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

By

Nusrat Jahan
Student ID: 19146001

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
BRAC University
February 2023

Declaration

It is hereby declared that

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

Student's Full Name & Signature:

Nusrat Jahan
ID: 19146001

Approval

The thesis titled “A pharmacovigilance study on Donepezil: signal detection of rhabdomyolysis and death” submitted by Nusrat Jahan (19146001) of Summer, 2022 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy,

Supervisor:

_____

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

Approved by:

_____

Dean:

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

Program Director:

_____

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

Ethics Statement

This study does not involve any kind of animal and human trial.

Abstract

Alzheimer’s disease is an age-related neurodegenerative disease that effects the cognitive ability of a person. The cholinesterase inhibitor “donepezil” is used to treat Alzheimer's disease. Donepezil has shown the greatest advantages for improving patient’s lifestyles and cognitive abilities. The goal of this research is to offer a precise statistical analysis of the mortality benefit and rhabdomyolysis ratio in AD patients using the drug donepezil. The FAERS database was utilized to gather information on adverse events that were reported, and ROR was used as a statistical method to determine the mortality and rhabdomyolysis ratio in patients using donepezil. According to our research, donepezil has a positive impact on patient mortality than other cholinesterase inhibitors. On the other hand, in comparison to other cholinesterase inhibitors, donepezil also showed a relatively higher incidence of rhabdomyolysis cases. It has been discovered that donepezil increases patient’s life expectancy, but it has some limitations.

Keywords: Alzheimer’s disease; Dementia; Donepezil; Mortality benefit; Rhabdomyolysis

Dedication

I dedicate this thesis to my amazing parents and my supervisor. Without their support, patience and understanding, the completion of this paper would not have been possible.

Acknowledgement

I would like to acknowledge and express my deepest gratitude for the help and support extended by the following persons who had a very big contribution in completion of this paper.

My supervisor, Dr. Hasina Yasmin, Professor, Assistant Dean and Program Director, School of Pharmacy, BRAC University and Co-Principal Investigator of EBM (Evidence Base Medicine) Research Group of BRAC University, for her constant guidance, continuous support, words of encouragement and invaluable advice made this work possible. Her immense knowledge and plentiful experience have encouraged me all the time of my academic life.

Dr. Mesbah Talukder, Professor, School of Pharmacy, BRAC University and Principal Investigator of EBM (Evidence Base Medicine) Research Group of BRAC University, for his guidance, provision and suggestions that made this study possible. Sharing his knowledge and helped in the extraction and analysis of the data and its statistical computations. And last by helping us constantly to finish the thesis. I am very grateful for his valuable inputs in this paper.

Dr. Eva Rahman Kabir, Dean and Professor, School of Pharmacy, BRAC University and Chief Advisor of EBM (Evidence Base Medicine) Research Group of BRAC University. My sincere gratitude to her for all she has done for us, for opening so many new doors of opportunities and scope to grow and enrich our knowledge, for encouraging us to focus on learning leadership qualities, job opportunities and ethics, advancements of the medicine and medical fields and so much more through various seminars, competitions and workshops along with academic education, for reshaping us and helping us to prepare ourselves for the competitive job market and other fields. And lastly, for inspiring us to be a better version of ourselves.

Also, all the respected faculties of School of Pharmacy, BRAC University, who made me capable enough to be able to write this paper.

Last but not the least, my friends, who helped me, supported me and believed in me whenever I needed.

Table of Contents

List of Tables

List of Figures

List of Acronyms

AD Alzheimer’s Disease

Aβ Amyloid Beta

NFT Neurofibrillary tangles

CNS Central Nervous System

NMDA N-Methyl-D-Aspartate

ChEI Cholinesterase Inhibitor

Chapter 1

Introduction

1.1.1 Alzheimer’s Disease (AD)

Alzheimer’s disease is the common cause of dementia and various neurological disorders that affects the normal and healthy lifestyle of older people. Millions of people around the world is getting effected by this disease. This is a progressive degenerative neurological condition associated with cognitive decline. Age, genetics, lifestyle, traumatic brain injury, depression, and vascular disease are some of the potential contributing factors to AD. Risk factors in terms of lifestyle choices include a poor diet, lack of exercise, smoking and alcohol dependence, all of which might increase the chance of developing AD. Several risk factors have been linked to the disease's early development and progression. Although the triggering molecular processes are unknown, but it has been clear in recent years that environmental and nutritional factors may have a causative, disruptive, and supportive role in the progression of AD. According to various study, higher levels of aluminum and transition metals like copper, zinc and iron has contribution in the development of AD (Shcherbatykh & Carpenter, 2007). Along with all these factors, mutation of some specific genes like Presenilin 1 and 2 can also cause this disease.

There are three major stages of this disease progression. In the first stage the cognitive function of the patient is severely hampered. The second stage is characterized by decreasing visual and spatial functions and lastly in the third stage mental and behavioral problems arise. Dr. Reisberg's Global Deterioration Scale (GDS) and Functional Assessment Staging Scale (FAST) provided an unparalleled level of clinical data regarding the progression of AD (Figure 1). Additionally, he

methodically described and created treatments for various Behavioral and Psychological Signs of Dementia (BPSD) (*The Global Deterioration Scale: The Stages of Alzheimer's Disease*, n.d.)

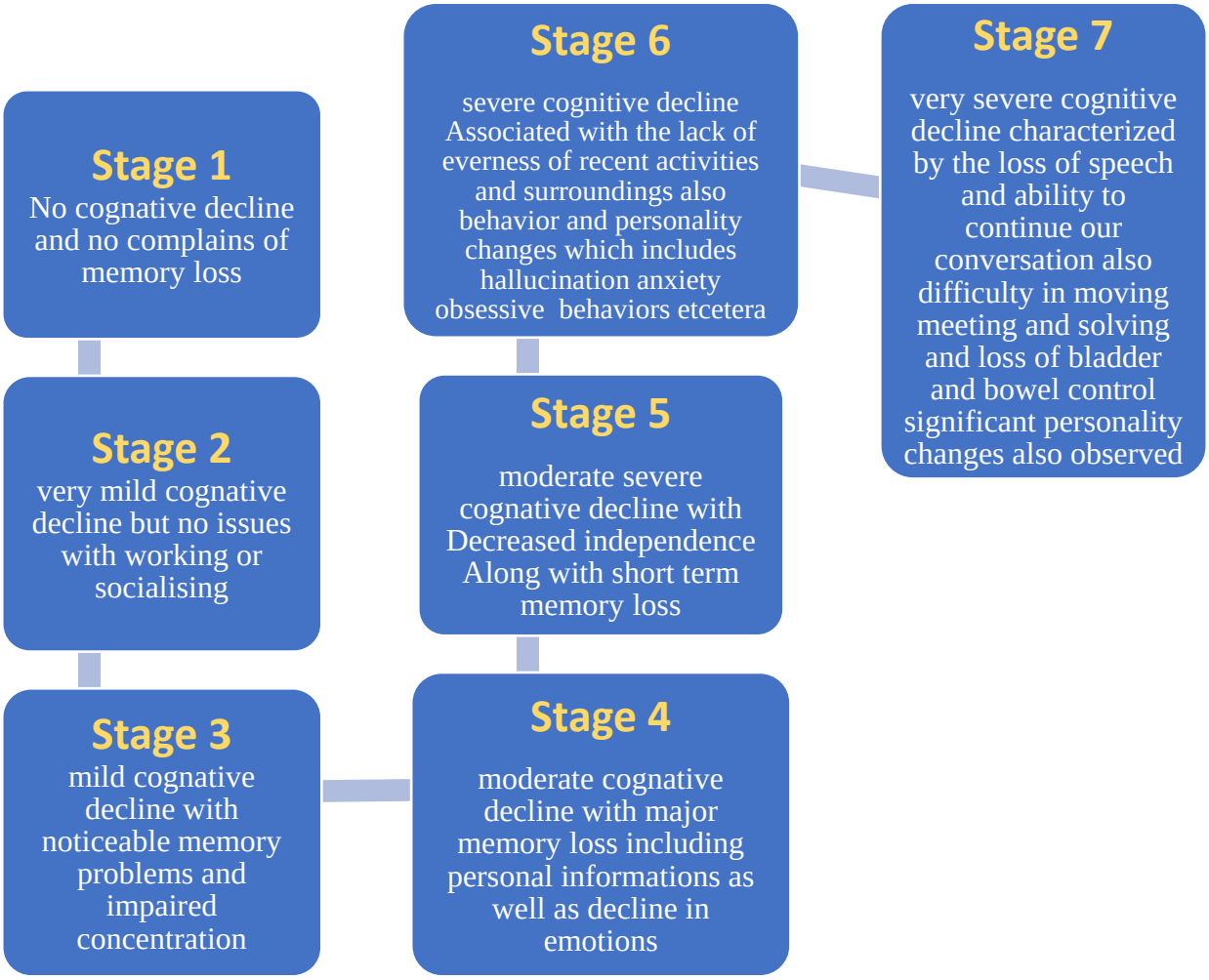

Figure 1: Reisberg's stages of Alzheimer's (modified from: alzheimersdisease.net)

