A Pharmacovigilance Study of Gender Differences in Rhabdomyolysis Risk Among Donepezil Users with Alzheimer`s Disease

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

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Declaration

It is hereby declared that

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

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Approval

The thesis/project titled “A Pharmacovigilance Study of Gender Differences in Rhabdomyolysis Risk Among Donepezil Users with Alzheimer`s Disease” submitted by Zubaier Ahmed (19346020) of Summer, 2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of f Bachelor of Pharmacy on October, 2023.

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Ethics Statement

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

Abstract

Alzheimer's disease is the most common disease for older patients marked by symptoms of dementia. This study was conducted for the pharmacovigilance investigation of donepezil related to adverse event rhabdomyolysis among gender variation by collecting data from FDA Adverse Event Reporting System database (January 2016 to June 2023). RStudio was used to calculate the reporting odds ratio (ROR). In case of male, the ROR along with 95% CI value was 10.97, when considering the whole database as a comparator and 4.93, when considering the AChEIs class as a comparator. On the other hand, the ROR (95% CI) was found to be 5.71 by considering the whole database as a comparator and 1.82 by considering AChEIs class as a comparator in case of female patients. After calculating and interpreting ROR, male patients are more associated with rhabdomyolysis. More research can be conducted in the future on those findings.

Keywords: Pharmacovigilance; Alzheimer's Disease; Dementia; Donepezil; Rhabdomyolysis.

Dedication

Dedicated to my parents, who inspires me in every step of my life.

Acknowledgement

At first, I would like to thank Almighty Allah for giving me strength, knowledge, and wisdom, for blessing me with patience as well as assistance to complete this project. Foremost, I wish to express my deepest gratitude to my project supervisor Professor Dr. Hasina Yasmin, Assistant Dean and Program Director, School of Pharmacy, BRAC University for her guidance, encouragement, and helpful directions throughout my project work. Her continuous support and deepest knowledge make it possible to complete my project work. I would like to thank and put forward my most sincere regards to Dr. Eva Rahman Kabir, Professor and Dean, School of Pharmacy, BRAC University for her guidance and support.

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List of Acronyms

AD	Alzheimer`s Disease
ACh	Acetylcholine
AChEIs	Acetylcholinesterase inhibitors
MMSE	Mini-Mental State Examination
ASRs	Age-standardized rates
ApoE	Apolipoprotein E
APP	Amyloid precursor protein
NFTs	Neurofibrillary tangles
NMDA	N-methyl-D-aspartate
MedDRA	Medical Dictionary for Regulatory Activities

Chapter 1

Introduction

1.1 Alzheimer's Disease

Alzheimer's Disease (AD) disease is a neurodegenerative disorder which is most commonly occurs in older population. In AD, commonly memory loss, disorientation, cognitive impairment is seen in the patient. Day by day, this disease is increasing and affects people's daily life. Patient with AD is not capable to continue their daily life. They cannot remember their new memories. This disease is caused by the blockage of the brain with proteins which are called plaques and tangles. They are made by amyloid and tau. This two-protein present normally in healthy patient but works abnormally in AD patients. The amyloid form plagues outside the neuron and tau form tangles inside the neuron. This causing cell death and the brain will shrink. Research is going on to find out the exact cause of AD. There is no cure or treatment for AD yet, but only symptomatic treatment is available (Yiannopoulou & Papageorgiou, 2020). The understanding of AD pathogenesis is not well established, that's why discovering novel therapies or targeted drug is delaying. At present, worldwide AD patients are around 50 million and the number will turn into 152 million by 2050 (Breijyeh et al., n.d.).

AD has several risk factors including genetic factor, smoking, family history, alcoholism, high fat diet, head injury and trauma, age etc. It is a progressive disorder and defined as most common type of dementia. Vitamin B_{12} is associated with neurodegenerative function and can increase the risk of this disease. Several diagnostic method are developed to diagnosis AD including MRI, MMSE test, laboratory and family history (Davis, 2000). The psychiatrist plays and important role to diagnosis cognitive impairment for detecting Alzheimer`s disease. Women is at high risk with AD and men is in the fastest risk with AD in recent years. Avoiding

smoking and controlling obesity helps to decrease the risk of Alzheimer`s disease. The adverse events of AD drug`s therapy can minimize by adjusting the dose of this medications.

