# Signal Detection of Rhabdomyolysis and Death for Rivastigmine: A Pharmacovigilance Study

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# Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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# Approval

The project titled “Signal Detection of Rhabdomyolysis and Death for rivastigmine: A Pharmacovigilance Study” submitted by Sadique Abdal Mahee (19146027) 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

This study does not involve any human or animal trials.

## Abstract

The following study utilized the Food and Drug Administration Adverse Event Reporting System (FAERS) database to determine the AChI inhibitor, rivastigmine's effect on patient mortality as well as its side effect of rhabdomyolysis. The statistical analysis involved finding the number of cases of death/rhabdomyolysis for rivastigmine (using both the whole database and only the AChI class as comparators). The reporting odds ratios (ROR) was then calculated. In terms of patient mortality, the results showed that rivastigmine was significantly associated with more cases of deaths both when compared within the class (ROR = 10.62; CI 95% = 7.84 – 14.38; $P < 0.0001$) and also with the whole database (ROR = 5.90; CI 95% = 5.43 – 6.41; $P < 0.0001$). Additionally, no cases of reported rhabdomyolysis were found for rivastigmine. Hence, rivastigmine's apparent negative effect on patient mortality should be something to consider while selecting the drug for therapy.



**Keywords:** Alzheimer's disease, Dementia, rivastigmine. Death, Rhabdomyolysis.

## Acknowledgement

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## List of Acronyms

| | |
|---|---|
| AD | Alzheimer’s disease |
| Aβ | Amyloid-β peptide |
| SP | Senile plaques |
| NFTs | Neurofibrillary tangles |
| EOAD | Early-onset Alzheimer’s disease |
| LOAD | Late-onset Alzheimer’s disease |
| APP | Aβ precursor protein |
| NMDAR | N-methyl-D-aspartate receptor |
| Ach | Acetylcholine |
| AChEIs | Acetylcholinesterase inhibitors |
| BBB | Blood brain barrier |
| BuChE | Butyrylcholinesterase |
| ADAS-Cog | Alzheimer's disease assessment scale-cognitive subscale |
| CYP450 | Cytochrome P450 enzyme |
| FAERS | FDA Adverse Event Reporting System |
| FDA | Food and Drug Administration |

# Chapter 1

# Introduction

## 1.1 Alzheimer’s Disease and Dementia

Dementia is a clinical illness marked by a constant and significant degradation of a minimum of 2 cognitive functions, namely attitude/ behavior, speech, motor functions, memory etc that directly lead to a lessened ability of a person to perform everyday tasks and overall decreases quality of life (Weller & Budson, 2018).

The most abundant cause of dementia is said to be Alzheimer's disease (AD) which results in the destruction of brain cells. A combined effect of environmental / genetic / lifestyle parameters may be the cause of AD. Its two primary disease characterizations are: neurofibrillary tau tangles and the development of β-amyloid plaques (Weller & Budson, 2018). Memory impairment, difficulties in problem-solving or planning, difficulty completing routine tasks, confusion about time or location, difficulty comprehending visual pictures and spatial relationships, and new word-related impairments in speaking or writing are common clinical symptoms of AD.In the current clinical scenario, there is no permanent treatment solution to cure AD. However, recent advancements in the field are intended to help people preserve their mental and behavioral functions, as well as to postpone the disease's symptoms (Rahman et al., 2017).

According to Breijyeh & Karaman, 2020, AD can be listed into the following categories:

1. The Preclinical stages of AD: Hallmarks are minimal losses of memory and early pathological changes in the cortex and hippocampus, but there is no functional impairment in everyday activities and no clinical evidence of AD symptoms or signs. It lasts for a number of years or longer.

2. Early stages of AD - The symptoms include depression, mood swings, memory loss and decreased attention spans leading to impaired daily activities.
3. Moderate AD stage: As the disease progresses, it affects more cerebral cortical regions, which causes memory loss that is more severe, makes it harder to identify family members and friends, a lack of impulse control, and difficulties with reading, writing, and speaking.
4. Severe/late-stage AD – Significant loss of memory translates to patients not being able to recognize even family, may become bedridden with problems swallowing and urinating, and eventually die as a result of these complications. This is because the disease has spread to the entire cortex area and there has been a severe accumulation of neuritic plaques and neurofibrillary tangles.

In order to get the definitive diagnosis of AD, examination of brain tissue is required. However in living patients, AD can be diagnosed within a reasonable degree of certainty through the analysis of Cerebrospinal fluid using positron emission tomography (PET) biomarkers. The National Institute of Neurological and Communicative and Strokes - Alzheimer's Disease and related Disorders Association (NINCDS-ADRDA) updated its criteria for the diagnosis of AD in 2011 in order to implement better specificity (Breijyeh & Karaman, 2020).

## 1.2 Etiology

The specific reasons behind the various pathological changes concerned with Alzheimer's disease are still somewhat unknown. Although there are a few theories that attempt to explain the cause of AD, a universally recognized hypothesis is still unknown. (Breijyeh & Karaman, 2020). Two of the more widely accepted theories are:

1. Cholinergic Hypothesis - ACh is manufactured inside of cholinergic neurons from choline and acetyl-coenzyme A by the ChAT enzyme and transported to the synaptic vesicles by vesicular acetylcholine transporter (VAChT). In the brain, ACh is involved in several physiological processes such as memory, attention, sensory information, learning, and other critical functions. Degeneration of the cholinergic neurons was found to take place in AD and to cause alteration in cognitive function and memory loss. B-amyloid is believed to affect cholinergic neurotransmission and to cause a reduction in the choline uptake and a release of ACh. Studies demonstrated that cholinergic synaptic loss and amyloid fibril formation are related to Aβ oligomers' neurotoxicity and to interactions between AChE and Aβ peptide. Additional factors also contribute to the progression of AD, such as a reduction in nicotinic and muscarinic (M2) Ach receptors, located on presynaptic cholinergic terminals, and the deficit in excitatory amino acid (EAA) neurotransmission, where glutamate concentration and D-aspartate uptake are significantly reduced in many cortical areas in AD brains. This is in addition to the use of cholinergic receptor antagonists such as scopolamine, which was found to induce amnesia. This effect can be reversed by using compounds that activate acetylcholine formation. As a result, the cholinergic hypothesis is based on three concepts: reduced presynaptic cholinergic markers in the cerebral cortex, severe neurodegeneration of nucleus basalis of Meynert (NBM) in the basal forebrain, and the effect in memory impairment that antagonists of Cholinesterase seems to exert (Breijyeh & Karaman,2020)

2. Amyloid Hypothesis - Aberrant β-sheet deposition in the central nervous system strongly correlated with dementia. However, it was shown that with aging, amyloid plaques (AP) also form in the normal, healthy brains, raising the question of whether or not AP deposition is the cause of AD onset. According to the amyloid hypothesis, aging or pathological conditions impairs the breakdown of Aβ, which results in the accumulation

of Aβ peptides (Aβ40 and Aβ42). An increase in the Aβ42/Aβ40 ratio causes the creation of Aβ amyloid fibrils, which causes neurotoxicity and the development of tau pathology, ultimately ending in the death and degeneration of neuronal cells (Breijyeh & Karaman, 2020).

Some of the risk factors associated with AD include:

1. Age - Risk of AD increases with age for both women and men. International Alzheimer's Disease Report estimates that 47 million people worldwide are living with AD in 2015, and this is estimated to increase to 131 million people by 2050. After the age of 65, the lifetime risk of AD is one in six for women (16.7%), whereas it is one in eleven for men (9.1%) (Rahman et al., 2017).
2. Obesity - There is upto a 40% increased risk of AD for obese individuals. Weight loss and low body mass index are significantly correlated with elevated risk of AD in older adults, whereas a higher body mass index may be protective at advanced ages (Rahman et al., 2017).
3. Genetics - Development of AD seems to depend significantly on genetic factors as well. Random changes in important genes such as the apolipoprotein E (ApoE), Amyloid precursor protein (APP), Presenilin-1 (PSEN-1), and PSEN-2 are said to lead to AD (Breijyeh & Karaman, 2020).
4. Others - Down syndrome, trauma to the brain, CVD etc are all thought to be risk factors for AD but there is not enough research to fully support this claim (Rahman et al., 2017).