1.1.2 Pathology of AD

Synapse loss, followed by neuron atrophy across the cerebral cortex and most severely, in the medial temporal lobe, are the characteristics of AD. Prior to spreading to the fronto-temporal cortices, pathology appears to start in the entorhinal and hippocampal regions. This phenomenon only affects striatum and thalamus and doesn't affect the cerebellum. MRI images suggest that

these areas are shrinking on a large scale. Pyramidal cells that are found in the CA1 region of the hippocampus are vulnerable to morphological changes and cell death, this corresponds to the primary symptom of memory loss. A plaque and Neurofibrillary tangles form before clinical symptoms appear, suggesting that years of degenerative changes have already taken place by the time symptoms appear, making early intervention difficult (Sheppard & Coleman, 2020). Neurofibrillary tangles and amyloid plaques are pathological signs of AD. The majority of treatment strategies are focused on the two major biomarkers of AD, which are increased amyloid production and hyperphosphorylation of tau.

Amyloid Beta (Aβ**) Plaques:** The majority of age-related plaques are made up of 36–43 residue long amyloid peptides that bind together to form Aβ plaque that cannot be broken down. These plaque start forming in the frontal, temporal and occipital lobes of the brain. After spreading into the cerebral cortex, the plaques start affecting the striatum and thalamus regions. Amyloid pathology appears to come before tau pathology, with NFTs being observed in areas where amyloid was already present. Numerous investigations have demonstrated that cognitively normal elderly people can have considerable Aβ deposition, however, some have established a link between deposition and dementia severity and cognitive decline (Sheppard & Coleman, 2020) (Figure 2).

Neuro Fibrillary Tau Tangles: Tau protein is a microtubule-associated protein, that is highly soluble in the cytoplasm. Tau protein that is misfolded, hyperphosphorylated and insoluble in the cytoplasm are known as NFTs. NFT is one of the histopathological indicators of AD, along with amyloid β-(Aβ) plaques and cerebrovascular amyloid angiopathy (Youssef et al., 2016). According to the tau hypothesis, adult-normal tau can be transformed into PHF-tau (paired helical filament

tau) and NFTs if there is an excessive or abnormal amount of tau phosphorylation (Mohandas et al., 2009) (Figure 2).

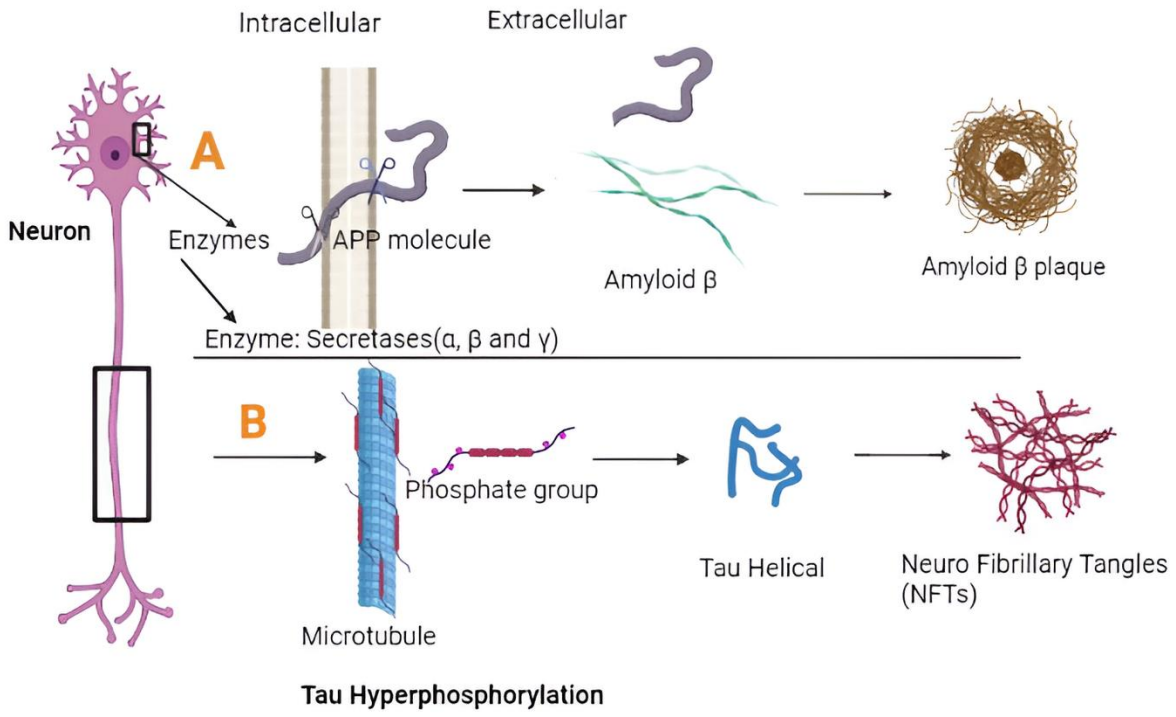

Figure 2: (A) formation of amyloid-beta plaques (B) formation of neurofibrillary tau tangles (modified from: Rastogi et al., 2021))

1.1.3 Prevalence of AD

According to the CDC (Centers for Disease Control and Prevention) in America almost 5.8 million people are affected by this disease. After age 60, the disease's symptoms might start to show up, and as you become older, your risk of getting it rises. Every five years after age 65, the proportion of those who have the condition doubles. AD is less frequent in younger individuals, yet it is still possible. Now if we differentiate them by their race and ethnicity then we can say that almost 14%

African American who are 65 years or older are suffering from Alzheimer's but in Hispanics the rate is 12% and but non-Hispanic whites have lower percentage, to be precise only 10% are suffering from this disease(Matthews et al., 2022). After officially ranking as the sixth-leading cause of death in 2019 and 2020, respectively, AD was listed as the seventh-leading cause of death in the US when COVID-19 entered the top 10 causes of death list in 2020 and 2021. For Americans aged 65 and older, AD is still the fifth-leading cause of death. While reported fatalities from AD climbed by more than 145% between 2000 and 2019, mortality from heart disease, HIV, and stroke declined("2022 Alzheimer's Disease Facts and Figures," 2022). According to WHO, Women are disproportionately afflicted by dementia or AD worldwide. Disability-adjusted life years (DALYs) are approximately 60% more common in women than in males, and women account for 65% of all dementia-related deaths.

1.1.4 Diagnosis of AD

To identify Alzheimer's dementia, doctors do tests to assess cognitive abilities, including memory impairment, functional abilities, and behavioral abnormalities. They also do a number of tests to rule out any further potential sources of impairment. The doctor can suggest a CSF fluid testing to help with the diagnosis. The proteins tau and amyloid can be checked in the cerebrospinal fluid. Alzheimer's disease can be recognized by the ratio of these proteins. Patients with Alzheimer's disease often do not need a cerebrospinal fluid examination, but it may be beneficial in rare or rapidly worsening cases. Alzheimer's disease is brought on by the slow deterioration of brain cells. Brain scans can show this degeneration in a variety of ways. However, these scans alone are unable to provide a diagnosis. Scans are not used to identify the illness since there is overlap between what medical practitioners consider to be normal aging-related brain change and abnormal change. Recently, PET scans have been created that can detect amyloid protein aggregates (plaques) or tau

tangles (neurofibrillary tangles), both of which are connected to Alzheimer's disease (Diagnosing Alzheimer's: How Alzheimer's Is Diagnosed - Mayo Clinic, n.d.). The Mini-Mental State Examination (MMSE), a short assessment of cognitive capacity, is commonly used in dementia screening protocols. The Mini-Mental State Examination (MMSE), a short assessment of cognitive capacity, is commonly used in dementia screening protocols. A thorough neurologic evaluation must include a mental status assessment. While the neurologic examination aims to assess several neuraxis components, the mental status test largely concentrates on the cerebrum. Similar to the core neurologic examination, the mental status assessment is broken down into sections to assess each significant cognitive domain. Language, executive function, visual-perceptual-spatial functioning, and memory are some of the cognitive processes that are targeted. These processes are really complicated. As a result, it is challenging to link a specific physical component to the cognitive processes that the mental status test examines (Grossman & Irwin, 2016a). In a large clinical setting, there are various rapid procedures for assessing mental status accessible. These screening techniques, however, should not be considered a reliable substitute for a complete assessment of mental health. Examples of rapid tests are the Mini-Mental State Examination (MMSE), Addenbrooke Cognitive Examination (ACE), and Montreal Cognitive Assessment (MoCA) (Grossman & Irwin, 2016b).