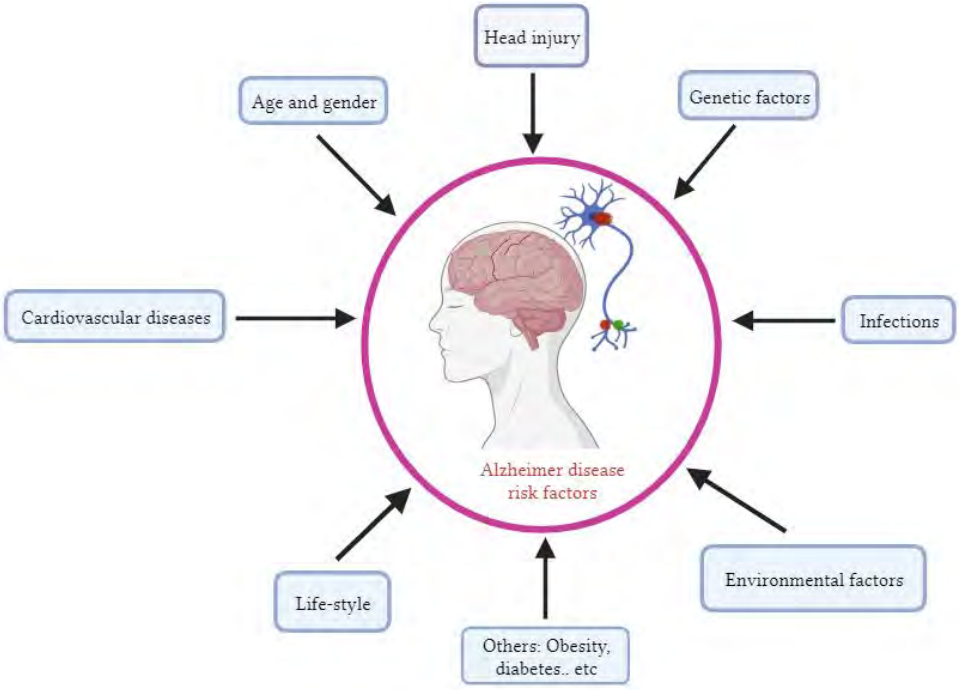

Figure 1:The risk factors for Alzheimer's disease (modified from Breijyeh & Karaman, 2020).

Day by day, the number of AD patients is increasing. This disease creates a great suffering in lifestyle of the patients. Some symptomatic treatments are available to relief from the symptoms. Ant-amyloid therapy was focus by last 25 years as a targeted therapy. But clinical data shows, limited efficacy as well as safety. So, the scientists are more inspire about tau pathology. They are working on anti-tau agents to treat AD. New targets are also investigated and immunotherapy exhibits an excellent result again AD pathology. The treatment of AD disease is expensive. Delaying institutionalization as well as improving quality of life can reduce economic cost for medical treatment. Psychoeducation, advance planning, behavioral techniques and environments factors can improve AD patients wellbeing (Yiannopoulou & Papageorgiou, 2020).

1.2 Prevalence of AD

A study was conducted by collecting data from Global Burden of Disease (GBD) database from 1990 to 2009 to analyzed the prevalence, death, age-standardized rates (ASRs) as well as the numbers of AD and dementias. Alzheimer's disease burden raises in these periods worldwide. Female population are in higher risk of these disease and male develops the risk faster. This study also showed that prevalence and incidence of AD and dementias raise by 147.95 and 160.84%. According to this study, obesity is the main risk factors for female to develop AD whereas smoking is an important risk factors for male (X. Li et al., 2022).