Mutations in the APP, PSEN1 or PSEN2 genes can result in dominantly inherited familial AD (FAD). Genetic risk factors have been identified to be linked to late onset AD (LOAD), eg, including the apolipoprotein E gene (APOE). The main risk factors for developing AD include history of disease in a close family, the APOE4 genotype, as well as age. The risk

ratio for AD in people with heterozygous APOE4 is 3 compared to non-carriers. The odds ratio for those with homozygous APOE4 is 12. Additionally, the APOE4 allele seems to increase the risk of traumatic brain damage, Down's syndrome, Lewy body dementia, and vascular dementia. Genome-wide association studies have identified TREM2, ADAM10, and PLD3 as additional LOAD risk factors (Deture & Dickson, 2019).

## 1.3 Epidemiology:

Currently, we have estimates of around 47 million people worldwide with dementia. Among these, AD dementia is 60 - 80% and is the most common form. Due to an aging population,a projection of greater than 131 million people with some form of dementia within 2050 is expected. Aging is the biggest risk factor for AD. The prevalence of AD is 40% for people older than 80 and a lowered 10% for people older than 65 (Deture & Dickson, 2019).

Data from European studies of population reveal that the prevalence of dementia and AD (age-standardized), respectively, is 6.4% and 4.4%, among adults 65 and older. According to estimates, worldwide, 3.9% of people over the age of 60 have dementia. REgionally, the prevalence is 6.4% in North America, 5.4% in Western Europe, 4.6% in Latin America, 1.6% in Africa and 4.0% in China. According to a study that conducted a systematic review, in emerging nations, AD prevalence was 3.4% (Qiu et al., 2009). Incidence of AD in Europe was 19.4 (per 100 people) for people above 65 years of age. The Cache County Study also discovered that for both men and women, AD incidence rose in accordance with age, reached a peak, and fell down again at extremely advanced ages. Research from Europe have revealed that women had a higher incidence of AD than males do, but North American studies did not find this difference due to gender. Studies have shown that the incidence of AD is typically lower in emerging nations than it is in North America and Europe (Qiu et al., 2009).

In Bangladesh, deaths due to Alzheimer's / dementia was 9917 in 2017, accounting for 1.26% of all fatalities, according to WHO data. This places Bangladesh at position 152 globally (Roy et al., 2020). Due to a lack of funding for AD research in Bangladesh, there is currently little information available regarding the data of AD epidemiology (Rahman et al., 2017).

## 1.4 Pathophysiology:

Alzheimer's disease pathophysiology is marked through instances of memory impairment along with a variety of cognitive deficits in domains like decision-making, executive function, language, and visuospatial skills. Further complicating early diagnosis and therapy is the fact that this determination of this illness is only possible through the histological assay to check for neuronal loss, senile plaques (SP) and neurofibrillary tau tangles (Pardo-Moreno et al., 2022). In AD, there are two categories of neuropathological alterations that offer proof of the progression and manifestations of the illness. Positive lesions (owing to aggregation), are the first of these categories defined by the buildup of amyloid plaques and tau tangles. Negative lesions are the other category characterized by atrophy because of loss of neurons. (Breijyeh & Karaman, 2020).

Neuropathological characteristic of senile plaques (SP) in AD-affected brains continues to be a plausible source of effective cell loss. Senile plaques are produced due to parenchymal amyloid-(A) accumulating over time. It is a peptide that results through amyloidogenic pathway-following sequential activity of Aβ precursor protein (APP) by the enzymes β- and γ-secretase as shown in Figure 1 below. Because AD has a more pronounced amyloidogenic pathway, APP peptide / β-secretase enzyme mutations may hasten the beginning of the condition. According to some theories, the development of AD may even cause Aβ to induce neuronal death in the entorhinal cortex and hippocampal regions. Additionally, these regions are crucial for learning and memory, making them extremely sensitive to this condition. The

blood-brain barrier (BBB) is damaged or impaired as a result of Aβ deposition in the vasculature, known as cerebral amyloid angiopathy (CAA). This affects the BBB's functionality (Pardo-Moreno et al., 2022).

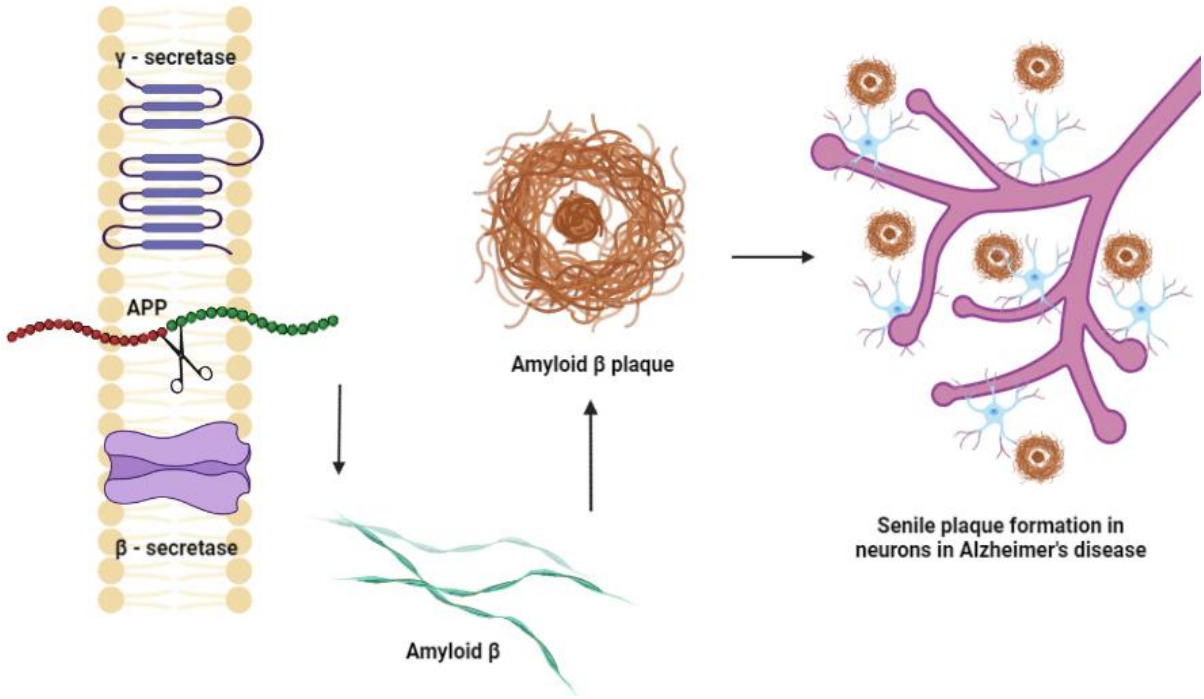



*Figure 1: Illustration of Amyloid-β Pathology*

Hyperphosphorylated accumulation of the protein tau to form neurofibrillary tangles (Figure 2) is another important pathological feature of AD. Tau refers to a protein that is associated with microtubules. It is produced in the brain in large quantities and binds to tubulin to enhance the formation of microtubules. It controls a number of crucial neuronal processes and maintains other cytoskeletal structures. Since tau protein can accumulate inside neurons and forms masses of filaments inside the dendrites and soma when inappropriately phosphorylated, the protein majorly contributes in AD pathogenesis. The argyrophilic fiber masses that make up neurofibrillary tangles can stain thioflavin-S strongly. Additionally, neurofibrillary tangles are thought to appear as a pathogenic processes that is downstream in AD (Pardo-Moreno et al., 2022).