1.1.5 Treatment Options for AD

Now if we talk about the treatment options for Alzheimer's disease scientist are still figuring out the treatment plans to completely cure this disease. Treatment strategies are planned not only based on the cure of this disease but also ensuring the patients comfort, empowerment and independence by controlling or minimizing the symptoms. The most traditional way of treating AD is using Cholinesterase inhibitors or NMDA inhibitors (Figure 3). These medications help AD patients

with their everyday functioning, memory loss, and thinking and reasoning difficulties. Even though they cannot cure the disease, drugs for Alzheimer's can improve quality of life and bring independence. The exact mechanism of these drugs is still not completely understood by the scientists. But it is confirmed that they exert their effect by working of acetylcholine and glutamate. Where acetylcholine is crucial for controlling thoughts and memories and glutamate overactivation is related to neurotoxicity in CNS. But as the disease progresses these drugs become less effective because the amount of the neurotransmitter reduces significantly.

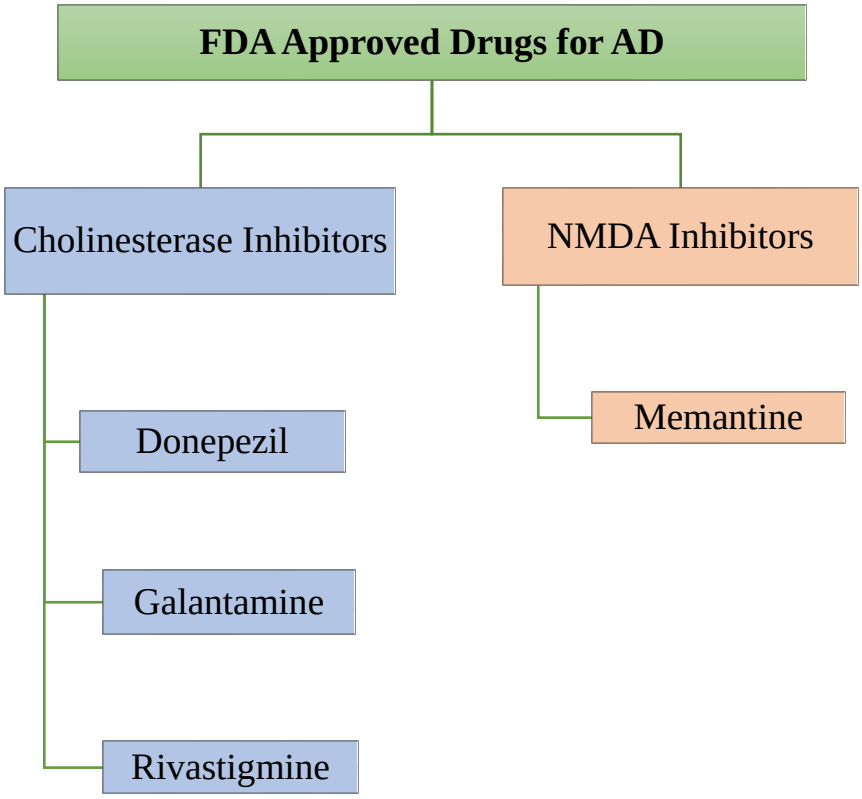

Figure 3: Classification of FDA approved drugs for AD

Some of the newly developed therapies for Alzheimer's disease concentrate on minute beta-amyloid protein clumps (plaques). Alzheimer's disease is often accompanied by plaques. Among the methods used to treat beta-amyloid are:

- Numerous drugs, sometimes referred to as monoclonal antibodies, may help the body remove beta-amyloid from the brain by preventing beta-amyloid from accumulating into plaques or by reducing existing beta-amyloid plaques. Monoclonal antibodies resemble the antibodies that our body naturally produces in response to vaccinations or foreign organisms. In June 2021, the Food and Drug Administration (FDA) approved the medication aducanumab (Aduhelm) for the treatment of many Alzheimer's patients. The medication has been studied on people with moderate cognitive impairment and early-stage Alzheimer's disease.
- Lecanemab has showed potential for people with mild cognitive impairment caused by Alzheimer's disease. It could be available in 2023. A phase 3 clinical trial found that the medication significantly slowed cognitive decline in those with early Alzheimer's disease by 27%. Lecanemab works by preventing the aggregation of amyloid plaques in the brain. This study was the largest to date and evaluated whether eliminating amyloid plaque clusters from the brain can stop the disease (Shi et al., 2022a).
- The drug saracatinib, which was first developed as a possible cancer treatment, is presently being investigated for Alzheimer's disease. By inhibiting a protein that allowed synapses to restore functioning, the medicine helped rats that had partial memory loss. As a possible treatment for Alzheimer's disease, saracatinib is now being tested on humans (Tolar et al., 2020).
- The quantity of beta-amyloid that forms in the brain may be decreased by production blockers. According to research, beta-amyloid is created from a "parent protein" in two phases by several enzymes. Several investigational medications try to stop these enzymes from working. They are known as beta- and gamma-secretase inhibitors(Tolar et al., 2020).

- Chronic, mild inflammation of brain cells is brought on by Alzheimer's. The inflammatory mechanisms that contribute to Alzheimer's disease are being treated by researchers. Research is being done on the medication sargramostim (Leukine). The medicine may boost the immune system's capacity to defend the brain against dangerous proteins, according to some theories. To see if beta-amyloid and inflammation in the brain may be reduced by the diabetes medication pioglitazone (Actos), researchers tested it (Ahn et al., 2019).

While some of these drugs are still under clinical trials or not that popular in the treatment of AD that's why FDA approved cholinesterase and NMDA inhibitors are commonly used to deal with the symptoms of this condition.

1.2.1 Cholinesterase Inhibitors (ChEIs)

AD negatively affects the brain by decreasing acetylcholine levels, a key chemical messenger for attention, memory, cognition, and judgment. Cholinesterase inhibitors enhance the amount of acetylcholine available in the synapse of the brain by inhibiting its breakdown (Shi et al., 2022b). Most commonly used acetylcholinesterase inhibitors to treat AD are donepezil, rivastigmine and galantamine (Fleet et al., 2019).

ChEIs work by preventing the enzyme cholinesterase from breaking down acetylcholine into its component parts, which are acetate and choline. This results in an increase in the amount of acetylcholine that is available at neuromuscular junctions and in the length of time that it remains active there. An anionic site is generated by tryptophan, while an esteractic site is formed by serine in the cholinesterase enzyme. Both active sites are required for the enzyme to function properly. As a result of their interaction with the serine esteractic site, ChEIs like organophosphates stop the enzyme from hydrolyzing acetylcholine. As a result, acetylcholine will keep accumulating and

activating the receptors that are linked to it. ChEIs fall into three categories, Reversible, irreversible, and pseudo-reversible. Therapeutic applications are often the most common uses for reversible ChEIs. On the other hand, irreversible and pseudo-reversible inhibitors are often used in the production of insecticides and bioweapons (nerve agents) (Singh & Sadiq, 2022).

1.2.2 Side Effects

ChEIs increases the total amount of acetylcholine in the synapses. Excessive accumulation of this neurotransmitter causes muscarinic and nicotinic toxicity, as a result muscle weakness along with muscle twitching and cramps, diarrhea, increased salivary secretion, blurry vision, tachycardia, even paralysis can happen. When administering cholinesterase inhibitors or exposing patients to organophosphates, one of the primary concerns is the possibility for the patient to experience a cholinergic crisis, Followed by diaphoresis, gastrointestinal issues and emesis. When patients are first started on cholinesterase inhibitors, they may have temporary side effects such as headaches, sleeplessness, and mild gastrointestinal problems. Lightheadedness, weakness, and a loss of weight are three other consequences that are more problematic. Patients who have been exposed to cholinesterase inhibitors may also have prolonged muscular contraction as one of their presenting symptoms (Singh & Sadiq, 2022).