Dementia is developed from Alzheimer`s disease and more than 50 million people suffers from dementia worldwide. By 2050, it is expected that the number of dementia patients will increase to 150 million (Aisen et al., 2017). The number of AD patients are 6 million in America which will turn to nearly 13 million by 2050. 1 senior citizen from every 3 dies with AD or other dementias. Older black Americans are twice time more likely to develop Alzheimer`s disease than older white. In Australia and New Zealand, more than 413,106 and 62,287 people are living with dementia respectively (Eratne et al., 2018). As age increase, more chances to develop AD. Age at 65, the prevalence is 6.4% for dementia and 4.4% for AD in Europe. On the other hand, prevalence for AD is 9.7% for people who are at 70 years old. Approximately 10% older people have chance to develop some degree of dementias in developed nations (Qiu et al., 2009).

According to WHO, the number AD and dementia deaths in Bangladesh is 14,993 in 2020 which was 2.09% of total deaths. In Bangladesh, exact epidemiological data on Alzheimer`s disease is not published every year yet. Majority of the population of Bangladesh are young and the research funding of AD is minimal amount. So, less research is conducted on that field. But now-a-days, Bangladeshi researchers are becoming interested in neurological filed, specifically in AD. Lack of awareness about Alzheimer`s disease increase the risk in

Bangladeshi population. So, the healthcare professionals, top management, researchers, government should take necessary steps to manage Alzheimer's disease in Bangladesh.

1.3 Etiology of AD

The exact etiology of Alzheimer`s disease is unknown, but some factors that contribute in AD are known. The researcher finds out both genetic, lifestyle and environmental risks factors play and important role in AD. Moreover, aging and familiar history are also considered an important risk factor. The chances of having AD at 65 is 3% which is rapidly increase to 30% at the age of 85. So, the people under the age of 65 are less prone to develop AD (Sheppard & Coleman, 2020). The early onset of AD (EOAD) develops before age 65. On the other hand, the late onset of AD (LOAD) appears at age after 65. Besides, it also shows a familiar link that means family history can develop this disease to the future generation.

Mutations of various gene such as APP, Amyloid Aβ, PSEN1 or PSEN2 causes early onset of AD (EOAD). The mutations of these gen can increase the production of β amyloid which can develop plaques in the brain. This aggregation of beta-amyloid can disrupt the neuronal function of the brain. On the other hand, Apolipoprotein E (ApoE) is a risk factor for developing late onset of AD. If homozygote carries of ApoE ε4, the risk of AD increase to 10-12 folds (Jellinger, 2006). Moreover, uneducated or low educational level, injury in the brain, heart disease, atherosclerosis may contribute to Alzheimer`s disease. Elevated cholesterol level and estrogen deficit in the female are also remarkable risk factors for developing AD. Chronic inflammation in the brain plays an important role in disease progression of AD. Some putative risk factors may contribute in AD progression which includes low caloric diet, NSAIDs, statins and lifelong activity. Depression increases the risk of promoting putative risk factors.

Overall, several risk factors cause the AD. But scientist still investigate the exact etiology of Alzheimer`s disease. Aging, familiar history, mutations of some gens may develop this disease.

Furthermore, inflammation in the brain or head injury, uneducated, episode depression is also considered as factors to promote disease progression.

1.4 Pathology

The Complex neuropathology of AD makes it difficult to treat and develop new agents for slowing the progression of the disease. Aβ and tau aggregation, formation of extracellular plaques, inflammation in the brains and oxidative damage can cause AD. Furthermore, cholinergic neurons injury can develop AD. The amyloid precursor protein (APP) is a glycoprotein which produce Aβ peptide. Moreover, the α-secretase and γ-secretase enzyme cleave APP, thus neurotoxic Aβ peptide is synthesized. The deposition of Aβ peptide outside the cells leads to form oligomers, fibrils which turned into insoluble plaques (Vaz & Silvestre, 2020). These plaques cause the damage of synapse of the neuron. As a result, neuronal death occurs. The most prone peptide to aggregate is Aβ42 peptide includes 42 amino acids residues. The accumulation of amyloid plaques are present in hippocampus, cerebral cortex, dendrites can promote the loss of axons, synapse, eventually death of the neuron (Chen et al., 2017).

