

1.5.1 AchE inhibitors

Cholinergic neurotransmission plays a significant role in both AD and adult-onset dementia diseases, which are characterized by impaired cognitive function. Enhancing cholinergic

neurotransmission is the main treatment method for the cognitive and behavioral signs of mild and moderate AD. The two cholinesterases AChE and butyrylcholinesterase (BuChE) hydrolytically break down ACh in the brain. AChE is more prevalent than BuChE in the brain tissue of people with Alzheimer's disease, which promotes the breakdown of ACh in the cerebral cortex and hippocampus. According to research, the AChE activity of the temporal lobe and hippocampus declines by 67% as Alzheimer's disease progresses (Marucci et al., 2021). Physostigmine, velnacrine, and tetrahydroaminoacridine (tacrine) were some of the first AChE inhibitors to be discovered. Only tacrine had extensive clinical testing before being commercialized in parts of Europe and the United States. Next, the more recent drugs donepezil, rivastigmine, and galantamine were introduced.

Donepezil

In 1996, donepezil became the second drug to be licensed by the FDA to be used in treating mild-moderate AD. It was given FDA clearance in 2010 to be used at a dose of 23 mg daily to treat mild to chronic condition. The pharmacological characteristics of donepezil include improvements in neural plasticity, decrease of pro-inflammatory cytokines, and cerebral blood flow, all of which are consistent with its ability to modulate several neurotransmissions. Additionally, it affects the production of AChE isoforms, regulates cholinergic actions and oxidative stress, decreases the amount of APP and excitotoxic damage, and interacts with the regulation of nicotinic receptors in the cerebral cortex (Jacobson & Sabbagh, 2008). The reversible acetylcholinesterase-binding property of donepezil prevents acetylcholine from being hydrolyzed, boosting its availability at synapses and promoting cholinergic transmission. According to some in vitro research, donepezil's anticholinesterase effect is relatively specific to the brain's acetylcholinesterase (Marucci et al., 2021).

Rivastigmine

In 2000, the FDA authorized the use of rivastigmine in its oral form as a pseudo-irreversible carbamate-selective AchE and BuChE inhibitor for the management of mild-to-moderate AD. The pseudo-irreversible carbamate inhibitor rivastigmine inhibits both BuChE and AChE noncompetitively. In fact, these two enzymes that are responsible for the catabolism of ACh promote the development of neurofibrillary tangles and neuritic plaques, which are hallmarks of the pathophysiology of AD. To improve bioavailability, this drug is also delivered as a transdermal patch. Rivastigmine blocks peripheral BuChE by around 33% at a dosage of 12 mg/day, whereas it suppresses brain AChE and BuChE by 61.7% and 61.8%, accordingly. This demonstrates the compound's high cholinergic system specificity (Marucci et al., 2021).

Galantamine

Galantamine is a selective, reversible AchE inhibitor that modifies the allosteric properties of nicotinic cholinergic receptors. Galantamine is a tertiary alkaloid that selectively and competitively inhibits AChE rather than BuChE. In order to enhance the effects of agonists at nicotinic acetylcholine receptors, it also interacts allosterically with these receptors. Galantamine's therapeutic effectiveness may be aided by this potentiating action because the extent of cognitive deficits in AD is correlated with the depletion of nicotinic receptors. Conversely, cholinergic stimulation enhances the survivability and development of brain progenitor cells (Marucci et al., 2021)

1.5.2 NMDA Antagonists

The most important neurotransmitter within that brain that causes excitability is glutamate. Excessive glutamatergic stimulation can cause neuronal injury, a process known as excitotoxicity. Such excitotoxicity eventually causes calcium overflow in neurons and has been

related to degenerative neurological disorders. Glutamate stimulates a number of postsynaptic receptors, including the N-methyl-D-aspartate (NMDA) receptor, which has been extensively related with cognitive functions, dementia, and the development of Alzheimer's disease. A non-competitive NMDA-receptor antagonist called memantine may be used to treat Alzheimer's disease. Both AD and adult-onset dementia disorders, which are defined by declining cognitive ability, depend significantly on cholinergic neurotransmission (Reisberg et al., 2003).

1.6 Future Treatment Options

Future treatments for AD will target on the pathologies that cause it, such as senile plaques(Aβ) and neurofibrillary tangles (p-tau).

1.6.1 Anti-amyloid

In 2013, researchers found that this abnormal amyloid plaque causes tau protein to become phosphorylated, which then spreads infectiously to adjacent neurons via microtubule transport, causing neuronal death (Pooler et al., 2013). One type of drug developed according to these discoveries is monoclonal antibodies (passive immunotherapy). This type of treatment involves injecting a specific antibody that facilitates the removal of abnormal A from the brain. In order to eliminate these plaques from AD patients' brains, two of these monoclonal antibodies were first designed in 2014 (Weller & Budson, 2018). Researchers came to the conclusion that these drugs may be most helpful when used in the initial phases of mild dementia because neither of them boosted cognitive scores in individuals with mild disorder (MMSE 16–26). Inhibiting the enzymes that create the Aβ peptide out of its precursor, APP, seems to be another strategy for reducing the amount of Aβ plaque in the brain. Several medications that target BACE1, a protein that is considered to be crucial for the creation of Aβ peptides, are being developed right now. A 40-fold decrease in Aβ levels was recently obtained with the new drug

verubecestat, which has also demonstrated a favorable safety profile in preliminary human studies (Kennedy et al., 2016).

In 2014, studies revealed that using a monoclonal antibody and a BACE1 inhibitor in combination greatly decreased the quantity of Aβ in mice that produced amyloid. Although there are presently no human studies employing this method, many experts believe that combination treatments combining both approaches to remove Aβ will ultimately be successful in treating AD (Perry et al., 2015).

1.6.2 Anti-tau

Drugs to lower the load of this protein are also being developed since it seems that p-tau is the downstream disease as well as the main reason for symptoms in AD. In animal models, several distinct tau vaccines have confirmed both safety and efficacy, and also in new small research, an anti-tau medication had an excellent safety profile and indeed triggered a beneficial immune system response in human trials (Weller & Budson, 2018).