Rhabdomyolysis is another side effect caused by these cholinesterase inhibitors. Rhabdomyolysis is a life-threatening illness that, in certain cases, may lead to a lifelong impairment or even death. When muscles are damaged, they release proteins and electrolytes into the bloodstream, causing this condition. Damaged muscle tissues reach in to the kidney via the bloodstream, but kidneys are unable to filter these tissues. As a result, rhabdomyolysis can lead to renal impairment. These drugs are also known to cause harm to the heart, which may lead to lifelong impairment or even death

(Rhabdomyolysis | NIOSH | CDC, n.d.). Specially donepezil has higher risk of causing this side effect than Galantamine and Rivastigmine.

1.2.3 Contraindication

Due to the tendency to raise vagal tone through stimulation of the parasympathetic nervous system, care is required when providing cholinesterase inhibitors to patients with bradycardia or cardiac conduction disorders such as sick sinus syndrome. Patients taking antihypertensive drugs should also be cautious owing to the likelihood of severe hypotension. In addition, Due to the increased risk of gastrointestinal bleeding in people with gastric ulcers, ChEIs are not recommended. Also, patients with urine retention should not administer ChEIs because they have the tendency to cause more urine retention. Patients with hypersensitivity to ChEIs and their derivatives should also avoid these drugs (Singh & Sadiq, 2022)

1.3.1 NMDA Inhibitor

Memantine has been approved by the FDA for the management of mild to moderate AD. It works by controlling the activity of glutamate, a chemical messenger important in many cognitive processing, including memory and learning. Memantine is a glutamate NMDA (N-Methyl-D-Aspartate)-receptor subtype antagonist. It is used to decrease the neurotoxicity that is suspected to be connected to AD and other neurodegenerative disorders. Memantine prevents overactivation of glutamine receptors by inhibiting the NMDA-receptor subtype of glutamate receptors. Its inhibitory effects balance the central nervous system's (CNS) hyperactive glutaminergic pathway, which is suspected to be a factor in the neurotoxicity found in AD. The excitatory neurotransmitter glutamate is the most abundant in the brain. The NMDA receptor, which is critical for activities including as learning and memory, is one of the receptors activated by glutamate. Excessive

activation of NMDARs has been linked to neuronal loss/damage, which contributes to a variety of acute and chronic neurological diseases, including dementia. Nevertheless, In order for neurons to work properly, NMDA receptors must be physiologically activated. Extreme clinical side effects are expected with any drug that blocks NMDA-receptor activation completely. To avoid interfering with regular synaptic transmission, memantine acts as a noncompetitive, low-affinity, open-channel blocker, preferentially entering the receptor-associated ion channel upon its over activation. That’s how, further excitotoxicity-related neuronal cell death is prevented. In conjunction with ChEIs, memantine is thus used to treat Alzheimer's dementia (Williams & Buvanendran, 2022).

1.3.2 Side Effects

Dizziness, headache, disorientation, diarrhea, and constipation are the most prevalent adverse effects observed in clinical studies. Along with fatigue, discomfort, hypertension, weight gain, hallucination, disorientation, aggressive behavior, vomiting, stomach pain, and urine incontinence (Williams & Buvanendran, 2022b).

1.3.3 Contraindications

People who are allergic to memantine hydrochloride or any of the other ingredients. Some urinary tract conditions that raise the pH of urine may make it harder for memantine to leave the body through urine. Also in clinical trials, there were more cases of cardiac failure, angina, and high blood pressure. Moreover, it can have detrimental effects on liver (Williams & Buvanendran, 2022b). Elimination of memantine takes place in both the liver and the kidneys. In patients who have substantial impairment of either their liver or kidneys, doctors should prescribe a reduced dosage of memantine in accordance with the severity of the patient's condition. No modification

is required for people who have a moderate to severe impairment of their renal function. On the other hand, it is suggested that patients who have severe renal impairment take no more than 5 mg of this medication twice day. Memantine's clearance will be impacted by any drugs that influence renal secretion, particularly those that change the pH of the urine (Thomas & Grossberg, 2009).

1.4 Purpose of the Study

Several long-term studies have shown that cognitive decline with age is a bad indicator of survival in the future. Even after considering medical conditions and how healthy people think they are, this link is still there. This has been linked to the effects of less biological vitality. But it has also been said that the link between cognition and death is about more than just a loss of biological vitality. Systematic reviews have concluded that the terminal decline is caused by a number of different things that happen throughout a person's life (Meguro et al., 2014). Studies has found that among all four FDA approved drugs, donepezil has the highest mortality benefit. It has higher percentage of improving patients cognitive functions and overall life quality as well as expectancy. On the other hand, several reports of Rhabdomyolysis have been reported in various health care organizations associating this drug. This study is going to quantify the mortality benefit ratios and rhabdomyolysis cases via systematic review by analyzing ADRs from FAERS.

Chapter 2

Donepezil

2.1 Overview of Donepezil

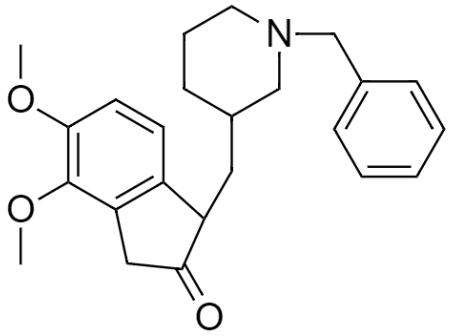

Figure 4: Structure of Donepezil ((RS)-2-[(1-Benzyl-4-piperidyl)methyl]-5,6-dimethoxy-2,3-dihydroinden-1-one) (modified from: Pubchem)

Donepezil is the most commonly prescribed ChEI for the treatment of AD. More than 2 million prescriptions for donepezil were filled in Canada in 2013 (Fleet et al., 2019a). Structure of donepezil is shown in Figure 4. Acetylcholine is essential for memory function and hippocampus-dependent learning. But this memory function is severely affected by damaged cholinergic system caused by AD. Multiple factors contribute to the complexity of ACh's effect on memory. ACh regulates memory function just for specific types of learning (i.e. hippocampus-dependent learning). Procedural memory, also known as implicit memory, has been shown to be independent of the hippocampus, unlike declarative memory, which includes episodic and semantic memory (Bird & Burgess, 2008). Prior research using cholinergic receptor antagonists reveals that cholinergic receptor activation has little effect on procedural memory, however episodic and spatial memory are affected (Blokland et al., 1992). Furthermore, when the number of cholinergic

neurons in the medial septum is reduced significantly, spatial memory is impaired although non-spatial memory is preserved. (Berger-Sweeney et al., 2001).

2.2 Pharmacodynamics

Indications: Mainly for, Mild, moderate, and severe AD. But has some effect on,

- Vascular dementia
- Lewy body dementia
- Parkinson's disease dementia
- Mild cognitive impairment (Asiri & Mostafa, 2021).

Approved Dosage forms and strength: Oral and transdermal dosage forms of donepezil have been approved by FDA at 5mg and 10mg dose.

Drug-Drug interaction:

- When donepezil and 1,2-Benzodiazepine are administered together, the risk of severe side effects increase.
- Donepezil's serum concentration may be raised when coupled with abametapir.
- When donepezil is taken with Abatacept, its metabolism may be enhanced.
- Abemaciclib decrease the elimination of donepezil, resulting in the increase of serum concentration.
- Abiraterone can slow the metabolism rate of donepezil.
- The metabolism of Abrocitinib may be lowered when taken with donepezil.
- Donepezil may enhance Acebutolol's bradycardic effects.

- Donepezil can slow the metabolism rate of Acenocoumarol.
- Acetaminophen can also prolong the metabolism rate of donepezil,
- When Acetazolamide and donepezil are taken together, there is an increased chances of severe side effects (Asiri & Mostafa, 2021).