To stabilize cytoskeletal microtubules, tau protein plays a crucial role. But the abnormal hyperphosphorylation of this protein makes it less appropriate to bind microtubules. The disruption of this link between microtubules and tau protein can disrupt the function of microtubules. It also can increase the level of cytosolic levels of p-tau and promote the formation of neurofibrillary tangles (NFTs). The accumulation of abnormal tau can pair with helical filaments (PHF). As a result, neuronal loss is occurred. All of the tau isoforms are abnormally hyperphosphorylated in AD. As, the phosphorylated tau aggregation increase, the severity of the symptoms and disease progression also increases. In AD patient`s brain, hyperphosphorylated tau protein makes the microtubules disassembles and release free tau molecules to aggregate. Finally, loss or dame of neuron results (Medeiros et al., 2011).

The loss of synapse can cause cognitive impairment which is observed in the early stages of AD. The inflammation in the brain eventually causes the axonal dystrophy. Vitamin B12 deficiency can raise the neurological problems and increase the risk of AD. Females suffers from AD more than male. ApoE4 allele increase the risk of AD. Moreover, estrogen receptor gene plays an important role to cause AD.

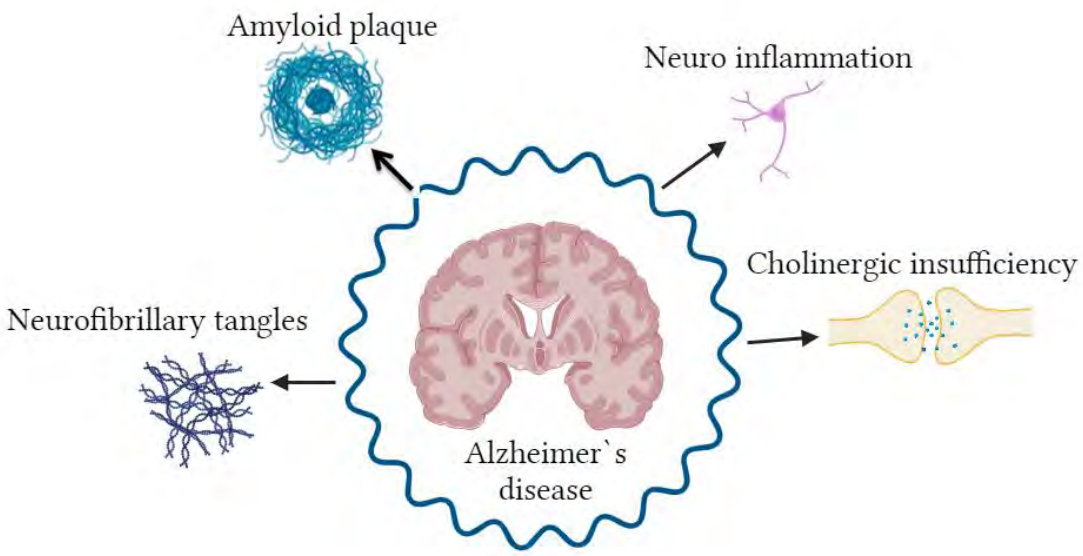

Figure 2: Pathology of Alzheimer`s Disease (modified from Castellani et al., 2014)

1.5 Signs of Alzheimer's Disease

Alzheimer's disease shows many signs and symptoms in the affected patients. As the exact etiology of the disease is not known, the treatment is based on the signs and symptoms of this disease. The most common sign and symptom of Alzheimer's disease is memory loss (Bature et al., 2017) . Other signs and symptoms are given in below:

- Loss of memory, unable to do the daily task
- Take a bad decision, decrease the power of judgment
- Altered mood and personality also changes
- Less attention

- Does not cope with a new environment
- Hallucinations also occur
- Decrease the power of learning
- Thoughts and thinking problems.
- Forgot easily
- Forgot the current location easily
- Decline language
- Depressed mood

1.6 Current Treatment Options for Alzheimer's Disease

The exact cause of AD is unknown. So, most of the treatment is based on a symptomatic approach. The complexity of AD sometimes requires combination therapy for successful treatment. Currently, US FDA-approved drug for the treatment of AD includes Acetylcholinesterase inhibitors (ChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonist. Galantamine, rivastigmine, and donepezil are used as AChEIs and memantine is used as NMDAR antagonist. Moreover, donepezil and memantine are also used as combination therapy for symptomatic treatment approved by FDA (Cummings et al., 2019). Besides, FDA licenses aducanumab as a drug for the treatment of AD, it is a human monoclonal antibody and removes Aβ plaques from the brain (Budd Haeberlein et al., 2022).