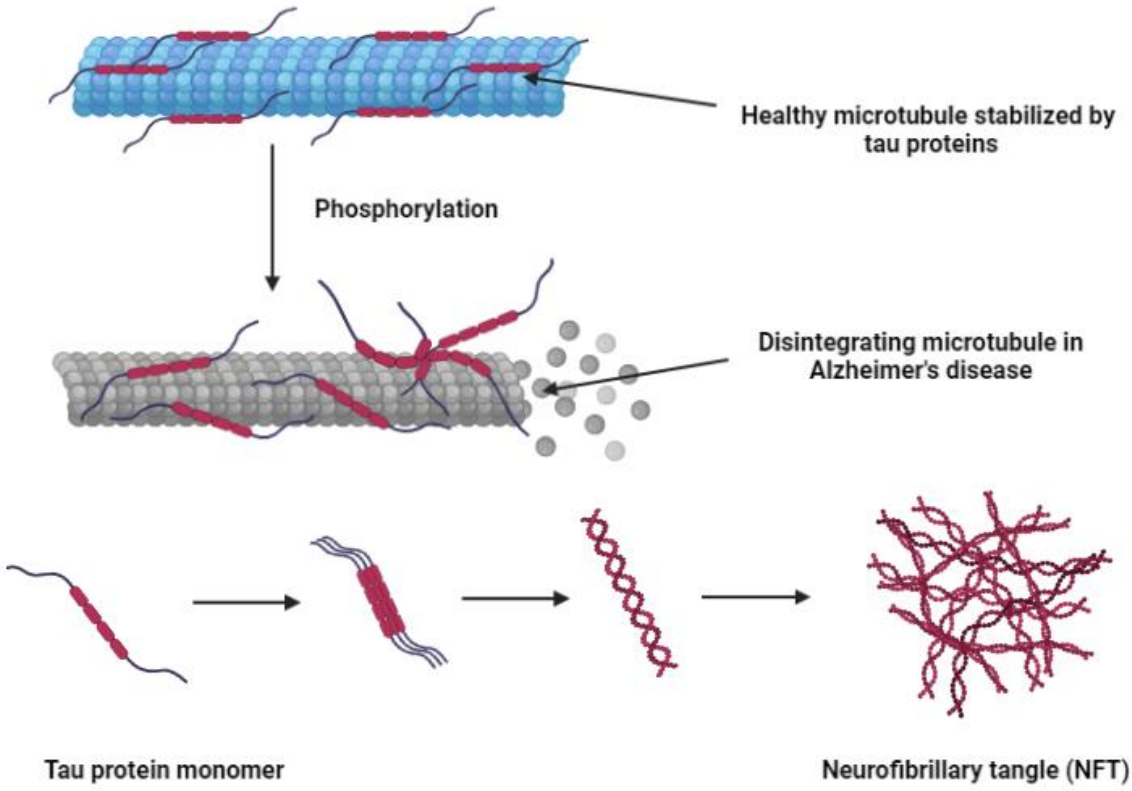



*Figure 2: Illustration of Tau Pathology*

Losses in neuronal and synaptic masses is a significant pathological feature of dementia, with it also being the major reason for cortical atrophy in AD. Areas of lost neurons correlate with the locations of tau tangles. Inflammation, and oxidative stress may also lead to degeneration of neurons The mechanism of inflammation involves cytokines secretion, leading to greater blood circulation is a specific area and also microglial cell action to remove damaged cells. Inflammation can also cause damage to tissue and ultimately result in neuronal death. The BBB may also suffer harm from an increase in reactive oxygen species production which damages DNA, lipids proteins etc through oxidative stress. In line with this theory, it has been suggested that antioxidant enzymes may operate less effectively or decrease in AD, which may contribute to neuronal death (Pardo-Moreno et al., 2022).

## 1.5 Treatment Options of AD:

The drug class, Cholinesterase inhibitors which includes drugs such as rivastigmine, galantamine and donepezil is commonly used as treatment options for all levels of Alzheimer's Disease (AD) dementia in addition to Parkinson's Disease (PD) dementia. Cases of severe AD can be prescribed memantine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist (Weller & Budson, 2018).

### 1.5.1 Rivastigmine:

Rivastigmine (Figure 3) inhibits butyrylcholinesterase (BuChE) as well as acetylcholinesterase (AChE) in a pseudo-irreversible manner courtesy of drug binding to both the anionic and estearic sites of enzymes, stopping the metabolism of ACh. Metabolized by AChE and BuChE, rivastigmine dissociates at a slower rate than AChE, which is why it is known as a pseudo-irreversible (Breijyeh & Karaman, 2020). It is used to treat both mild / moderate AD and PD dementia enhancing cognitive abilities and everyday activities. 3-6 mg/12 h is the most common and efficient dose available as tablets/capsules (Pardo-Moreno et al., 2022). Negative side effects from taking the medication orally include loss of weight, nausea, vomiting, asthenia and dyspepsia, rivastigmine can also be administered via transdermal patches, which offer better tolerability and caregiver satisfaction while allowing for controlled, continuous medication delivery through the skin. Additionally, the patches may offer a lower amount than pills, which minimizes negative effects. The majority of AD patients experience memory loss and swallowing issues, so patient compliance is also higher (Breijyeh & Karaman, 2020).

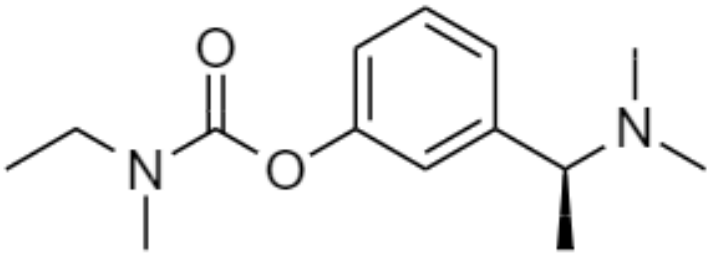


*Figure 3: Chemical Structure of Rivastigmine*

### 1.5.2 Donepezil:

A second generation AChEI and derivative of indanone benzylpiperidine, donepezil is regarded as the most effective medication for treating AD. According to Breijyeh and Karaman (2020), donepezil reversibly combines with acetylcholinesterase and thus prevents the breakdown of acetylcholine. Additionally, donepezil also affects the pathogenesis of AD at the molecular and cellular levels by inhibiting glutamate-induced excitotoxicity, lowering production of inflammatory cytokines, and decreasing the effects of oxidative stress. Transdermal application of donepezil is an additional option for oral administration. Donepezil, 10 mg/day doses enhance cognitive function and fundamental daily living functions. It should be mentioned that donepezil has not been successful in stopping the course of AD, but it is known to have minimal side effects and good tolerance, particularly concerning the neurological system or GI tract (Pardo-Moreno et al., 2022).

### 1.5.3 Galantamine:

Galantamine is regarded as a conventional primary treatment for mild / moderate cases of AD It acts as a competitive inhibitor of the AChE enzyme and is also a selective tertiary isoquinoline alkaloid that binds and activate nicotinic receptors (Breijyeh & Karaman, 2020). Oral administration is used, and the doses are 4, 8, 12, 16, and 24 mg. What makes galantamine so intriguing is its action on the CNS and lack of action at the PNS. According to

a recent study, this medication not only works well at reducing behavioral problems but also helps with basic daily tasks and cognitive function. Despite the fact that this medication has a high safety and tolerability record, there are certain side effects associated with its usage, including breathlessness, dizziness, nausea, vomiting, stomach cramps and convulsions (Pardo-Moreno et al., 2022).