Mechanism Of Action: Donepezil has the capacity to selectively and reversibly inhibit the enzyme known as acetylcholinesterase. This enzyme is responsible for the breakdown of acetylcholine. It is believed that the inhibition of the enzyme in question is the principal mechanism by which this medicine exerts its pharmacological effects on the human body. One of these consequences is an increase in cholinergic transmission, which, as previously mentioned, works to reduce the severity of the symptoms of AD. Donepezil may also work by reducing NMDA receptor activity and controlling amyloid proteins, both of which play roles in glutamate-induced excitatory transmission. These are also examples of other presumed modes of action for this drug. It has been shown that each of these different methods have a substantial bearing on the course of AD. In addition to the methods that have already been outlined, another presumption about the mechanism of this drug is that it inhibits various inflammatory signaling pathway and enhance neuroprotection (Asiri & Mostafa, 2021). The mechanism of action is illustrated in figure 5.

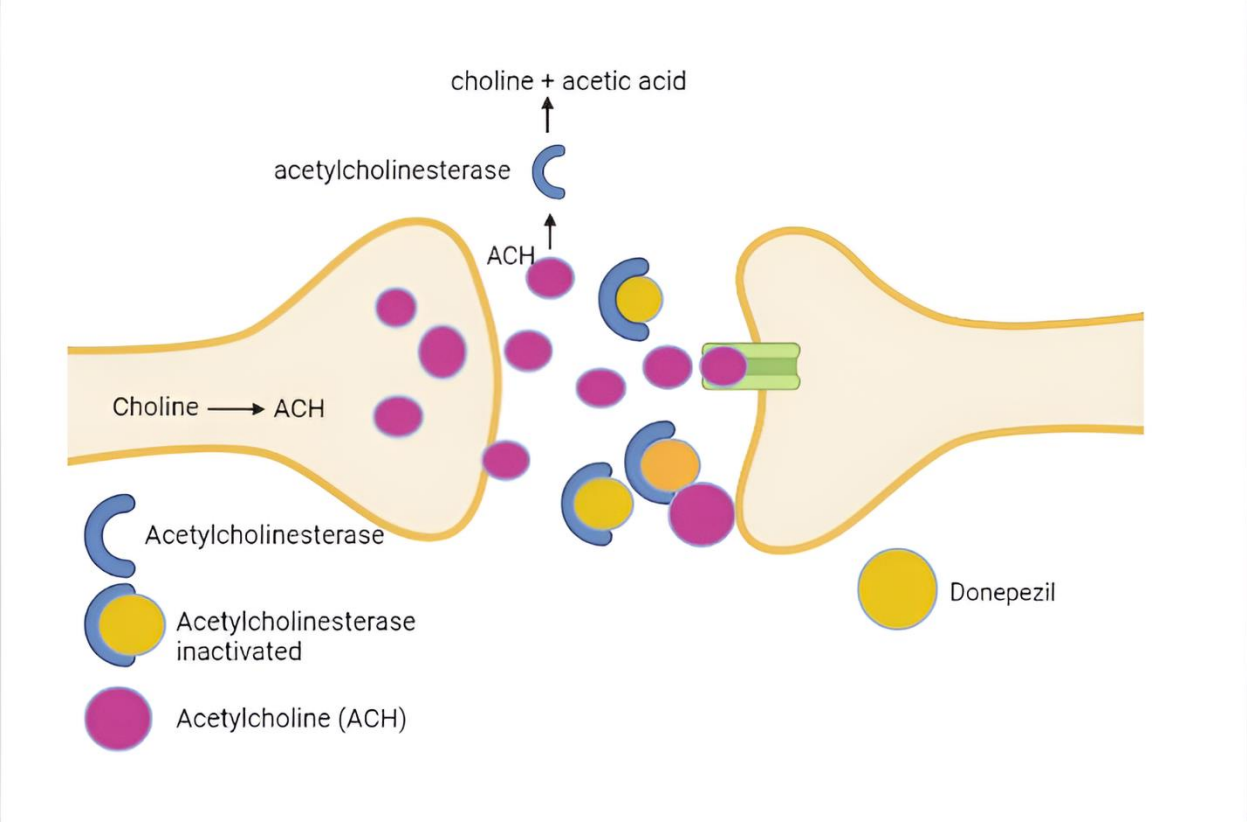

Figure 5: Mechanism of Action of Donepezil (modified from: Hara & Kawabe, 2019)

2.3 Pharmacokinetics

Absorption: According to FDA label, after being taken by mouth, donepezil is very slowly absorbed by the body via the gastrointestinal system. The time to maximum concentration (Tmax) is between three and four hours, the bioavailability is one hundred percent, and steady-state concentrations are reached between fifteen and twenty-one days after treatment. In one pharmacokinetic study, the Tmax was shown to be 4.1 hours, with a 1.5-hour standard variation. According to the Canadian monograph, the Cmax of donepezil tablets containing 5 milligrams is estimated to be 8.34 nanograms per milliliter. The area under the curve (AUC) for 5 mg donepezil tablets was determined to be 221.90-225.36 ng.hr/mL.(fda & cder, n.d.-a) (Table 1).

Distribution: When given in 5 mg doses, donepezil has a volume of distribution of 11.8 1.7 L/kg, whereas in 10 mg doses, it has a volume of distribution of 11.6 1.91 L/kg. Its presence in the extravascular compartments may be substantial. Donepezil can cross the blood-brain barrier; at the doses mentioned above, its concentration in cerebrospinal fluid was estimated to be 15.7%. The FDA label for donepezil states that the steady-state volume of distribution ranges from 12 to 16 liters per kilogram (fda & cder, n.d.-a) (Table 1).

Metabolism: Donepezil is attached to proteins at a rate of 96 percent, with about 75 percent of its interaction taking place with albumin and roughly 21 percent taking place with alpha-1 glycoprotein. Donepezil is metabolized in the liver by a process known as first pass metabolism, which is largely carried out by CYP3A4, in addition to CYP2D6. Following this stage, O-dealkylation, hydroxylation, N-oxidation, hydrolysis, and O-glucuronidation occur, resulting in the formation of a number of metabolites with equivalent half-lives to the original parent drug. The remaining 11% was determined to be the metabolite 6-O-desmethyl donepezil, which inhibits the cholinesterase enzyme with a similar degree of efficacy as donepezil. This medication undergoes a significant amount of metabolism, which results in the production of four major metabolites, two of which are regarded as possessing pharmacological activity, as well as other inactive and unidentified metabolites (fda & cder, n.d.-a) (Table 1).

Table 1: *Pharmacokinetic Parameters of Oral and Transdermal Donepezil* (fda & cder, n.d.).

Pharmacokinetic parameters		Oral Donepezil	Transdermal Donepezil
Absorption	Bioavailability	~ 100%	~ 100%
	C_{max}	23.13 ng/mL	23.13 ng/mL
	T_{max}	3 hrs (10 mg)	5 weeks
	AUC	218.175 ng*h/mL	349.08 ng*h/mL
Distribution	Vd	12-16 L/kg	697.6 L
	V_{max}	376.16 mg/h	254.9 mg/h
	Km	107.08 ng/mL	62.2 ng/mL
	Plasma protein binding	~ 96%	~ 96%
	BBB(Blood Brain Barrier) crossing	yes	yes
Metabolism		Metabolized by CYP-450 isoenzymes CYP2D6 and CYP3A4	Metabolized by CYP-450 isoenzymes CYP2D6 and CYP3A4
Excretion	Clearance (CL/F)	0.13-0.19 L/hr/kg	0.12 L/hr/kg
	Half-life($t_{1/2}$)	~ 70 hours	91 hours
	Excretion of drugs and its metabolites	Urine (~57%) Feces (~15%)	Urine (~57%) Feces (~15%)

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

Excretion: This medication has an apparent plasma clearance that ranges between 0.13 and 0.19 liters per kilogram per hour, as stated on the FDA label. Plasma clearance of donepezil at a dosage of 5 milligrams per kilogram was measured to be almost 0.110 liters per hour in healthy people. The clearance in 10 patients with alcoholic cirrhosis showed a mean decline of 20% when compared to the clearance in 10 healthy people. In contrast, this is the clearance in 10 healthy individuals. Researchers discovered no appreciable variation in clearance between four participants with severe renal impairment and four healthy individuals. It was discovered in studies when donepezil was administered radiolabeled to healthy subjects that 57% of the observed radioactivity was detected in the urine and 5% in the feces (fda & cder, n.d.-a) (Table 1).