1.6.1 AChE inhibitors

In AD patients, both neuropathological and imaging studies show cholinergic deficits. Moreover, these deficits are primarily seen in the hippocampus of the patients. This kind of deficit reduces the amount of acetylcholine in the synapse of the brain. Thus, cognitive impairment, memory loss, weakness, and loss of sense occur. Acetylcholinesterase is a cholinergic enzyme that aided the breakdown of acetylcholine. AChE inhibitors prevent the

breakdown of acetylcholine into choline and acetate. So, acetylcholine is increased in the synapse of the brain. The administration of AChEIs increases the ACh level in the synapse and treats memory impairments (Y.Y. Szeto & J.G. Lewis, 2016). Some studies show that AChEIs are safe and well tolerated for the treatment of AD. Although donepezil, galantamine, and rivastigmine are efficacious against mild to moderate AD, these drugs are effective for short periods (1-3 years). So, they cannot alter the AD progression (Xiao et al., 2021). All of these drugs are used for symptomatic relief, they cannot treat AD permanently. Slight variation among these medications was observed, but no evidence was found about the differences between these medications. Some adverse effects are also reported with these drugs including vomiting, nausea, diarrhea etc. Other compounds such as organophosphate can also inhibit AChE enzymatic activity.

Donepezil

Donepezil is a cholinesterase inhibitors drug that is used to treat AD. It improves the symptoms of AD, improves memory function, and the ability to speak and think, interact with others. As we know AChE enzyme is responsible for the breakdown of ACh into choline and acetate. Donepezil inhibits the enzyme; thus, acetylcholine is not degraded. Therefore, the amount of ACh is increased in the synaptic cleft. It is also reversible and highly selective of AChE. In 1996, Donepezil was approved by FDA for the treatment of mild to moderate AD. After administering donepezil, cognition was improved substantially which was proved by a 6-month double-blind, placebo-controlled study of donepezil treatment (Forchetti, 2005). According to a study of Donepezil, the older patient shows more severe symptoms of AD and requires the necessity of medications. The dose recommends of Donepezil for starting the treatment of mild to moderate AD is initially 5 mg per day which can be increased to 10 mg per day for 4-6 weeks. A 10 mg/day dose regimen has been showing improvement in cognitive function, daily activities as well as lifestyle/behavior (Jia et al., 2017). Donepezil is established as good patient

tolerance and shows some adverse effects on GIT or the nervous system (Y.Y. Szeto & J.G. Lewis, 2016).

Galantamine

Galantamine is another AChE inhibitor commonly used to treat mild to moderate AD patients. The older patients have benefited in case of language and communication by taking galantamine. There are two mechanisms of action of galantamine. Firstly, it inhibits the acetylcholinesterase enzyme. Secondly, it binds with nicotinic ACh receptors that allosterically exert ligand actions (Y.Y. Szeto & J.G. Lewis, 2016). Galantamine has high bioavailability, less plasma protein binding, and good drug clearance from the body. In 2001, galantamine was approved by FDA for the treatment of mild to moderate AD. The doses of galantamine are 4, 8, 12, 16, and 24 mg with oral route. A quick-release solution should take two times daily and extended-release capsules in one daily. The initial dose of galantamine is 8mg per day which can be increased up to 16 mg per day after 4-8 weeks (Ph et al., 2010). The most efficacious dose is considered 16-24 mg per day. Galantamine also shows mild adverse effects which include gastrointestinal effects that can be decreased or controlled by dose reduction (Razay & Wilcock, 2008). A recent meta-analysis stated that this drug also improves daily life and the performance of daily activities of AD patients. Moreover, improve cognitive functions, fatigue and weakness in thinking and remembering (D. D. Li et al., 2019).