1.7 Purpose of the study

In order to determine if galantamine treatments for AD dementia patients have any effect on death rates or the likelihood of developing rhabdomyolysis, the study is being conducted among these patients. The pharmacovigilance and adverse reaction data from the FDA Adverse Event Reporting System (FAERS) will be investigated in this study.

Chapter 2

Galantamine in the Treatment of AD

2.1 Galantamine

Galantamine is known chemically as ((4aS,6R,8aS)-5,6,9,10,11,12-Hexahydro-3-methoxy-11-methyl-4aH-[1] benzofuro [3a, 3,2-ef][2]benzazepin-6-ol). Galanthus woronowii's bulbs and blooms were used to extract this heterocyclic phenantridine derivative. This alkaloid, which is a member of the Amaryllidaceae family, has a variety of different structural forms.

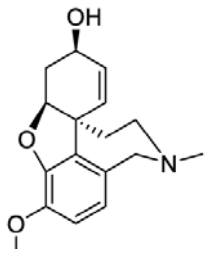

Figure 3: Structure of Galantamine

The chemical structure of galantamine has been illustrates on Figure 3. Galantamine has the ability to selectively activate AChE in the central nervous system while having little impact on peripheral tissues, which makes it an effective therapy for AD. The limiting availability of galantamine from natural sources, together with its unique biological function, has generated interest in methods for its complete synthesis. In order to enhance the biological profile of the natural product, several research organizations were able to design and evaluating the biological effects of structural analogues as well as galantamine derivatives (Rinner et al., 2016). Memogain, a pro-drug of galantamine, was created for this purpose. When compared to galantamine at the same dose, Memogain's bioavailability within the brain seems to be more than 15 times greater. Memogain can induce a more prominent cognitive enhancement than the relatively similar dosages of galantamine because it is enzymatically degraded to galantamine,

and it does so without much higher levels of gastrointestinal complications (Marucci et al., 2021).

Galantamine has two different mechanisms of action that suppress cholinesterase. Since it boosts the intrinsic action of acetylcholine on nicotinic receptors and acts as a reversible inhibitor of acetylcholine esterase, it increases cholinergic neurotransmission in the central nervous system (Razay & Wilcock, 2008). According to several studies, galantamine stimulates the M1 muscarinic receptor, which in turn stimulates the proliferation of neural progenitor cells in the subgranular zone of the hippocampus, and also the survival of newly divided cells in the granule cell layer, which triggers the nicotinic receptor α7. Galantamine has been shown in studies to prevent plaque growth or even behavioral deterioration in the 5XFAD mice model of AD (Bhattacharya et al., 2014). Galantamine reduces amyloid β accumulation as well as neuroinflammation in transgenic mice. These results led to the suggestion that galantamine would be a potential drug for multi-target anti-AD treatment due to the synergistic effects of AChE inhibitory action and also the prevention of amyloid- β formation (Marucci et al., 2021). The use of galantamine significantly reduced death rates and produced long-lasting improvements in cognitive and daily functioning skills.

2.2 Pharmacodynamics of galantamine

2.2.1 Indication

Galantamine was given FDA approval in 2001 for treating mild to moderately severe Alzheimer's (Lilienfeld, 2006). The list below includes other off-label uses for galantamine that are not FDA-approved.

- Galantamine is used to treat vascular dementia, and it is also used to treat AD together with memantine.

- It is beneficial in treating dementia caused by Parkinson's disease.
- To alleviate cognitive impairment caused by Lewy body disease.
- It is employed in the treatment of frontotemporal dementia.
- Galantamine is also effective in treating Multiple Sclerosis-related dementia.
- Galantamine, either by itself or in combination with memantine, is efficient in treating cognitive deficits brought on by TBI.
- The oculomotor, trochlear, and post-traumatic nerve palsies can all be treated with it.
- Electroconvulsive therapy (ECT)-related cognitive loss can be managed with galantamine either alone or in combination with memantine.
- Positive, cognitive, and negative schizophrenia-related symptoms may be controlled with galantamine in addition to antipsychotics and memantine. It relieves some of the symptoms associated with autism in children when used in combination with risperidone.
- Galantamine therapy improves verbal expression and interpersonal interactions in adults with autism.
- It works well for treating acute scopolamine poisoning.
- Treatment with galantamine is effective for persistent post-stroke aphasia.
- It is a form of substitution treatment used to help people with alcohol dependence quit smoking.
- It helps the bipolar disorder-related cognitive impairment.
- Galantamine is an effective treatment for organophosphorus poisoning and can promote quality sleep in persons with mild to severe Alzheimer's disease, vascular dementia, or both.
- It is employed to treat Down syndrome-related dementia.

The cholinergic regulation of inflammation, metabolic disorders, and cognitive decline in obesity-related diseases, by galantamine has provided a basis for further improvements in therapeutic research (Kalola et al.,2022).

2.2.2 Approved dosage form & and dosage regimen

Galantamine is typically administered orally. To improve memory and cause lucid dreams, it is easily accessible over the counter as a supplement in two dosage forms of 4 mg tablets and 8 mg capsules. There are now 2 different dosage form types available on the market: immediate release and extended release.