Chapter 3

Methodology

3.1 Data Source

For this observational and pharmacovigilance study we collected data from FAERS. FAERS is the most effective and useful reporting tool of the US Food and Drug administration, each year almost 1.5 million adverse events regarding medications medical devices and vaccinations are reported. Spontaneous reports made by medical professionals, manufacturers and consumers about adverse events are submitted into the fairs database. this database includes demographic, suspected drug, outcome, reporting nation and interacting drug information (Vestergaard Kvist et al., 2021). For the appropriate keywords to document the incidents in Fars database MedRA (Medical dictionary for Regulatory Activities) is used. Reported adverse effects of FAERS database are raising public awareness and contributing to the identification of drug related safety (Mazhar et al., 2021). quarterly data off adverse events reported in FDA can be accessed by public (Vestergaard Kvist et al., 2021). Consequently, huge number of adverse events regarding FDA approved Acetylcholinesterase inhibitors that are used for the treatment of Alzheimer's disease was obtained, these events were reported by patients, pharmaceutical industries and healthcare providers.

26,004,135 reports where's submitted into the database till today. For this study, we looked for the reports from January 2015 to September 2022 and the search was carried out on January 2023. generic name “Donepezil” was used as the search term. Furthermore, the words for adverse event categorization were chosen from The Medical Dictionary for Regulatory Activities (MedDRA).

3.2 Inclusion and Exclusion Criteria

For this study we collected data dated from January 2015 to September 2022 from the fares database. We chose some preferred terms (PTs) from MedRA to specify the reported adverse events for our study. “Death”, “sudden cardiac death”, “Brain death”, “sudden death”, “Brain death”, “Accidental death”, “Apparent death”, All of these are collected consolidated into single term “Death” and “Rhabdomyolysis”. In this database we found all the adverse events related to the generic name of our drug – donepezil. We only included the data for our targeted drug and remove the data of adverse events that were suspected to be caused by other drugs. That's why the sole suspected drug for our expected adverse effect was “donepezil”. Furthermore, we also filtered out all the duplicate reports by the help of the case numbers and crossmatching the age, sex and event date.

3.3 Statistical Analysis

Using the FAERS database, the data extraction and analysis were carried out in January 2023. In this analysis, we used the reported odds ratio (ROR), which has a 95% confidence interval (CI), to perform a disproportionality analysis. With the use of this research, we were able to find indicators that the medicine in question (donepezil) and its side effects were being reported together (Death and Rhabdomyolysis). ROR was used since it is an established case-non case approach for identifying safety signals of the desired drug (Bene et al., 2014). One of the most popular methods for determining the disproportionality measurements is known as ROR. A 2 by 2 contingency table with instances of the drug's intended side effects and non-cases of its undesirable side effects was used to determine the ROR (van Puijenbroek et al., 2003). As a result, the ROR is applied to evaluate the extent of disproportionality, and the CI establishes the statistical significance of the

finding. if the confidence interval's lower limit is higher than 1, it signals that there have been more reports of these side effects for the targeted drug than with other medications that are also known to cause them. However, if the lower limit of the confidence interval equals or falls below 1, it denotes that there is no signal for the adverse effect, indicating that it is less frequently reported compared to other Drugs (Sato et al., 2020).

In this study, the entire database was used as the comparator, and we computed ROR and the accompanying 95% CI to discover the reported relationship between the adverse events (Death and Rhabdomyolysis) and the targeted drug (Donepezil) (Sato et al., 2020). As a result, we were able to determine the statistical significance of the link between donepezil and the adverse effects when compared to all the other drugs in the database. Then, using other drugs from the same class as a comparator, the ROR and 95% CI were computed for the concerned drug with the same adverse effects. This allowed us to identify the class with the highest reporting association of the adverse event. A drug's reporting relationship is stronger than other drugs if its ROR is higher. Using R (4.2.1) all data analysis were carried out.

Chapter 4

Results

We did a statistical study of the Adverse Event Reporting System (FAERS) of the Food and Drug Administration about the adverse effects of donepezil. The frequency and reporting odds ratios (ROR) were the statistics that were computed for each adverse event. When we took whole database as comparator only 22 cases of death were found for donepezil where 456144 cases of death were reported for other drugs from 2015 to 2022. The reporting odds ratio for donepezil compared with the drugs of whole database in FAERS was (ROR = 0.35; Confidence Interval 95% = 0.23-0.53; P < 0.0001) (Table 2). To niche the data more, we compared the data of donepezil with the number of death cases reported for other drugs of the same class. We saw that 682 death cases were reported in the timeline of 2015 to 2022, whereas the donepezil has only 22 death cases reported in the same timeline. In this comparison the ROR for donepezil compared with other drugs from the same class in FAERS was (ROR = 0.067; Confidence Interval 95% = 0.044-0.10; P < 0.0001) (Table 2).

Table 2: Results for cases of death using donepezil and other drugs

FAERS Database values from 2015-2022			
	Cases of Death	ROR (CI)	*p Value*
Donepezil	22		
Other drugs (whole database as comparator)	456144	0.35 (0.23 - 0.53)	$p < 0.0001$
Other drugs (class as comparator)	682	0.067 (0.044 - 0.10)	$p < 0.0001$

Similarly for rhabdomyolysis cases related to donepezil, we did the statistical study based on the data we found from the FAERS and looked for the frequency and ROR values for our targeted drug. Only 19 cases of rhabdomyolysis were found for donepezil when the entire database was used as a comparator, whereas 16379 cases of rhabdomyolysis were reported for other drugs from 2015 to 2022. In FAERS, the reporting odds ratio for donepezil compared with the drugs of whole database was (ROR = 8.61; 95% CI = 5.48-13.53; P < 0.0001) (Table 3). To further narrow the data, we compared the donepezil data to the number of deaths reported for other drugs of Cholinesterase inhibitors. We saw that only 8 rhabdomyolysis cases were reported between 2015 and 2022, whereas donepezil had 19 rhabdomyolysis cases reported during the same period. In this study, the ROR for donepezil compared with other drugs from the same class in FAERS was (ROR = 5.69; 95% CI = 2.48-13.01; P < 0.0001) (Table 3).

The whole comparison of RORs between donepezil and whole database as comparator and donepezil and other drugs from the same class for both the death and rhabdomyolysis cases are shown in figure 6.

Table 3: Results for cases of rhabdomyolysis using donepezil and other drugs.

FAERS Database values from 2015-2022			
	Cases of Rhabdomyolysis	ROR (CI)	*p* Value
Donepezil	19		
Other drugs (whole database as comparator)	16379	8.61 (5.48 to 13.53)	$p < 0.0001$
Other drugs (class as comparator)	8	5.69 (2.48 - 13.01)	$p < 0.0001$

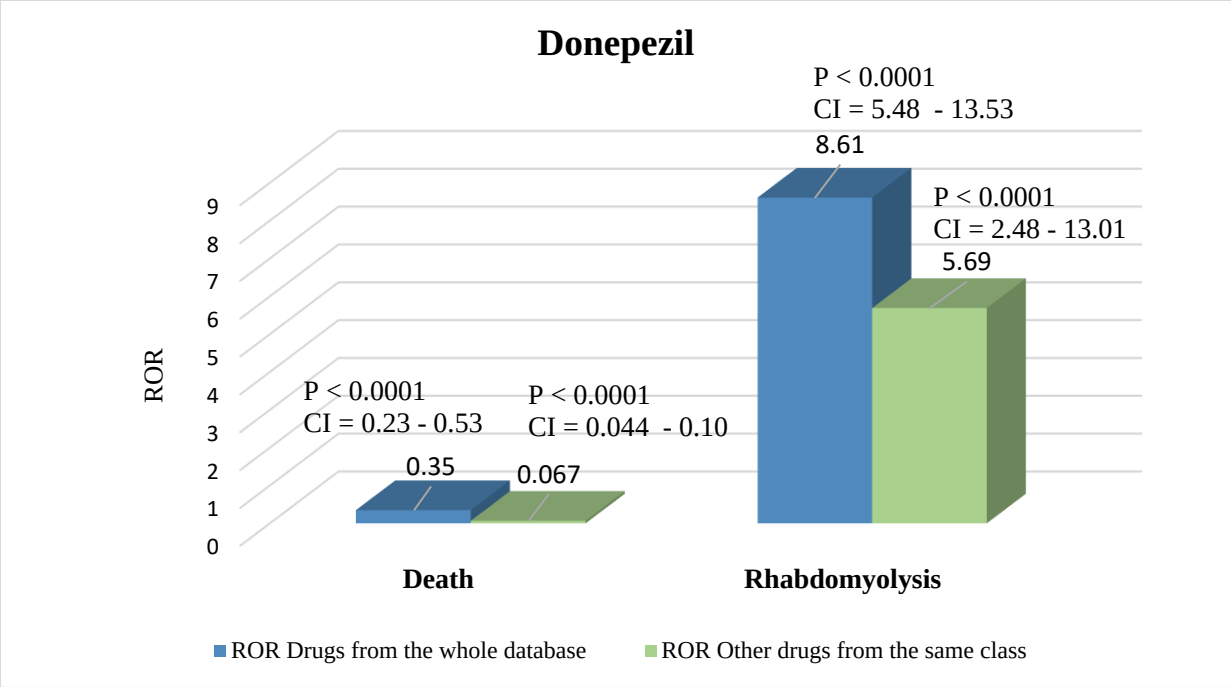

Figure 6: Comparison of the ROR values for cases of Death and Rhabdomyolysis using both whole database and drug class as comparators.