### 1.5.4 Memantine:

Memantine is a non-competitive NMDA receptor antagonist of modest affinity.that counteracts pathologically high levels of glutamate. Both the manifestation of symptoms and the development of AD into neurodegenerative dementia are influenced by the dysfunction of neurotransmission involving glutamate mainly at NMDA receptors. It is offered in 10 mg tablets, 2 mg / mL solution, as well as 7 / 14 / 21 and 28 mg slow-release capsules (Pardo-Moreno et al., 2022). Memantine can be used as combination therapy with other AChIs or on its own. Due to memantine being easily replaced from NMDAR in favor of glutamate, normal transmission in the synapse is left unhindered making the drug well tolerated and safe (Breijyeh & Karaman, 2020). This prevents a prolonged blockage. The following negative consequences should be noted: fatigue, discomfort, hallucinations, disorientation, nausea, vomiting, weight gain, Increased blood pressure, stomach pain, and diarrhea, and constipation (Breijyeh & Karaman, 2020).

### 1.5.5 Other Treatment Options:

Disease-modifying treatments (DMT) affect a number of pathophysiological pathways to slow the course of AD. Symptomatic therapy is different and focuses on enhancing cognitive abilities and reducing signs and symptoms of AD. DMTs, which include oral administration of small compounds or immunotherapies, are being created to halt the course of AD or prevent it (Breijyeh & Karaman, 2020).

A number of DMTs have been created and are currently undergoing clinical trials. For eg, AN-1792 which is a synthetic Aβ peptide that was stopped from use at phase II trials because it caused meningoencephalitis in 6% of the patients. Other medications include the anti-A antibody (bapineuzumab / solanezumab), gamma-Secretase inhibitors (tarenflurbil / avagacestat), and β-Secretase inhibitors ,(atabecestat / verubecestat). However they did not pass the clinical trials. Over the years, a number of immunotherapies have been created, including CNP520 (umibecestat), a tiny drug that blocks beta-scretase-1 (BACE-1) and hence prevents the formation of Aβ production. Next, CAD106, was created that causes Aβ antibodies. Additionally, crenezumab, aducanumab, and gantenerumab, human Aβ monoclonal antibodies that are still being clinically tested alongside other DMTs (Breijyeh & Karaman, 2020). Another family of drugs that target the α-secretase enzyme was created and is being explored for use as medication. Inhibitors of tau tangled are another promising DMT in addition to anti-amyloid drugs. Sodium valproate, lithium and pyrazolopyrazines are examples of these substances (Breijyeh & Karaman, 2020).

## 1.6 Purpose of the study:

Existing research indicates that medication for AD had a small positive impact on the behavior and functioning of patients as well as cognitive decline. However, few studies have linked the use of AD drugs to an increased risk of death and hospitalization (Bhattacharjee et al., 2019). Furthermore, risk of rhabdomyolysis when using AChE inhibitors (mostly donepezil) has also been reported by regulatory authorities.

In light of this information, the following study will be conducted with the purpose of exploring the effects of the acetylcholinesterase inhibitor rivastigmine on mortality (death) as well as the development of rhabdomyolysis in patients who have been prescribed the drug as treatment for AD dementia. In this study, we will be analyzing pharmacovigilance and

adverse drug reaction information derived from the FDA Adverse Event Reporting System (FAERS) database in order to see the effect of rivastigmine on patient mortality and whether it provides a significant mortality benefit; as well as its contribution in the development of the specific side effect of rhabdomyolysis.

# Chapter 2

# Rivastigmine

## 2.1 Pharmacodynamics

### 2.1.1 Indications

The main Indication for rivastigmine (EXELON) is to treat mild/moderate Alzheimer's disease (AD) dementia . IT is also used in the treatment of Parkinson’s disease (PD) dementia (fda & cder, n.d.). Additionally, current research suggests that rivastigmine has the ability to:

1. Enhance stability in walking to lower the chance of falling in Parkinson's patients (Ezzat et al., 2022).
2. Enhance gait stability to lower the chance of falling in Parkinson's patients (Ezzat et al., 2022).
3. Based on a computerized cognitive evaluation, improve cognition in those with Lewy body dementia. Patients receiving rivastigmine showed improvement of 30% or more compared to the placebo group, as well as generally reduced anxiety and fewer bouts of hallucinations (Ezzat et al., 2022).

### 2.1.2 Approved Strengths and Dosage Forms:

EXELON is present within the market to buy in the following dosage forms:

1. EXELON Capsules: contains rivastigmine tartrate of strengths 1.5 mg / 3 mg / 4.5 mg / 6 mg (fda & cder, n.d.).
2. EXELON Oral Solution: clear yellow solution which contains rivastigmine tartrate at a strength of 2 mg/mL (fda & cder, n.d.).
3. EXELON Transdermal Patch: A relatively thin transdermal matrix with three layers makes up a single patch . The adhesive layer is covered by a fourth layer, which needs to

be taken off before applying on the skin. 5 $cm^2$ patches contain 9 mg of rivastigmine, and have a rate of release of 4.6 mg / 24 hours in-vivo. 10 $cm^2$ patches on the other hand, consist of 18 mg rivastigmine, and a release rate of 9.5 mg / 24 hours in-vivo (Fda, n.d.).

### 2.1.3 Dosage Regimen and Administration Considerations:

Treatment of both AD and PD Dementia should involve divided doses of oral rivastigmine at morning and evening times alongside food. Suggested dose of EXELON Oral Solution in Alzheimer's disease is stated to be 6 - 12 mg daily ( 3 - 6 mg daily for capsules), given twice daily. Alternatively, the suggested dosage in the treatment of PD Dementia is 3 - 12 mg per day( 1.5 - 6 mg daily for capsules), again twice daily. Two times a day, a 1.5 mg dose should be used to start the treatment. Then after a minimum of two weeks (for Alzheimer's Disease) and if the patient shows good tolerance, the dose should be doubled to 3 mg twice a day (4 weeks for Parkinson's Disease Dementia). If the preceding dose was well tolerated, dose can be increased to 4.5 mg BID and 6 mg BID. This is only after a minimum of 2 weeks for Alzheimer's disease / 4 weeks for Parkinson's disease dementia. 6 mg two times a day is the maximum dosage (12 mg per day) (fda & cder, n.d.).

When it comes to transdermal rivastigmine patches, the initial dose of Exelon Patch is 4.6mg per 24 hours. The suggested effective dose for the patch is 9.5 mg per 24 hours, which should be increased after4 weeks minimum of treatment and also depending on whether it is well tolerated. Good toleration of the previous dose allows dose to be increased, however only after 4 weeks have passed since the prior dose. The highest dose that is advised is 9.5 mg every 24 hours. Higher doses do not significantly increase any benefits and significantly increase the likelihood of adverse effects (Fda, n.d.).

Patients should be given proper instructions on how to administer the medication. They are instructed to take the syringe used for oral dosing out of its casing, take the amount of

indicated dosage of rivastigmine Oral Solution from the container using the given syringe, and then replace the syringe. A modest amount of cool fruit juice, water or soda can be added before swallowing the dosage of solution. The combination should be stirred before being consumed by patients (fda & cder, n.d.).

Once a day, rivastigmine patches should be put to a healthy, dry and clean spot on the upper parts of the arm, back or chest. Applying the patch to skin that is injured/inflamed is not advised. It should be made sure that the patch is firmly applied until the edges are adhered. Patches can be applied in the same area one after the other, however, it is advised to change the patch application site every day to prevent any irritation. Every 24 hours, a new site should be utilized in place of the previous one that was used within the previous 14 days (Fda, n.d.).