The extended-release (ER) dosage form comes in three distinct strengths for capsules: 8 mg, 16 mg, and 24 mg which are shown in Table 1. With a single morning dose, the ER capsule provides the benefit of a simple dosage regimen. Patient adherence with treatment plan is subsequently boosted as a result. (Brodaty et al. 2005). It is best to swallow an ER capsule whole rather than opening or chewing one that contains the whole daily dosage. It is best to take the ER pill with meals in order to alleviate or totally prevent uncomfortable symptoms of nausea, vomiting, and stomach irritability. The dose range for extended-release capsules that has demonstrated effectiveness for dementia caused by AD in a controlled clinical study is 16 to 24 mg/day. 8 mg daily, administered once with breakfast for at least four weeks, is the recommended initial dose for dementia therapy. The dosage can then be extended until it reaches the prescribed maintenance dose of 16 mg per day. After at least 4 weeks of taking the 16 mg/day dosage, it may be advised to increase the dose further to keep the patient at 24 mg per day. If doses need to be changed, consideration is given to the patient's medical benefits and degree of dose tolerance. The two most common drug-delivery vehicles are tablets and solutions. Galantamine is available in several strengths for tablets, including 4 mg, 8 mg, and 12 mg. The solution form has a concentration of 4 mg / ml. Randomized clinical research for

dementia caused by AD found that immediate-release tablets taken daily in doses between 16 and 32 mg were beneficial. Dosage regimen of immediate release has shown in Table 2. The suggested dosage limit is 16 to 24 mg/day, administered in two separate doses with meals to reduce or totally eliminate gastrointestinal unpleasant effects including nausea and vomiting, although studies reveal that the 32 mg daily dosage has become less acceptable than other smaller dosage.

Table 1- *Dosage regimen of extended-release oral capsule*

Dose	**Strength**	**Frequency of dosing**
Initial dose	8mg	Once per day
After 4 weeks	16mg	Once per day
After additional 4 weeks	24mg	Once per day
Maintenance dose	16-24mg	Once per day
Maximum dose	24mg	-----

It is recommended to begin the treatment plan with the lowest possible dosage and gradually increase it after thoroughly evaluating the patients for clinical advantages and adherence to the prior dosage. The starting dosage for the treatment program is a 4 mg dose taken twice day with meals. The suggested starting maintenance dose is 16 mg/day, which can be raised after at least 4 weeks. After at least four weeks of taking 16 mg daily, it is possible to consider increasing your dosage to 24 mg daily. Since a clinical investigation has not evidenced that a dosage of 24 mg/day is statistically substantially more beneficial, continue the patient on 16 mg/day if at all possible. However, in certain people, a dose of 24 mg/day could provide better therapeutic advantages. If one dosage is skipped, the patient should take it as quickly as they recall. If it is almost time to take the next dosage, the missing dose is avoided in order to maintain the regular dosing schedule. To make up for missed doses, the dosage cannot be

increased. If a dose is missed for longer than 72 hours, the therapy will resume at the lowest dose and be progressively increased to the existing dosage level. Galantamine has the capability to produce dehydration, thus the patient and caregivers need to be informed about the need of getting enough fluids in their systems.

Table 2*- Dosage regimen of immediate-release oral tablet*

Dose	**Strength**	**Frequency of dosing**
Initial dose	4mg	Twice per day
After 4 weeks	8mg	Twice per day
After additional 4 weeks	12mg	Twice per day
Maintenance dose	16-24mg	Twice per day (divided into 2 doses)
Maximum dose	24mg	-------

The normal maximum limit for galantamine dose in individuals with renal insufficiency as well as creatinine clearance between 9 - 59 ml/min is 16 mg/day. Galantamine therapy, regardless of wether immediate or delayed release, is often not advised if the patient's creatinine clearance becomes less than 9 ml/min. When titrating the dose for individuals with moderately severe hepatic impairment, attention must be used, and the daily maximum dosage must typically not exceed 16 mg. Galantamine, instant or extended-release, is contraindicated in patients with severe liver disease.

The abrupt withdrawal of immediate-release or delayed-release galantamine in patients receiving dosages that are within the optimum range is not associated with a higher incidence of adverse effects as compared to the group of people who continue to take the same doses of galantamine. But once the drug is discontinued, the galantamine's therapeutic effects disappear.

(Kalola et al.,2022). If donepezil, yet another acetylcholinesterase inhibitor, is ineffective or poorly tolerated by patients, galantamine could be a viable alternative (Olazarán Rodrguez & Navarro Merino, 2005).

2.2.3 Drug Interactions:

Galantamine is a cholinergic agent that can be pharmacologically affected by anticholinergic drugs.

Cholinesterase Inhibitors with cholinomimetics: Galantamine, a cholinesterase inhibitor, is likely to have a synergistic activity with the other cholinesterase inhibitors as well as cholinergic agonists including such bethanechol, succinylcholine, and comparable neuromuscular blocking drugs.

Effect of Other Drugs on Galantamine

The CYP3A4 inhibitors erythromycin and ketoconazole, when taken with galantamine, reduce the amount of the drug that is cleared from the body. Galantamine's oral bioavailability is enhanced with the addition of CYP2D6 inhibitors such as ketoconazole, paroxetine, amitriptyline, fluoxetine, fluvoxamine, and quinidine.

Its bioavailability is also increased when it is taken together with the H2-receptor antagonist cimetidine. Galantamine will be broken down more quickly by medications including carbamazepine, phenytoin, phenobarbital, rifampin, and dexamethasone that are frequently used to increase hepatic cytochrome P450 CYP 3A4 or CYP 2D6 enzymes.

When given with oral galantamine at a dosage of 16 mg twice day, memantine, has no effect on the pharmacokinetics of the drug. When treating Alzheimer's disease, the combination of donepezil with memantine is preferable than that of galantamine and memantine. Research

published in vitro reveal that galantamine did not interfere with the CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6, or CYP2E1-catalyzed metabolic processes. This suggests that galantamine has relatively little ability to inhibit the main types of cytochrome P450.

Galantamine inhibits heart function and also is vagotonic. Atrioventricular block and bradycardia can also be brought on by antihypertensive drugs including beta-blockers (acebutolol), alpha and beta-blockers (carvedilol), as well as calcium channel blockers (diltiazem). These medicines may have an additional bradycardic impact when galantamine is taken with them. Galantamine can be safely provided alongside ACE inhibitors like ramipril because they have no interactions or effects on the pharmacokinetics of galantamine (Kalola et al.,2022).