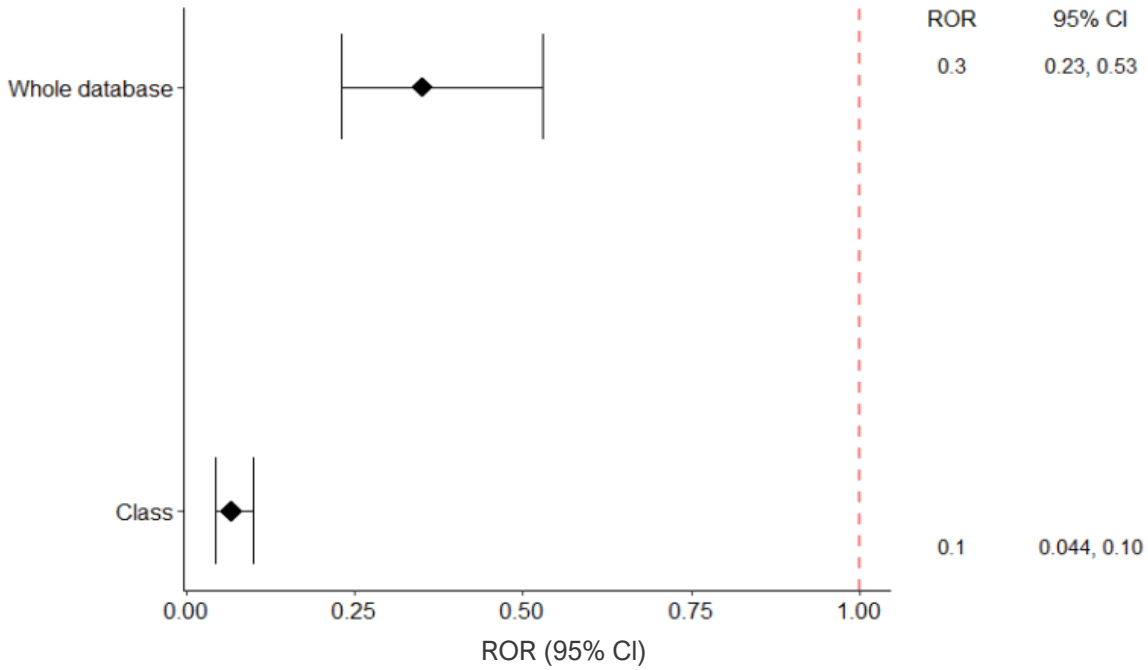

Figure 7: Forest plot of association between death and donepezil

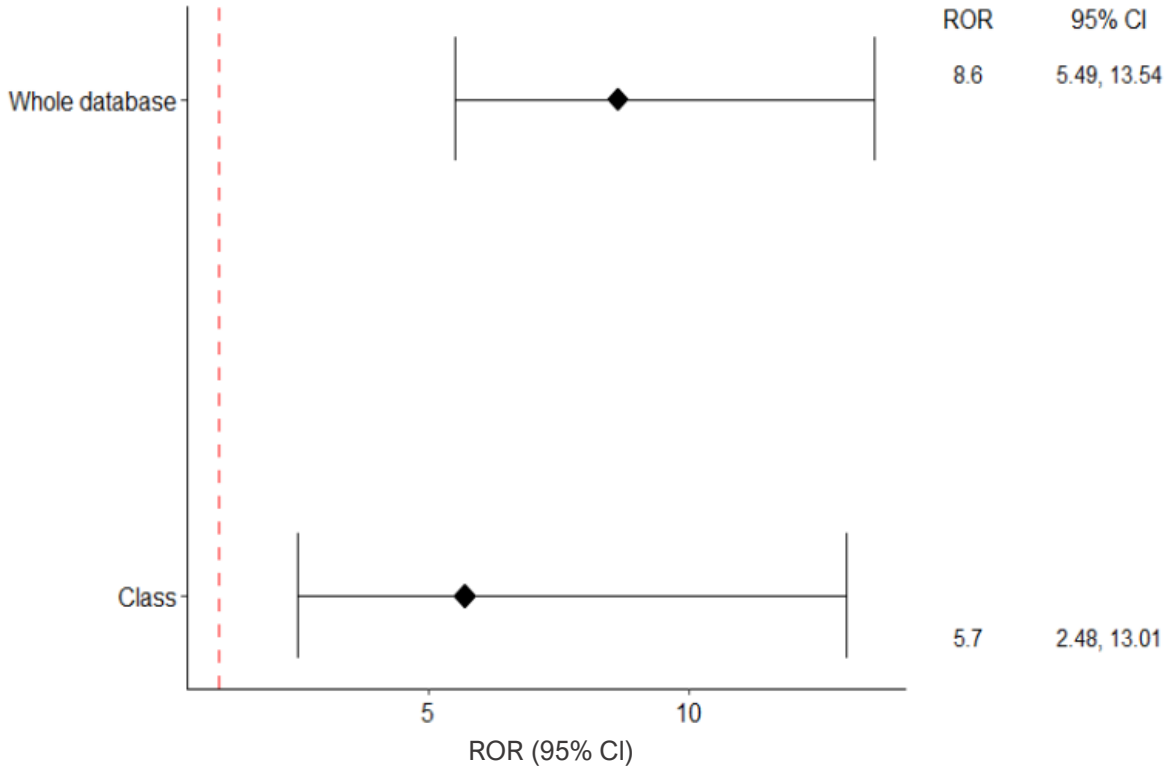

Figure 8: Forest plot of association between rhabdomyolysis and donepezil

4.1 Discussion

The findings from the FAERS database Reporting Odds Ratios show that donepezil has significant outcomes for death reports (p value < 0.0001). According to the ROR data, death was more often reported for other drugs of Cholinesterase inhibitor class than donepezil (Table 2). The reason for less death cases for donepezil can depend on many factors. One of them is that due to the drug's excitatory effect on vagus nerve and anti-inflammatory effects on atherosclerosis, a recent cohort research found that using donepezil was related with a decreased risk of mortality and myocardial infarction. Patients treated with donepezil had greater cardiovascular and overall survival, which stands in contrast to the drug's effect and the increased risk for sinus node dysfunction or cardiac

conduction impairment. Animal research corroborated these results, revealing that oral donepezil reduced the risk of death from pumping failure and cardiac reconfiguration in a mouse model of congestive heart failure (Meguro et al., 2014b). Another factor is donepezil has better effect on cognitive functions of the AD patients. Patients who are treated with donepezil shows better performance in MMSE (Mini-Mental State Examination) and FRSSD (Functional Rating Scale for Symptoms of Dementia) than Rivastigmine and Galantamine (Kazmierski et al., 2018). That's how their overall life quality increases and that leads to low mortality rate. On the contrary, we can see from our findings that donepezil has more reports of rhabdomyolysis than other drugs of the same class, means Galantamine and Rivastigmine. There are 19 cases of rhabdomyolysis was reported from 2015 to 2022 for donepezil where Rivastigmine and Galantamine cumulatively has only 8 reported cases of rhabdomyolysis in this timeline (Table 3). According to the ROR donepezil is highly associated with the muscle related adverse effects (ROR = 5.69; 95% CI = 2.48-13.01; $P < 0.0001$). A recent case report agrees with our findings and suggests that donepezil may have been responsible for inducing acute renal failure due to rhabdomyolysis. An 84-year-old patient with Alzheimer's disease who had been taking 5mg of donepezil twice daily for two months presented to the emergency room complaining of apathy, lack of cooperation, and weakness. Due to an acute renal failure diagnosis, donepezil was first discontinued from the patient. Renal function returned to normal after 12 days of therapy for this patient after he stopped using donepezil (Meguro et al., 2014b). Based on 1 case report in Canada and 88 instances abroad, Health Canada issued a post market surveillance warning in January 2015 concerning the risk of rhabdomyolysis with donepezil usage. Rhabdomyolysis was not reported as a side effect of donepezil in the initial RCTs (Randomized Control Trials), although muscular cramps were. Updated product monographs with a similar warning of rhabdomyolysis were suggested by the US

Food and Drug Association in February 2015 and the European Medicines Agency in July 2015 (Fleet et al., 2019b). Donepezil-related rhabdomyolysis is thought to have unknown biological causes. It is well established that acetylcholine contributes to the transmission of action potentials across the neuromuscular junction, which causes muscle contraction. Consequently, stopping acetylcholine oxidation might result in irregular muscular contractions and eventually rhabdomyolysis (Fleet et al., 2019b). Also, donepezil is more commonly prescribed drug for AD than rivastigmine and galantamine. That's why it has more reported cases of rhabdomyolysis in the FAERS database.