If some side effects result in the development of intolerance during therapy, the patient should be advised to stop taking the medication for a number of doses. They can then later resume at similar or the next lesser dose level. Resuming at the same or at a lowered dose is satisfactory incase of a stoppage of 3 days or less. For a greater than 3 days stoppage, recontinuation should be done with 1.5 mg BID dose (fda & cder, n.d.). Some dosing considerations for rivastigmine in specific populations include:

1. Only lower doses may be tolerated by people with medium / severe renal impairment (fda & cder, n.d.).
2. It's possible that those with mild and severe hepatic impairment can only tolerate lesser doses (fda & cder, n.d.).
3. Low BMI index patients (less than 50 kg) should be carefully monitored for toxicities (such as severe nausea or vomiting), and the dose may need to be lowered if these symptoms appear (fda & cder, n.d.).

### 2.1.4 Side Effects, Adverse Reactions and Contraindications:

Rivastigmine can cause a number of unpleasant side effects, including headache, dizziness, fatigue, asthenia perspiration, nausea, vomiting, diarrhea, loss of appetite and increased gastric output. Sedation and weight gain are recorded, but not anticipated. The peripheral inhibition of butyrylcholinesterase and AChE can have consequences on the digestive system through GI side effects. The central inhibition of AChE plays a role in the symptoms of motion sickness, nausea, weight loss, and insomnia. If rivastigmine therapy is restarted without re-titrating the medication to full dose, it may result in severe vomiting and esophageal rupture. Slow titration and administration with food can lessen the likelihood of adverse events (Mimica & Presečki, 2009).

Gastrointestinal adverse effects of rivastigmine include severe nausea, vomiting, loss of weight, lowered appetite and diarrhea. Prolonged vomiting or diarrhea can lead to dehydration. These reactions are dose-dependent in terms of frequency and severity. As a result, a 1.5 mg BID maintenance dose should be started with. Regardless of the route of administration (oral / transdermal), reports of individuals who received rivastigmine who developed widespread allergic dermatitis. If disseminated allergic dermatitis develops, treatment should be stopped. Extrapyramidal symptoms, seizures, peptic ulcers/gastrointestinal bleeding, bradycardia, syncopal episodes, urinary obstruction, and exacerbation of asthma/obstructive pulmonary disease are other adverse reactions that may result from increased cholinergic activity (fda & cder, n.d.).

There may be less adverse effects from rivastigmine transdermal patch. The peak plasma drug concentration appears to have a correlation with nausea and vomiting. Since rivastigmine transdermal patches have a lower peak concentration, less gastrointestinal adverse effects are a result. When compared to the oral form, the rivastigmine patch at 9.5

mg/24 h had less reports of nausea and vomiting while still being just as effective. Additionally, the patch form is normally well tolerated by the skin. On the application site, shingles and itching were some of the skin adverse effects (Mimica & Presečki, 2009).

Patients known to be hypersensitive towards rivastigmine or other components in the formulation are contraindicated against rivastigmine. Rivastigmine is also contraindicated in individuals who have previous history of local reactions at the application site with the patch (fda & cder, n.d.).

### 2.1.5 Drug-Drug Interactions:

Clinically significant drug-drug interactions are uncommon for rivastigmine owing to its limited protein binding and lack of CYP450 enzyme metabolism. Furthermore, rivastigmine has lower protein binding than donepezil, which may be beneficial for older individuals with albumin levels in the lower side, namely those who are deficient in nutrition or have kidney and liver failure (Desai & Grossberg, 2005). The use of rivastigmine with the following drugs is not recommended:

1. Metoclopramide: With concurrent rivastigmine administration, the risk of additive extrapyramidal adverse effects rises (fda & cder, n.d.).
2. Anticholinergics, cholinomimetics and other cholinesterase inhibitors: rivastigmine may hinder the effects of anticholinergic drugs and boost the cholinergic effects of other cholinomimetic drugs. When cholinesterase inhibitors are used alongside neuromuscular blocking drugs or cholinergic agonists, a synergistic effect may be anticipated (Fda, n.d.).
3. Beta-blockers: When beta-blockers and rivastigmine are taken together, additive bradycardic effects that can cause syncope are possible (especially with cardioselective beta-blockers) (fda & cder, n.d.).

In investigations involving volunteers of good health, there were no interactions found involving oral rivastigmine and fluoxetine, digoxin, diazepam, and warfarin. CYP450 promoters / inhibitors don't really interfere in the regular biotransformation of rivastigmine. Oral rivastigmine pharmacokinetic parameters were not affected by commonly prescribed drugs like antacids, antihypertensives, anti-diabetics, calcium channel blockers, estrogens, NSAIDs, salicylate analgesics, antihistamines and more (fda & cder, n.d.).

### 2.1.6 Mechanism of Action of rivastigmine:

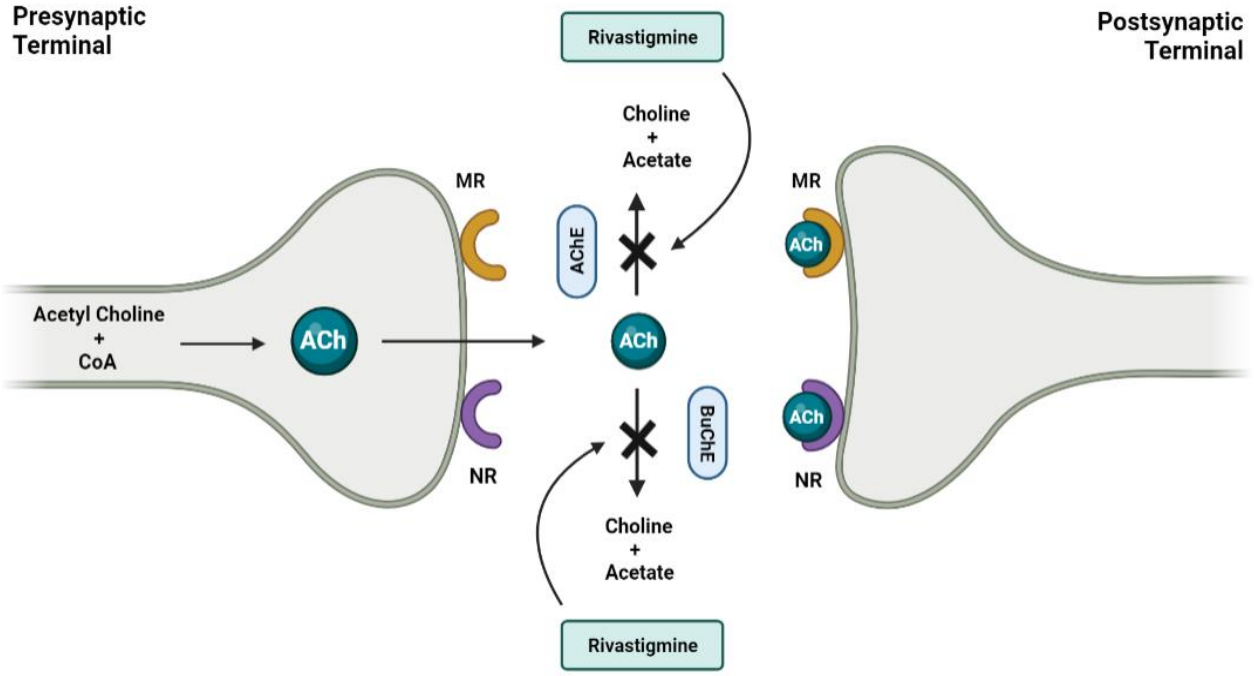
Dual inhibition of both butyrylcholinesterase (BuChE) and acetylcholinesterase (AChE) has been demonstrated for the phenylcarbamate derivative rivastigmine. More so than AChE inhibition alone, the simultaneous inhibition of both of these enzymes raises the levels of Ach in the brain. As AD advances, BuChE seems to rise in the temporal cortex and hippocampal areas along with decreased AChE activity in similar regions. This suggests that rivastigmine's potential to act as dual enzyme inhibitors may have therapeutic implications (Nguyen et al., 2021).