Rivastigmine

Rivastigmine is also an AChEIs that is used for symptomatic treatment of AD. It is available in both oral and transdermal formulations which inhibits both the AChE and butyrylcholinesterase (Nguyen et al., 2021). Rivastigmine was approved in 2000 by FDA to treat mild to moderate AD. It's also use for patients with mild to moderate Parkinson's dementia. The initial dose for rivastigmine is 1.5 mg in every 12 hours. The dose can be

increased to 6 mg in every 12 hours based on the tolerability. But there should be two weeks interval from the previous dose. In transdermal patches, the initial dose is 4.6 mg per day which can be increased to 13.3 mg per day after establishing enough tolerability (Pardo-Moreno et al., 2022). There is a benefit for transdermal patches which allows the release of drugs by 24 hours and also avoids GIT effects. Patient with memory loss and cognitive impairment faces difficulty to take medicine orally. Transdermal patches give advantages to these patients. The Gastrointestinal side effects (nausea, vomiting, diarrhea) are lower with transdermal patches. But skin reaction is seen with transdermal patches. Therefore, the transdermal form is preferred to the oral dosage of rivastigmine. On the other hand, an overdose of rivastigmine can cause chest pain, irregular breathing as well as increase or decrease heartbeat (Mimica & Presečki, 2009).

1.6.2 NMDA receptor antagonist

NMDAR antagonist is another class of drug that can be used to treat AD. Neurotransmitters carry all the signals of our body from cell to cell to process information and maintain balance. Glutamate is a type of neurotransmitter. It is attached to NMDA receptors when passed from one neuron to another which facilitates calcium ion influx (calcium ion enters into the cell). This step is important for memory function. Alzheimer`s disease patients have too much glutamate which binds with NMDA receptors and the cell gets more calcium. This can speed up the damage to them. By administering the NMDAR antagonist`s drug, it blocks the NMDA receptor and glutamate cannot bind with these receptors. But the signal flow remains normal between cells. NMDA glutamate receptor is responsible for synaptic plasticity and cellular process that includes memory function and learning. This receptor is found extensively in the central nervous system (Olivares et al., 2012). NMDR antagonists also use for many neurological disorders such as dementia, epilepsy, brain trauma, etc. Hallucinations may observe in some patients who take NMDAR antagonists.

Memantine

Memantine is an NMDAR antagonist which is used to treat moderate to severe AD. It blocks the toxic effect of overactive glutamate which can lead to neurological dysfunction, more specifically AD. Malfunction of glutamate medicated neurotransmission with NMDAR can lead to the progression of AD. It also shows the symptoms of AD including memory loss, and difficult to concentrate. US FDA approved this drug in 2003. 7, 14, 21, and 28 mg capsules, 10 mg tablets, and 2 mg/mL solution are available for memantine. So, 5mg per day should be administered in the first week, 5 mg twice a day should be administered in the second week and it can be increased to 15 mg in the third week (Pardo-Moreno et al., 2022). Some systematic reviews and meta-analyses show that memantine administration is favored as the first-line anti-dementia drug that is more effective to treat moderate to severe AD. The combination of memantine with AChE inhibitors such as donepezil gives further benefits to treat AD and its symptoms (Kishi et al., 2017). This combination would be the most effective treatment to improve cognition. Some adverse effects are seen with memantine administration including hypertension, headache, diarrhea, vomiting, abdominal pain, hallucination etc. The safety of the clinical dose of memantine is considered as well-established (Matsunaga et al., 2018).

1.7 Future Treatment Options

Currently, the treatment of AD patients is based on the symptomatic treatment. So, more potential drug therapy is required to change the progression of Alzheimer`s disease. As Alzheimer`s disease has two neuropathological hallmarks including neurofibrillary tangles and the deposition of extracellular plaques, disease-modifying agents will give a better result to treat AD. Many disease modifying drugs are on clinical trials. The most potential disease modifying agents targeting the two desired featured of AD pathology. So, the future therapies of AD are in two categories such as anti-amyloid therapy and anti-tau therapy. In last 30 years, the researcher focusing on targeting amyloid β. But some research failed to show clinical