In conclusion, donepezil is more efficient for the treatment of AD than any other cholinesterase inhibitors. It increases the life expectancy of the patients and give them the mortality benefit along with increased cognitive functions and better-quality life. But the risk factors of donepezil also need to be considered. Because donepezil has higher number of rhabdomyolysis cases reported than other cholinesterase inhibitors which can further lead to renal failure. That's why patients who are prescribed donepezil needs to be under close observation of the professional healthcare personnel.

Chapter 5

Conclusion

The findings from our study suggest that donepezil has a positive impact on life expectancy and overall quality of Alzheimer's patients. As compared to other Acetylcholinesterase inhibitors, donepezil is certainly more beneficial in terms mortality benefit. But the concerning amount of Rhabdomyolysis of donepezil is concerning. Patients who are already suffering from any renal complications or have traits of Parkinson's disease should be under strict observation or if possible, avoid donepezil.

Chapter 6

Reference

2022 Alzheimer's disease facts and figures. (2022). *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*, *18*(4), 700–789. https://doi.org/10.1002/ALZ.12638

Ahn, K. C., Learman, C. R., Baker, G. B., Weaver, C. L., Chung, P. S., Kim, H. G., & Song, M. S. (2019). Regulation of diabetes: A therapeutic strategy for Alzheimer's disease? *Journal of Korean Medical Science*, *34*(46). https://doi.org/10.3346/JKMS.2019.34.E297

Asiri, Y. A., & Mostafa, G. A. E. (2021). Donepezil. *Profiles of Drug Substances, Excipients and Related Methodology*, *35*, 117–150. https://doi.org/10.1016/S1871-5125(10)35003-5

Berger-Sweeney, J., Stearns, N. A., Murg, S. L., Floerke-Nashner, L. R., Lappi, D. A., & Baxter, M. G. (2001). Selective immunolesions of cholinergic neurons in mice: effects on neuroanatomy, neurochemistry, and behavior. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *21*(20), 8164–8173. https://doi.org/10.1523/JNEUROSCI.21-20-08164.2001

fda, & cder. (n.d.). *HIGHLIGHTS OF PRESCRIBING INFORMATION*. www.fda.gov/medwatch.

Fleet, J. L., McArthur, E., Patel, A., Weir, M. A., Montero-Odasso, M., & Garg, A. X. (2019a). Risk of rhabdomyolysis with donepezil compared with rivastigmine or galantamine: A population-based cohort study. *CMAJ*, *191*(37), E1018–E1024. https://doi.org/10.1503/CMAJ.190337/-/DC1

Fleet, J. L., McArthur, E., Patel, A., Weir, M. A., Montero-Odasso, M., & Garg, A. X. (2019b). Risk of rhabdomyolysis with donepezil compared with rivastigmine or galantamine: A population-based cohort study. *CMAJ*, *191*(37), E1018–E1024. https://doi.org/10.1503/cmaj.190337

Kazmierski, J., Messini-Zachou, C., Gkioka, M., & Tsolaki, M. (2018). The Impact of a Long-Term Rivastigmine and Donepezil Treatment on All-Cause Mortality in Patients With Alzheimer's Disease. *American Journal of Alzheimer's Disease and Other Dementias*, *33*(6), 385–393. https://doi.org/10.1177/1533317518775044

Matthews, K. A., Xu, W., Gaglioti, A. H., Holt, J. B., Croft, J. B., Mack, D., & McGuire, L. C. (2022). Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015–2060) in adults aged ≥65 years. *Alzheimer's and Dementia*, *15*(1), 17–24. https://doi.org/10.1016/J.JALZ.2018.06.3063

Meguro, K., Kasai, M., Akanuma, K., Meguro, M., Ishii, H., & Yamaguchi, S. (2014a). *Donepezil and life expectancy in Alzheimer's disease: A retrospective analysis in the Tajiri Project*. https://doi.org/10.1186/1471-2377-14-83

Meguro, K., Kasai, M., Akanuma, K., Meguro, M., Ishii, H., & Yamaguchi, S. (2014b). Donepezil and life expectancy in Alzheimer's disease: A retrospective analysis in the Tajiri Project. *BMC Neurology*, *14*(1). https://doi.org/10.1186/1471-2377-14-83

Rhabdomyolysis | NIOSH | CDC. (n.d.). Retrieved January 22, 2023, from https://www.cdc.gov/niosh/topics/rhabdo/default.html

Shcherbatykh, I., & Carpenter, D. O. (2007). The Role of Metals in the Etiology of Alzheimer's Disease. *Journal of Alzheimer's Disease*, *11*, 191–205. https://doi.org/10.3233/JAD-2007-11207

Shi, M., Chu, F., Zhu, F., & Zhu, J. (2022). Impact of Anti-amyloid-β Monoclonal Antibodies on the Pathology and Clinical Profile of Alzheimer's Disease: A Focus on Aducanumab and Lecanemab. *Frontiers in Aging Neuroscience*, *14*. https://doi.org/10.3389/FNAGI.2022.870517

Singh, R., & Sadiq, N. M. (2022). Cholinesterase Inhibitors. *StatPearls*. https://www.ncbi.nlm.nih.gov/books/NBK544336/

The Global Deterioration Scale: The Stages of Alzheimer's Disease. (n.d.). Retrieved February 3, 2023, from https://alzheimersdisease.net/living/stages

Thomas, S. J., & Grossberg, G. T. (2009). Clinical Interventions in Aging Memantine: a review of studies into its safety and efficacy in treating Alzheimer's disease and other dementias. *Clinical Interventions in Aging*, 4–367. https://www.dovepress.com/

Tolar, M., Abushakra, S., Hey, J. A., Porsteinsson, A., & Sabbagh, M. (2020). Aducanumab, gantenerumab, BAN2401, and ALZ-801 - The first wave of amyloid-targeting drugs for Alzheimer's disease with potential for near term approval. *Alzheimer's Research and Therapy*, *12*(1). https://doi.org/10.1186/S13195-020-00663-W

Williams, B. S., & Buvanendran, A. (2022a). Memantine. *The Essence of Analgesia and Analgesics*, 319–321. https://doi.org/10.1017/CBO9780511841378.077

Williams, B. S., & Buvanendran, A. (2022b). Memantine. *The Essence of Analgesia and Analgesics*, 319–321. https://doi.org/10.1017/CBO9780511841378.077

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

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

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

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

Vestergaard Kvist, A., Faruque, J., Vallejo-Yague, E., Weiler, S., Winter, E. M., & Burden, A. M. (2021). Cardiovascular Safety Profile of Romosozumab: A Pharmacovigilance Analysis of the US Food and Drug Administration Adverse Event Reporting System (FAERS). *J Clin Med*, *10*(8). https://doi.org/10.3390/jcm10081660

Rastogi, S., Sharma, V., Bharti, P. S., Rani, K., Modi, G., Nikolajeff, F., & Kumar, S. (2021). The Evolving Landscape of Exosomes in Neurodegenerative Diseases: Exosomes Characteristics and a Promising Role in Early Diagnosis. *International Journal of Molecular Sciences*, *22*(1), 440. https://doi.org/10.3390/ijms22010440

Hara, Y., & Kawabe, H. (2019). Donepezil (Aricept). *Donepezil*. https://doi.org/10.1007/978-981-13-8906-1_11