The carboxylic ester hydrolases AChE and BuChE are found in the brain. BuChE is largely linked to and secreted from glial cells, while AChE is primarily found in neurons in the CNS. AChE is responsible for around 80% of cholinesterase activity, and it is used for the nervous system's synapses to metabolize ACh. Less understood, broader BuChE activities in the brain are also present (Desai & Grossberg, 2005).

rivastigmine has lingering effects in blood plasma, making it pseudo-irreversible in nature as an inhibitor. It acts like ACh after absorption by binding to esteratic and anionic surfaces of AChE. Hydrolysis of rivastigmine leaves the esteratic AChE position carbamylated, blocking the enzyme instead of virtually instantly dissociating, as Ach does. Because of its unique structure, it can specifically inhibit AChE type G1, mainly found in AD sufferers' brains.

Usually, the G4 version of the enzyme is most abundant in young and healthy people, decreasing with age and AD (Nguyen et al., 2021).

In AD patients, rivastigmine results in a 12-month persistent suppression of both BuChE and AChE in the plasma as well as the CSF. The delayed dissociation from target enzymes may be the cause of this long-term effect, despite the fact that the exact mechanism is still unknown. Rivastigmine treatment for 12 months resulted in a 46 and 65% decrease in AChE and BuChE activity from baseline (11.8 mg / day mean dose). In contrast to results with the ChE inhibitors like galantamine, donepezil, and tacrine that are reversible, rivastigmine consistently inhibits both enzymes in the CSF, which seem to result in higher concentrations of AChE, their target enzyme (Desai & Grossberg, 2005).




**Abbreviations:** Ach – Acetylcholinesterase, N.R – nicotinic receptor, M.R – Muscarinic receptor, AChE – Acetylcholinesterase, BuChE – Butyrylcholinesterase

*Figure 4: Mechanism of Action of Rivastigmine*

## 2.2 Pharmacokinetics:

### 2.2.1 Absorption:

According to the data in Table 1, with a 3-mg dosage, oral rivastigmine has an absolute bioavailability of about 40% (Exelon FDA Accessdata, n.d.). While roughly 50% of the drug dose is absorbed by the body during the course of a 24-hour topical application (Fda, n.d.). The pharmacokinetics of oral and transdermal rivastigmine patch were compared in a study by Lefèvre et al., and it was shown that oral form of rivastigmine showed a greater rate of absorption. The median $T_{max}$ was roughly 1 h, applicable for all dosages. Oral administration of different doses (1.5, 3, 4.5, and 6 mg), produced mean (SD) rivastigmine $C_{max}$ values of 3.3, 9.7, 16.8, and 29.3 ng/ml. 12.5, 57.7, 106, and 191 ng.h / ml were the $(AUC)_{24\ h}$ values.

Following patch application, rivastigmine plasma concentrations rose more gradually, reaching tmax with all patch sizes within eight hours. Following 5, 10, 15, and 20 $cm^2$ patch size applications, the mean (SD) $C_{max}$ was 2.7, 7.9, 14.1, and 19.5 ng / ml. The mean (SD) area under the curve ($AUC_{24\ h}$) value was 46.3, 127, 233, and 345 ng.h / ml (Lefèvre et al., 2008). In comparison to fasting, taking rivastigmine with food slows down absorption with a $T_{max}$ of 1.4–1.6 hours and lowers maximum concentration by 30% (Nguyen et al., 2021).

### 2.2.2 Distribution:

Rivastigmine appears to be widely distributed throughout the body based on its low capacity to bind plasma proteins (40%) and has relatively high volume of distribution (V.d) (1.8–2.7 L/kg) according to Table 1. NAP 226-90, its primary metabolite, has a V.d that ranges from 4.3 - 5.9 L / kg. Furthermore, rivastigmine crosses the blood brain barrier (BBB). During the inhibition of BuChE and AChE within the CSF, rivastigmine has a dose-dependent effect. AChE inhibition is 20, 46, 55.6, and 61.7% on average pertaining to doses of 2, 6, 9, 12 mg / day. 23.9, 76.6, 54.9, and 61% of BuChE is inhibited for the same doses (Nguyen et al.,

2021). Over the therapeutic range, transdermal rivastigmine has a weak (about 40%) binding to plasma proteins. It easily passes the blood-brain barrier and takes 1.4–2.6 hours to reach CSF peak concentrations. It has a distribution volume that appears to be between 1.8 and 2.7 L/kg (Fda, n.d.).

### 2.2.3 Metabolism:

Rivastigmine is rapidly metabolized. It also has a relatively shorter elimination half life of 1 hr. It is subject to first pass metabolism, converting it to decarbamylated phenol NAP 226-90 (Figure 5), This is further changed into the sulfate conjugate,the major form in people. These metabolites barely limit the activity of AChE. Within two hours, NAP 226-90 is found in its highest plasma concentration (Nguyen et al., 2021).

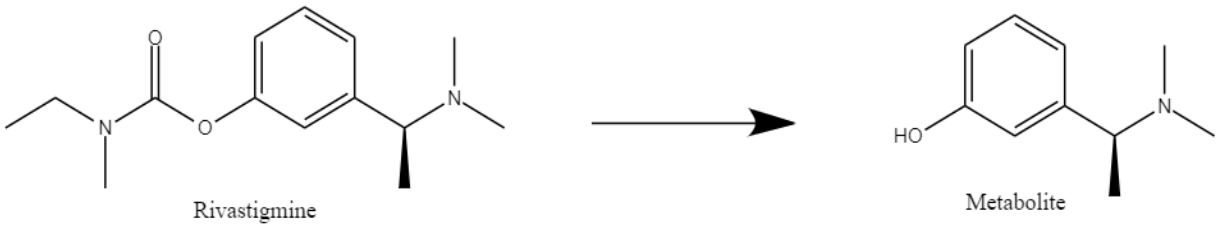



*Figure 5: Rivastigmine and its Metabolite*

With minimal CYP 450 enzyme interactions, rivastigmine is routinely converted to NAP226-90 (inactive metabolite) courtesy of AChE and BuChE. However, peripheral cholinesterases in the gut may still have a limited role in the first-pass metabolism of rivastigmine taken orally. Transdermal treatment resulted in a significantly lower NAP226-90 to rivastigmine ratio (0.60-0.72) than oral treatment (3.49). This suggests that rivastigmine given transdermally avoids phase I metabolism, boosting the drug's systemic bioavailability (Kurz et al., 2009).

### 2.2.4 Elimination:

The kidneys are the primary organs involved in elimination. In an experiment, six healthy individuals received rivastigmine, and over the course of 120 hours, there was a total recovery of 97% in the urine and 0.4% in the feces (>90% in urine and <1 % in feces for transdermal rivastigmine) (Fda, n.d.). Urine analysis revealed no parent drug. The decarbamylated metabolite's sulfate conjugate, which makes up 40% of the dose, is the main component eliminated in urine. The data from Table 1 shows that after twice a day, 6 mg administration, the mean oral clearance value of rivastigmine is 1.8 ± 0.6 L/min (*Exelon FDA Accessdata*, n.d.) while the clearance value of transdermal rivastigmine was 2.1 to 2.8 L / hr (Fda, n.d.). With oral dosing, $t_{1/2}$ was roughly 1.3 to 2.0 h. Transdermal administration has an elimination half-life of roughly 3.4 hours (Lefèvre et al., 2008).