2.2.4 Mechanism of Action

Reversible competitive inhibition of acetylcholinesterase and allosteric regulation of the nicotinic receptor are two of galantamine's multiple modes of action that may be beneficial for patients. It has been proven that the monoclonal antibody FK1 selectively blocks the galantamine-binding site without interfering with the acetylcholine binding site, suppressing the stimulatory effects of galantamine. Galantamine increases the amount of acetylcholine within that synaptic cleft by functioning as an acetylcholinesterase inhibitor, which reduces the rate of acetylcholine breakdown nicotinic modulation, that further increases receptor sensitivity, enhances the effects of acetylcholine on nicotinic receptors (Figure 4).

Galantamine has both excitatory and inhibitory actions on neural transmissions in rat and human brain tissue, according to Santos et al. Alternative AChEIs, such as donepezil, rivastigmine, and metrifonate, exhibited no synaptic transmission-altering effects because they

lacked allosteric potentiating ligand activity. Galantamine may have a broader impact on other neurotransmitter systems and reduce the behavioral symptoms associated with dementia by regulating the production of glutamate, serotonin, and -aminobutyric acid. Additionally, this approach could increase the expression of nicotinic acetylcholine receptors and halt neurodegeneration.

Since nicotinic receptors are crucial for cognition, nicotinic receptor manipulation may provide therapeutic benefits for dementia sufferers. Several neurotransmitters, including acetylcholine, glutamate, serotonin, and norepinephrine, that are significant neurotransmitters associated with modulating cognition and state of mind, are released under the direction of presynaptic nicotinic receptors. Research conducted on human individuals and animals have demonstrated that blocking nicotinic receptors worsens cognition while specifically activating or modulating certain nicotinic receptor subtypes enhances cognition as well as memory. For people with Alzheimer's disease or any other kinds of cholinergic deficiency-related dementias, a drug that enhances acetylcholine actions at nicotinic receptors, like the galantamine, might provide extra benefits above medications that work only on cholinesterase enzyme inhibition.

Preliminary research suggests that galantamine has nicotinic potentiating properties. Galantamine seems to attach with an allosteric position on the nicotinic receptor, changing its conformation and increasing the production of acetylcholine as well as the activation of nearby neurons, such as glutaminergic and serotoninergic ones. This method offers a way to balance the current cholinergic impairment in dementia patients since nicotinic receptor modification has no effect on the highest attainable degree of receptor activation. Due to its two mechanisms of action, galantamine may indeed be a potential therapy choice for those with Alzheimer's disease, vascular dementia, and Alzheimer's disease combined with cerebrovascular disorder

who have neither responded effectively to or have managed other acetylcholinesterase inhibitors weakly (Farlow, 2003).

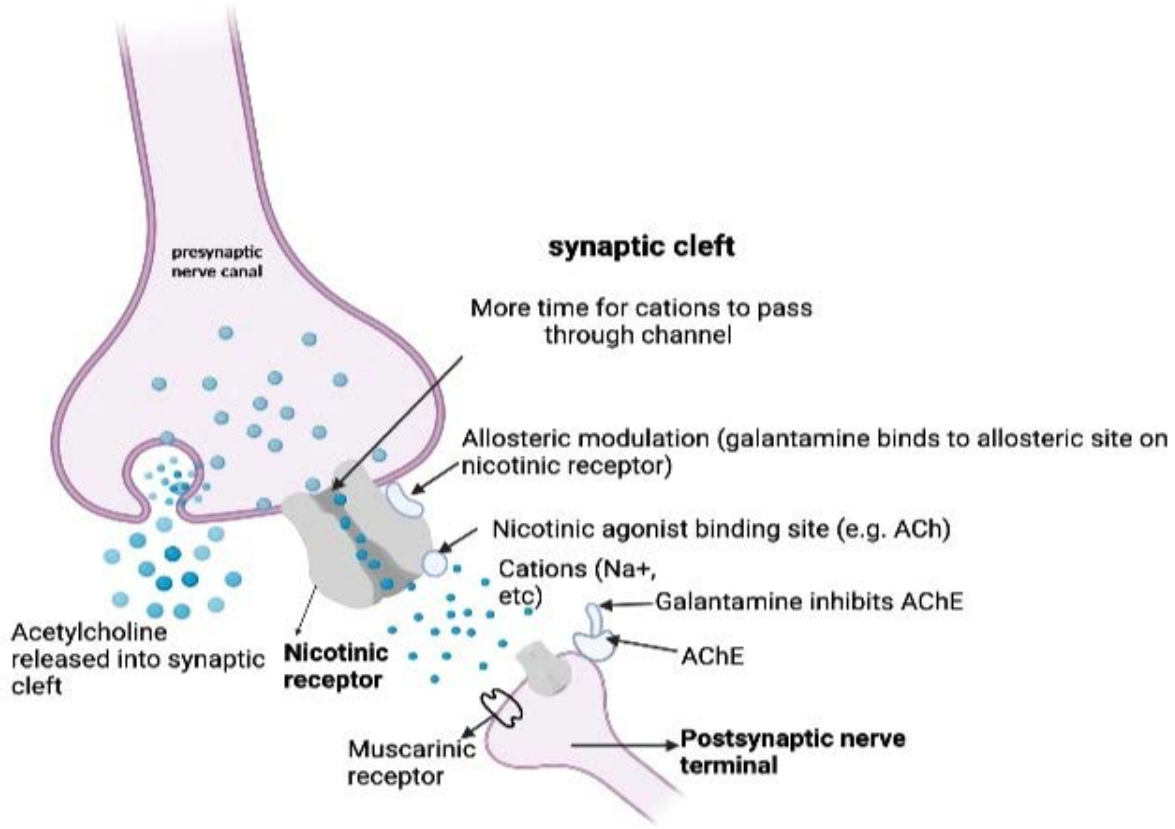

Figure 4: Mechanism of Acttion of Galantamine (Farlow, 2003).

2.2.5 Side effects

Cardiovascular system: Galantamine is a selective cholinesterase inhibitor, and as a result of its pharmacological activity, it exerts inhibitory vagotonic actions on the cardiovascular system. Sinus bradycardia results from the suppression of sinoatrial activity, as well as the first line of treatment for symptomatic bradycardia consists of stopping the harmful substance and administering atropine intravenously to counteract the cholinergic action of the galantamine (Leclerc et al., 2008).