*Table 1: Pharmacokinetic Overview of Oral/Transdermal Forms of Rivastigmine (adapted from: Fda (n.d.). HIGHLIGHTS OF PRESCRIBING INFORMATION. www.fda.gov/medwatch. ; fda, & cder (n.d.). HIGHLIGHTS OF PRESCRIBING INFORMATION. www.fda.gov/ )*

| **Pharmacokinetic Parameters** | | **Oral Rivastigmine** | **Transdermal Rivastigmine** |
|---|---|---|---|
| **Absorption** | Bioavailability | 40% | 50% |
| | $C_{max}$ | 19.5 ng/ml | 29.3 ng/ml |
| | $T_{max}$ | 1hr | 8hr |
| | AUC | 345 ng.h/ml | 191 ng.h/ml |
| | Effect of food | Delays absorption | No effect |
| **Distribution** | V.d | 1.8–2.7 L/kg | 1.8–2.7 L/kg |
| | Protein binding | 40% | 40% |
| | BBB permeability | yes | yes |
| **Metabolism** | Metabolizing enzymes | AChE and BuChE | AChE and BuChE |
| | First pass metabolism | Affected | Avoided |
| | Ratio of NAP226-90 to Rivastigmine | 0.60-0.72 | 3.49 |
| **Elimination** | Clearance | 1.8 ± 0.6 L/min | 2.1-2.8 L/hr. |
| | $T_{1/2}$ | 1.3hr to 2hr | 3.4hr |
| | Excretion route | Urine – 97%<br>Feces – 0.4% | Urine – >90%<br>Feces - <1% |

**Abbreviations:** $C_{max}$ - Maximum concentration in plasma, $T_{max}$ – time required to achieve $C_{max}$, AUC – area under curve, V.d – volume of distribution, $T_{½}$ - elimination half-life, ng.h / ml - nanogram hour per milliliter.

# Chapter 3

# Methodology

## 3.1 Data Source

The FAERS database was used as the source in order to carry out this observational and pharmacovigilance study. Each year, the FAERS database manages to get around 1.5 million reports of adverse events involving medications, medical devices, and vaccinations, making it the FDA's most impactful tool for reporting adverse effects. These reports of adverse effects were submitted to the database courtesy of medical professionals, manufacturers and consumers. Demographics, outcome, suspected drug, reporting nation and interacting drugs information are some of the fields that are covered in the database (Vestergaard Kvist et al., 2021). Additionally, through the use of appropriate MedDRA (Medical Dictionary for Regulatory Activities) keywords, these incidents are filed in the system. It is apparent that the adverse events that have already been reported to the FAERS database are raising public awareness about these unwanted effects and also helping in ensuring better drug safety (Mazhar et al., 2021). IT is also possible to get quarterly data on all the adverse event occurrences that have been reported (Vestergaard Kvist et al., 2021). Thus, the main adverse events for Acetyl cholinesterase inhibitors reported by patients, pharmaceutical industries and healthcare providers can be found by looking through the FAERS database.

To this day, the database consists of a total of 26,004,135 reports. Data from the period January, 2015 to September, 2022 was collected to be used in our study and in January, 2023 the data was analyzed. "Rivastigmine" was used as the search term with the adverse events classification terms being selected from the preferred terms of MedDRA.

## 3.2 Inclusion and Exclusion Criteria

For the purpose of this study, FAERS data was collected from January, 2015 to September, 2022 and the reported adverse events were picked using MedDRA preferred terms (PTs) such as “death”, “sudden death”, “sudden cardiac death”, “cardiac death”, “brain death”, “accidental death”, “apparent death”. These terms were then unified into the single terms “death” and “Rhabdomyolysis". The database showed all the adverse events of the drug with the generic name: “rivastigmine”. Data which showed that other drugs might be the cause of the adverse events, were all disregarded and only the data pertaining to rivastigmine was included, making rivastigmine the only drug in suspicion to cause the specific adverse events. Additionally, by using case number and by cross-matching the age, sex and event date all the duplicated reports were filtered.

## 3.3 Statistical Analysis

The processing and analysis of the collected data was performed in January, 2023. A disproportionality analysis was conducted in the form of the reported odds ratio (ROR) and its relating 95% Confidence interval (CI) which helped to show a considerable link between the drug (rivastigmine) and our adverse effects of concern (Death and Rhabdomyolysis). ROR is a certified case-non case method which is used to identify safety signals of the drugs (Bene et al., 2014) and stands among one of the most widely used approaches in finding disproportionality measures. A 2 by 2 contingency table with cases (desired side effect) and non-cases (undesired side effect) of the drug (van Puijenbroek et al., 2003) was utilized to give ROR (which showed the degree of disproportionality) and the CI which showed its statistical significance). For the confidence interval, a lower limit value of > 1, represents a signal that means it has significant reporting compared to the other drugs causing similar adverse effects. When the lower limit is = 1 or < 1, it means that there is no signal for the

adverse effect of interest, thus it is less significantly reported in comparison to the other drugs (Sato et al., 2020).

The ROR and corresponding 95% CI was found for rivastigmine, first using the whole database as the comparator, giving us an idea of the statistical significance of the association of the adverse effects (death and rhabdomyolysis) with rivastigmine when other drugs from the full FAERS database was used as the comparator. After this , ROR and 95% CI were calculated again, this time using other drugs from the same class as a comparator. This allowed for the determination of the highest reporting association of the adverse effect within the class. High ROR values hints towards a stronger reporting association (of rivastigmine) than the other drugs. R, version 4.2.1 was used to analyze all data.

# Chapter 4

# Results and Discussion

## 4.1 Effect of Rivastigmine on Death and Rhabdomyolysis

From the FAERS database (2015 to 2022), using the whole database as comparator, 658 cases of death were reported for rivastigmine and 456144 cases of death was reported for other drugs (Table 2). Both Figure 6 and 7 show that the Reporting odds ratios (ROR) was found to be 5.90 (CI = 5.43 to 6.41, $p < 0.0001$) which pairs up the cases of patient death by a specific drug (rivastigmine) to the number of cases for other drugs found in the whole database in order to compare them. Again, using only the class of drug (AChI) as comparator, analysis of FAERS data (2015 to 2022) returned 658 cases of death for rivastigmine but only 46 cases of death was reported for other drugs (Table 2). The Reporting odds ratios (ROR), this time according to Figure 6 and 7, was found to be 10.62 (CI = 7.84 to 14.38, $p <0.0001$). This was intended to make a comparison of the number of death cases in specific drugs (rivastigmine) and the number of cases for other drugs found within the drug class.

*Table 2 : Results for Cases of Death Using Rivastigmine and Other Drugs*

| **FAERS Database values from 2015-2022** | | | |
|---|---|---|---|
| | **Cases of Death** | **ROR (CI)** | ***p* Value** |
| **Rivastigmine** | 658 | | |
| **Other drugs (whole database as comparator)** | 456144 | 5.90 (5.43 to 6.41) | p < 0.0001 |
| **Other drugs (class as comparator)** | 46 | 10.62 (7.84 to 14.38) | |

Analysis of the cases of rhabdomyolysis for rivastigmine from the FAERS database (2015 to 2022) returned 0 cases of rhabdomyolysis. On the other hand, 16379 cases of Rhabdomyolysis were reported for other drugs using the whole database as a comparator

(Table 3). Since the cases of rhabdomyolysis for rivastigmine came back as zero, the Reporting odds ratios (ROR) was not applicable in this case. Again, analysis of FAERS data (2015 to 2022) returned again 0 cases of rhabdomyolysis for rivastigmine and 27 cases of rhabdomyolysis was reported for other drugs (using only the class of drug (AChI) as comparator). The Reporting odds ratios (ROR) is not obtained as cases of rhabdomyolysis were zero for rivastigmine.