An atrioventricular block may result from a stoppage in conductivity at an atrioventricular node. Patients have reported sinus bradycardia and a variety of heart blocks, both in individuals with and without having any underlying cardiac conduction problems. As a result, it is important to treat every patient as having a high chance of having negative effects on cardiac conduction. In order to avoid QT prolongation, syncope, or delirium, galantamine administration must be carefully monitored for risk factors (Fisher & Davis, 2008). Following the recommended dosage schedule, patients undergoing galantamine treatment at doses up to 24 mg/day have evidenced that the greater risk of syncope is dose-related.

Gastrointestinal system: Galantamine is a well-accepted antidementia medicine, with the exception of gastrointestinal (GI) side effects, that are an expected outcome of its cholinergic pharmacological features. The most frequent GI side effects include lack of appetite, nausea, vomiting, diarrhea, and losing weight (Imbimbo, 2001).

Thus, it is necessary to keep track of the patient's weight while they are receiving galantamine treatment. The degree of GI side effects often decreases with dose reduction and is typically minor and transient. According to clinical investigations, nausea and vomiting often last 5 to 6 days once therapy starts with each dosage increase. Patients having higher doses may have severe cholinergic adverse effects; these effects are typically a result of the first dosage titration's fast rate increase. Because of enhanced parasympathetic function, the cholinergic agent galantamine's principal impact may be predicted to boost stomach acid production. As a result, individuals who have an extra risk factor of having ulcers, for example those who have a background of peptic ulcer disorder or those who are using nonsteroidal anti-inflammatory drugs simultaneously, must be constantly examined for indications of having any active or occult bleeding from the gastrointestinal tract (Kalola et al.,2022).

2.3 Pharmacokinetics of Galantamine

Galantamine's pharmacokinetics are linear at doses between 8 and 32 mg each day. The four parameters of pharmacokinetics of galantamine have been shown in Table 3.

2.3.1 Absorption and Distribution

Galantamine gets absorbed over the course of approximately one hour, reaching its highest concentration. Galantamine has an absolute bioavailability of around 90%. The oral solution form and the tablet form both had the equal level of bioavailability. Meals had no effect on the AUC of galantamine, but they did cause a 25% reduction in C_{max} and a 1.5-hour delay in T_{max} when given with food. Galantamine has a mean volume of distribution of 175 L.

At therapeutically relevant dosages, galantamine has an 18% plasma protein binding. In total blood, blood cells get the majority (52.7%) of galantamine. Galantamine is present in blood and plasma in a ratio of 1.2.

2.3.2 Metabolism and Excretion

Galantamine is metabolized primarily via the cytochrome P450 isoenzymes CYP2D6 and CYP3A4, according to in vitro tests. Both of these pathways' inhibitors somewhat enhance the drug's oral bioavailability. O-demethylation, which was mediated by CYP2D6, was more prevalent in extensive CYP2D6 metabolizers than in poor metabolizers. Furthermore, the majority of the sample's radioactivity in plasma of both poor as well as extensive metabolizers came from unaltered galantamine along with its glucuronide. When H-galantamine was administered orally, both weak and extensive CYP2D6 metabolizers had unmodified galantamine as well as its glucuronide, which accounted for the bulk of the plasma radioactivity.

***Table 3**: Pharmacokinetic parameters of Galantamine (fda &cder, n.d.)*

Pharmacokinetic parameters		Oral
Absorption	Bioavailability T_{max} Bioavailability- effect of food Mean plasma concentration for 24 mg/day	90-100%. 1 hour Food does not affect the AUC C_{max} is reduced by 25%, and T_{max} is delayed by 1.5 hours 82-97 μg/L.
Distribution	Vd Plasma protein binding Blood to plasma conc ratio Blood brain barrier crossing	175 L. 18% 1.2 Yes
Metabolism	Metabolizing enzyme	hepatic cytochrome P450 isoenzymes CYP2D6 and CYP3A4.
Excretion	Clearance Half life Excretion of the drugs and its metabolites	renal clearance 65mL/min, total plasma clearance is about 300 mL/min. 7 hours Urine 95% Feces 5%

Galantamine glucuronide made for 14–24% of the radioactivity in the plasma up to 8 hours after the injection, whereas unmodified galantamine contributed for 39%–77%. 93-99% of the radioactivity had been recovered after 7 days, with 95% of it being found in urine and 5% in

feces. Average urine recovery of unmodified galantamine was 32% of the dosage while average urine recovery of galantamine glucuronide was 12% of the dose.

Following intravenous or oral treatment, approximately 20% of the dosage was eliminated in the urine within 24 hours as unmodified galantamine, corresponding to a renal clearance of around 65 mL/min, approximately 20–25% of the total plasma clearance of almost 300 mL/min. The terminal half-life of galantamine is approximately 7 hours (Fda, n.d.).

Chapter 3

Methodology

3.1 Data Source

This observational and pharmacovigilance research was carried out using information from the Food And Drug Administration Adverse Event Reporting System (FAERS) database. The phenomenal and significant adverse event reporting system developed by the US Food and Drug Administration, FAERS, receives approximately 1.5 million reports of adverse events caused by drugs, devices, and vaccines every year. The US FDA gets spontaneous reports of adverse events from manufacturers, customers, and healthcare providers. These reports are collected in the FAERS database. Information about demographics, results, suspicious drugs, reporting nations, and interacting drugs is included in the FAERS database (Vestergaard Kvist et al., 2021). These events are recorded in the FAERS database with the proper MedDRA (Medical Dictionary for Regulatory Activities) keywords. Adverse events submitted to the FAERS database promote public consciousness while also facilitating the discovery of drug-related safety issues (Mazhar et al., 2021). On all adverse events reported to the FDA, the public can see statistics on them every three months (Vestergaard Kvist et al., 2021). The FDA-approved "acetyl cholinesterase inhibitors" are administered to manage "indications," (mention indication) and by checking at the FDA Adverse Event Reporting System (FAERS), an adverse event-reporting database, we observe a considerable number of adverse events recorded by patients, pharmaceutical companies, and medical practitioners. The database currently has 26,004,135 records in it. The data used in this research were gathered between January 2015 and September 2022, and the analysis was conducted in January 2023. "Galantamine" was the searching keyword used for the generic name. The recommended terminology from The

Medical Dictionary for Regulatory Activities (MedDRA) were also used to classify adverse events.

3.2 Inclusion and Exclusion Criteria

The FAERS database was used to gather the information needed for this study from January 2015 to September 2022. The following reported adverse events were selected for this investigation employing MedDRA preferred terms (PTs): "death," "sudden death," "sudden cardiac death," "cardiac death," "brain death," "accidental death," and "apparent death." These words are all combined gathered into the terms "death" and "Rhabdomyolysis." The database included all of the adverse events associated with the drug known by its generic name, galantamine. When other drugs were suspected of being the source of the adverse events, we removed those data from our analysis and only included the data for these specific drugs. Therefore, "Galantamine" was the sole medicine claiming of causing the anticipated adverse events. Furthermore, we eliminated any duplicated entries by addressing them with case number as well as cross-matching the age, gender, and event date.

3.3 Statistical Analysis

In January 2023, the data were extracted and analyzed using the FAERS database. Using the reported odds ratio (ROR) and its accompanying 95% confidence interval, we conducted a disproportionality analysis in the present study (CI). With the use of this research, we were able to find indicators that the medicine in question (galantamine) was being reported in conjunction with negative side effects (Death and Rhabdomyolysis). Since ROR is an approach that has been proven to be effective in identifying drug safety signals in case-non-case studies, it was used (Bene et al., 2014). When determining the disproportionality measures, ROR is acknowledged to be one of the methods used most frequently. A 2 by 2 contingency table with cases of the drug's expected side effects and non- Therefore, the ROR is required to properly

evaluate the level of disproportionality, and the CI confirms its statistical significance. If the confidence interval's lower limit is higher than 1, it signals that there have been more reports of these side effects than with other drugs which are known to cause them. If, on the other hand, the lower limit of the confidence interval is equal to or less than one, it indicates that there is no signal for the adverse impact, implying that the adverse effect is less substantially recorded when comparing with other drugs (Sato et al., 2020).

To determine the reported correlation between the adverse effects (Death and Rhabdomyolysis) and the specific drug (Galantamine) in this study, we estimated ROR and the associated 95% CI, with the entire database being used as the comparator (Sato et al., 2020). As a result, we were able to figure out the statistical significance of the correlation between the drug in query and the adverse outcomes when compared to all the other medicines in the database. Then, using other drugs belonging to the similar class as a comparator, the ROR and 95% CI were estimated for the concerned drugs with the similar adverse events. This made it possible to identify the class with the highest reporting association of the adverse event. A drug's reporting relationship is greater than that of other drugs if its ROR score is higher. Using R 4.2.1, all data analysis were carried out.

Chapter 4

Results & Discussion

4.1 Results

The case control study was done about adverse effects of Galantamine from FAERS database. Table 4A and table 4B show the baseline characteristics by galantamine, other AChEI and other drugs treatment in patients with Alzheimer dementia during an average of 7 years of follow-up from 2015 to 2022. In order to figure out which drugs generate more cases of death and rhabdomyolysis, baseline characteristics of the patient subgroups were differentiated employing Galantamine and other drugs, as given. Forest plot of association between death and galantamine as well as rhabdomyolysis & galantamine has shown in Figure 6 & Figure 7. The frequency and Reporting Odd Ratio (ROR) were the parameter which were calculated for each adverse event of whole database and drug class (Figure 5).

When other drugs were compared with galantamine, only 24 death cases were reported from galantamine users whereas 456144 was reported from other drugs user within 7 years. The ROR for galantamine in FAERS in this case was 1.22 (95% CI: 0.81–1.83; p=0.3436). To compare the mortality benefit of Galantaamine more precisely its then compared with other classes of AChEIs in which FAERS got report of 680 death cases within 2015-2022 and the ROR was 0.31(95% CI: 0.21-0.47; p<0.0001) in this case.

FAERS database included 8 reports of rhabdomyolysis from galantamine users whereas 19 cases were from other classes of AChEIs and 16379 from other drugs (table 3). Overall galantamine might cause rhabdomyolysis but in compared to other drugs the rate was not that

much (ROR: 11.35; 95% CI: 5.85-22.80; p<0.0001). In comparison with other classes of AChEIs the ROR from FAERS database was 4.05 (95%CI: 1.77-9.29; p=0.0009).

Table 4A: *FAERS database analysis of reported death cases from 2015-2022*

Drugs	Cases of Death	ROR(CI)	P value
Galantamine	24		
Other drugs (whole database as comparator)	456120	1.22 (0.81 - 1.83)	P = 0.3435
other drugs of AChEIs (class as comparator)	680	0.31 (0.21-0.47)	P < 0.0001

Table 4B: *FAERS database analysis of reported Rhabdomyolysis cases from 2015-2022*

Drugs	Cases of Rhabdomyolysis	ROR(CI)	P value
Galantamine	8		
Other drugs (whole database as comparator)	16379	11.35(5.65- 22.80)	P < 0.0001
other drugs of AChEIs (class as comparator)	19	4.05 (1.77 to 9.29)	P = 0.0009