*Table 3 : Results for cases of Rhabdomyolysis using Rivastigmine and Other Drugs.*

| **FAERS Database values from 2015-2022** | | | |
|---|---|---|---|
| | **Cases of Rhabdomyolysis** | **ROR (CI)** | ***p* Value** |
| **Rivastigmine** | 0 | | |
| **Other drugs (whole database as comparator)** | 16379 | N/A | N/A |
| **Other drugs (class as comparator)** | 27 | N/A | |

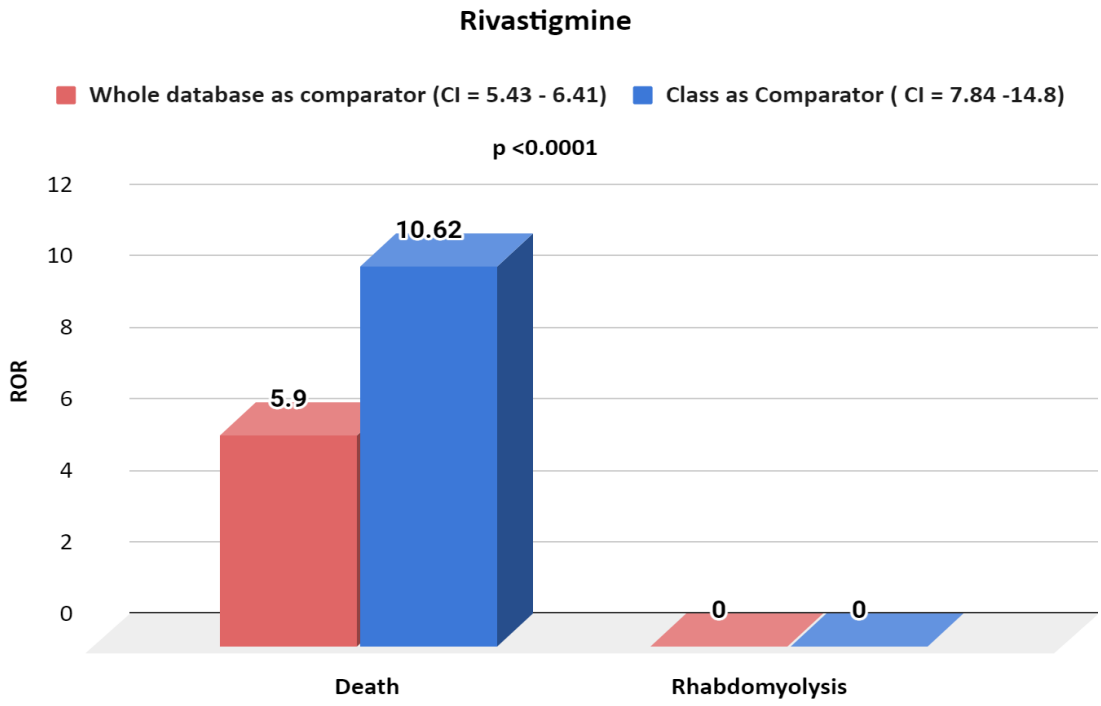



*Figure 6: Comparison of the ROR Values for Cases of Death and Rhabdomyolysis Using Both Whole Database and Class as Comparators.*

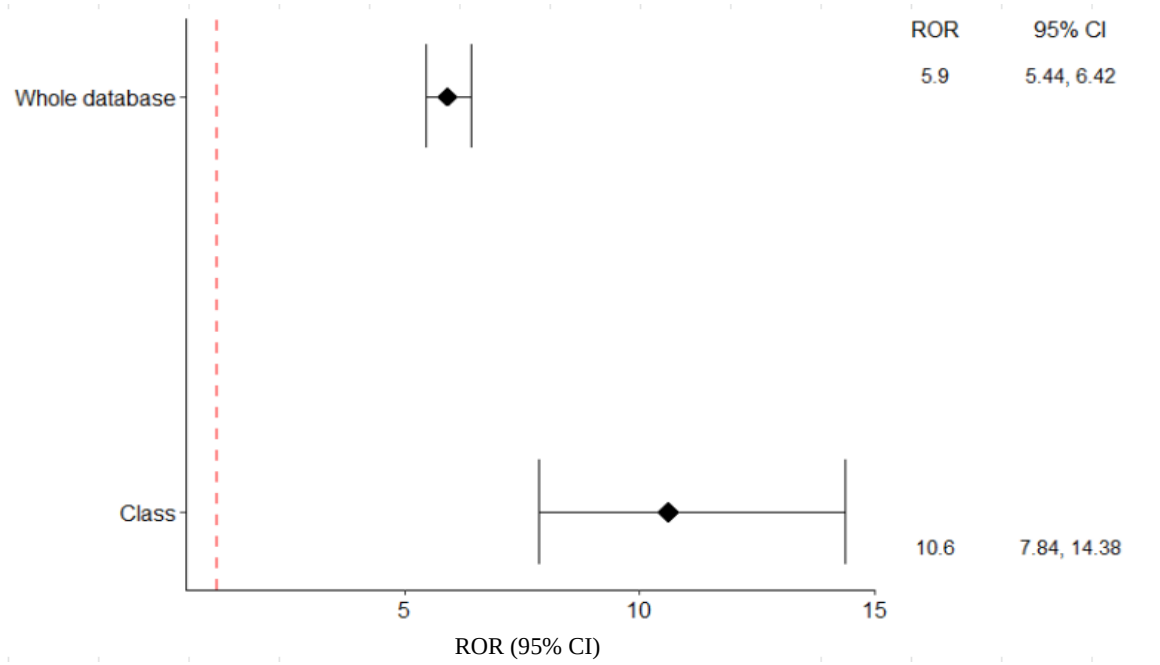



*Figure 7: Forest Plot of the Association Between Rivastigmine and Death*

## 4.2 Discussion

The data from Figures 6 and Figure 7 show results that the value of ROR was large/greater than 1 (both when compared to specific class or and the whole database large). Thus, the reports for death point out a significant effect for rivastigmine on the number of patient deaths (p value < 0.0001). Again, the data showed that there are no rhabdomyolysis reports for rivastigmine, both when compared to specific class and the whole database. Since the ROR value could not be calculated, it can be said that rivastigmine has not been associated with the side effect of rhabdomyolysis according to reports from the FAERS database.

Despite all of this, there is a possibility that an underreporting bias limitation could affect the results presented above. The utilized data was derived from the total number of volunteer adverse event reports and not from the total number of prescriptions for cholinesterase inhibitors. This makes the obtained results relative. Rivastigmine use is mostly seen in advanced stages of Alzheimer's disease, thus in the elderly, and may have an impact on the higher death reports associated with the drug that have been documented. However, there

might be other factors too such as rivastigmine being the only AChI with a transdermal patch delivery method, resulting in the application of numerous patches at once, which results in greater doses. Regarding the medications' chemical mechanisms of action, rivastigmine and other cholinesterase inhibitors differ from one another. Rivastigmine is categorized as a pseudo-irreversible intermediate-acting agent. A study on how rivastigmine exerts its effects on acetylcholinesterases showed that rivastigmine use lead to low levels of enzyme reactivation which could have unexpectedly increased the duration of action (Ali et al., 2015)

# Chapter 5

# Conclusion

AChIs such as rivastimne, donepezil, galantamine and NMDA antagonists like memantine are all viable options for the treatment of AD dementia in patients, especially the elderly. However, each of these drugs present some important limitations that should be considered. Cases of rhabdomyolysis when rivastigmine has been used was found to be null, thus rivastigmine is exempt from this serious side effect which has been found to be more prevalent with other AChI inhibitors such as donepezil. Although rivastigmine is an effective and broadly prescribed treatment option for, it still has its negative aspects. Data from this study shows rivastigmine's association with increased patient deaths and thus is something that should at the very least, be considered when assessing options for treatment of patients with AD dementia. These results hopefully should be able to aid healthcare professionals in selecting the correct drug for patients, so as to minimize side effects and maximize effectiveness of the treatment plan.

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