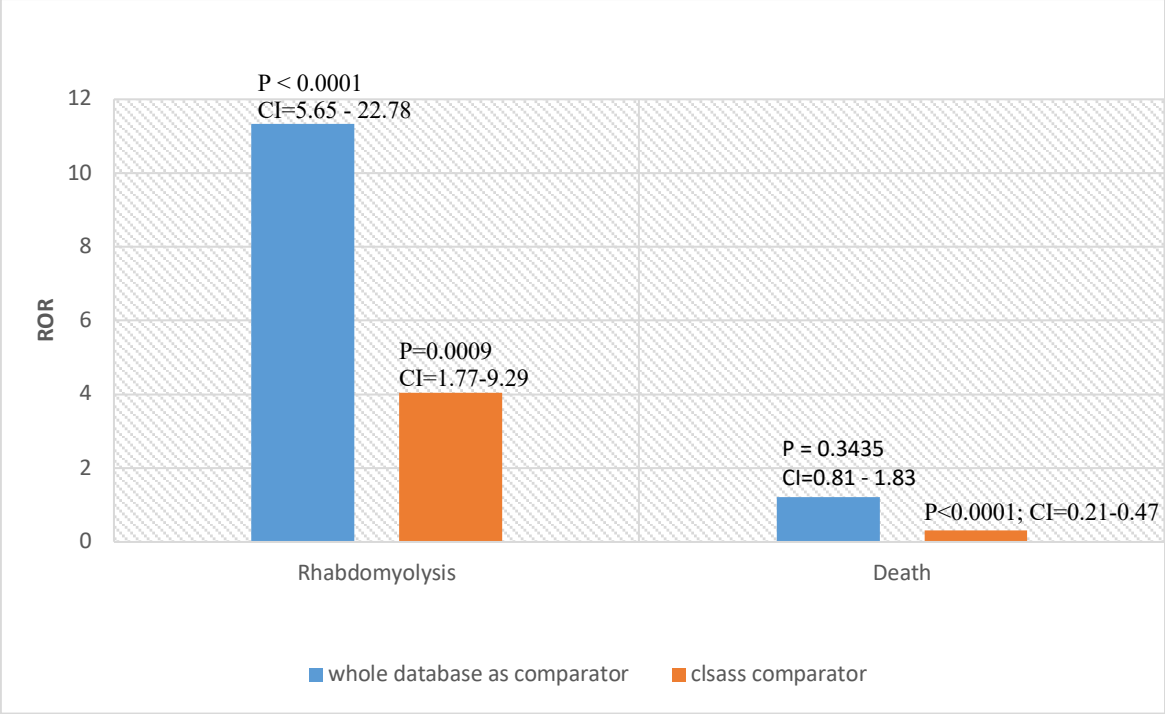

Figure 5: ROR of Death & Rhabdomyolysis for Galantamine & Other Drugs From FAERS

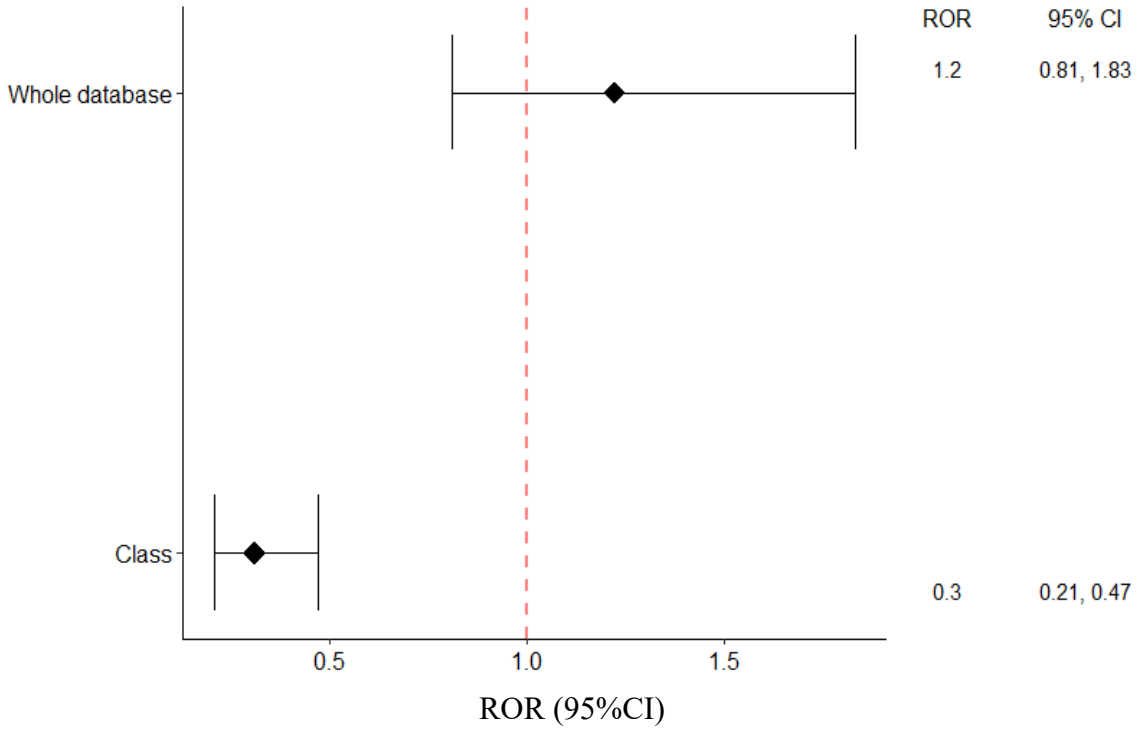

Figure 6: Forest Plot of Association Between Death & Galantamine

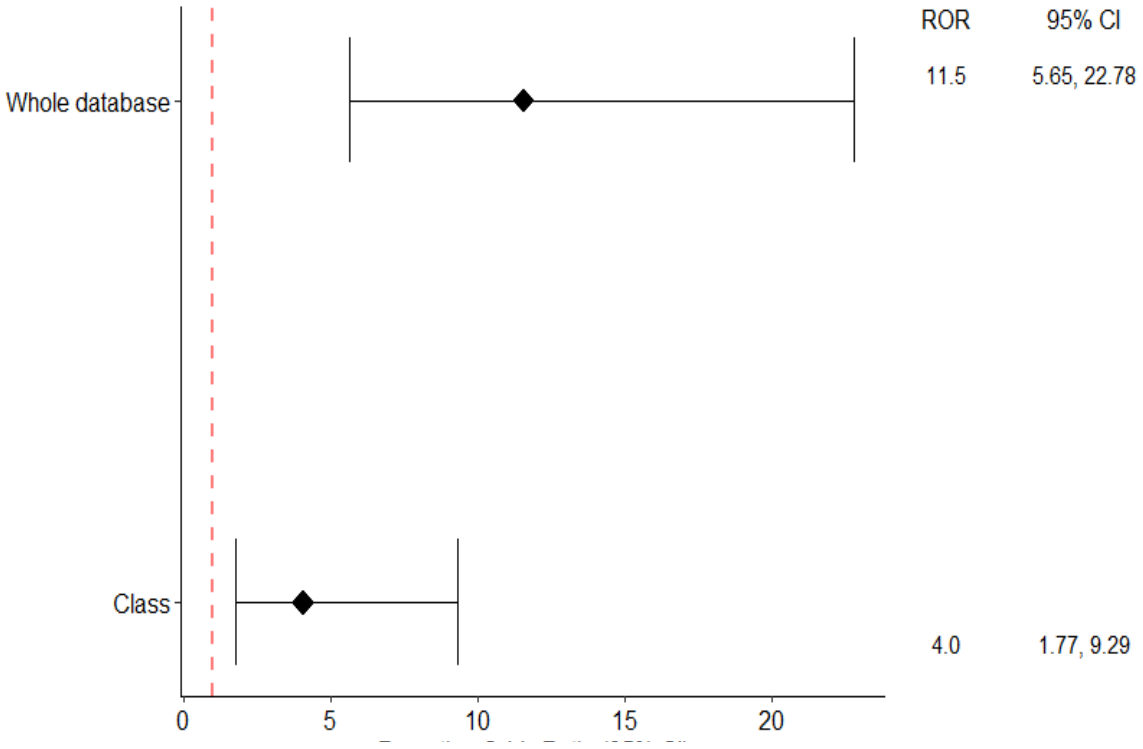

Figure 7: Forest Plot of Association Between Rhabdomyolysis & Galantamine

4.2 Discussion

Galantamine has shown statistical significance of the correlation of having mortality benefit in comparison with other drugs. More death cases were reported from the other drugs users than galantamine users. AChEIs are correlated with moderate cognitive improvements that remain over time. The mild cognitive benefits of AChEIs may likely contribute to their association with a lower risk of death. The drug with the biggest impact on cognition and the only one to show a noticeable decrease in the chance of having advanced dementia seemed to be galantamine. Furthermore, galantamine usage was related with a lower chance of severe dementia and death, as well as the greatest effect on the association with cognitive decline. The only ChEI that functions also as an allosteric nicotinic modulator is galantamine, a fast reversible ChEI. This dual action as a nicotinic receptor modulator and acetylcholinesterase inhibitor may account for its intensifying impacts (H. Xu et al., 2021). As a result of hospitalization, death, and the handling of the sociological aspects of severe dementia, patients with rapid cognitive impairment may have better chances of dropping out since these factors are likely to overshadow care efforts or hamper follow-up. Therefore, patients with significant impairments might miss follow-up appointments more frequently. Patients who are monitored as a result have a higher chance of beginning with greater cognition and experiencing slower cognitive impairment (H. Xu et al., 2021). Since several study found out that galantamine is more effective than others due to its dual action hence it does have more potentiality than others which might lead to less mortality rate.

Galantamine has few common side effects like gastrointestinal, cardiovascular but apart from this rhabdomyolysis is also noticed in few cases which were found in our study. According to our study result, galantamine got more reports of having rhabdomyolysis than any other drugs.

The primary function of the neurotransmitter acetylcholine is to transfer signals from nerve cells towards muscle cells. Acetylcholine is released across motor nerve cells' synapses to muscle cells when the specific signal from their nervous system is received. Acetylcholine activates receptors on these muscle cells to start the muscle contraction activity. It goes without saying that the neurotransmitter should always be broken down once the message has been transmitted because otherwise, a jumble of outdated neurotransmitter molecules may mislead following signals. AChE's purpose is to degrade old acetylcholine. Our results show that galantamine significantly increases the risk of rhabdomyolysis compared to all other classes of AChEIs or other drugs. Galantamine is thought to block the enzyme AChE, so it's possible that doing so could produce a considerable accumulation of ACh near synapses and neuromuscular junctions, which could result in symptoms of nicotinic and muscarinic poisoning. Cramping, excessive muscle contraction, muscle aches, and perhaps even muscular fasciculation may all lead to rhabdomyolysis.

Chapter 5

Conclusion

Patients with mild-to-moderate AD and dementia are usually treated with NMDA antagonists and cholinesterase inhibitors like donepezil, rivastigmine, and galantamine. Galantamine has been demonstrated in this study to have effects on mortality and rhabdomyolysis when compared to other drugs and other AChEI classes. One AChE inhibitor, galantamine, has a dual activity as an acetylcholinesterase inhibitor and nicotinic receptor modulator, which may reduce mortality. Since fewer deaths were reported, it may be seen as a more dependable alternative for treating Alzheimer's patients. Unfortunately, rhabdomyolysis may be a drawback of this treatment choice since we observed few rhabdomyolysis incidents reported from galantamine users. A mortality benefit and rhabdomyolysis from galantamine were statistically significant findings from this study, and these findings may be valuable for future studies on advanced treatments of AD and dementia as well as for assisting medical professionals in selecting the most effective course of therapy for this disease.

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Fda. (n.d.). *HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use RAZADYNE ® ER and RAZADYNE ® safely and effectively. See full prescribing information for RAZADYNE ® ER and RAZADYNE ®. RAZADYNE ® ER (galantamine hydrobromide) extended-release capsules, for oral use RAZADYNE ® (galantamine hydrobromide) tablets, for oral use RAZADYNE ® (galantamine hydrobromide) oral solution*. www.fda.gov/medwatch.

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