benefits of some drugs in phase III clinical trials. In recent times, the tau pathology received more attention. Drugs those targeting the tau protein shows excellent result in the preclinical trails and early stage clinical trials to slow down the progression of AD (Congdon & Sigurdsson, 2018). The anti tau therapies mainly demonstrate to inhibit kinase or tau aggregation. It also involves stabilization of microtubules. But lack of efficacy or toxicity hinder these approaches of tau targeting therapy. The combination therapy is another recent approach to treat AD. Some research suggest that the combination therapy of anti-amyloid and anti-tau approaches can be more effective than monotherapy (Bittar et al., 2020). More research is required to understand the complex pathology of AD. Moreover, continuous investigation is required to find new target and biomarkers for developing a potential disease-modifying agent for AD.

1.7.1 Anti-amyloid drugs

Amyloid hypothesis states that deposition of amyloid plaques and accumulation of Aβ peptide are responsible the neurogenerative process of AD. So, elimination of amyloid plaques is the effective method to reduce the disease progression. The amyloid precursor protein (APP) is cleaved to produce Aβ peptide. α-secretase and γ-secretase enzyme are responsible to cleave APP. The accumulation of amyloid plaque outside the cell leads to form protofibrils, fibrils and eventually insoluble plaques. Thus, synapse is disrupted and neuronal death is occurred. The amino acids Aβ42 peptide is most prone to accumulate which has 42 amino acids residues. However, the reduction of Aβ peptide is mandatory to reduce the level of amyloid plaques. Researcher proposed three approaches to slow down the progression of AD. The increase of Aβ clearance, reduction of Aβ accumulation and decrease of Aβ production are considered as anti-amyloid therapy (Selkoe & Hardy, 2016). β-secretase ((BACE1) and γ-secretase enzymes activities have a crucial role in Aβ production. The rate limiting step of Aβ production is blocked by BACE1 inhibitors. A few numbers of BACE1 inhibitors are in phase III clinical

trials. Thus, the inhibition of these two enzymes declines the Aβ production. Elenbecestat, a BACE1 inhibitors exhibits the improvement of cognitive impairment but it has several side effects. Aβ aggregation can lead degradation of synapse and neuronal loss in AD. So, anti Aβ aggregation agents are used to prevent aggregation. This agent binds with Aβ peptide and prevent their accumulation and neurotoxicity. Scyllo-inositol and tramiprosate are anti-aggregation agents studied as a disease modifying agent to treat AD. A dose 250 mg of scyllo-inositol has shown acceptable safety profile. But further research is required to ensure the safety and efficacy of this agent (Rafii et al., 2018). Finally, the promotion of Aβ clearance help to slow the progression of AD. The administration of anti- Aβ antibodies is a promising therapy for AD treatment. Research is going on immunotherapy targeting Aβ includes active and passive immunization. In last two decades, these approaches are widely investigated (Plotkin & Cashman, 2020).

1.7.2 Anti-tau therapy

In last 25 years, researcher conduct research with ant-amyloid therapy, but adequate clinical efficacy is not established in recent clinical trials. So, they are focusing on anti-tau therapy in recent days. The tau protein plays an important role in the assembly of cytoskeletal microtubules. But abnormal hyperphosphorylation of tau may disrupt the function of microtubules. As a result, neuronal loss occurs in AD patients. Firstly, the prevention of abnormal tau hyperphosphorylation is necessary to treat AD patients. GSK- 3β plays a vital role in tau phosphorylation. So, the inhibition of GSK- 3β is considered as rational drug therapy for AD (Matsunaga et al., 2019). The preclinical studies of Tideglusib have completed and shows a positive result that decrease tau phosphorylation. But the research is discontinued due to the negative result in phase II clinical trials. The preclinical studies of Salsalate shows that it reduces tau pathology. In March, 2017, the phase I clinical trial have completed but the result has not published yet (Congdon & Sigurdsson, 2018). Methylthioninium chloride inhibits tau

aggregation in in-vitro approaches. Moreover, its shows efficacy to treat mild to moderate AD treatment in Phase I clinical trials. Further research is required to confirm the efficacy. Immunotherapy to increase tau clearance is becoming the focusing area of many researchers. Tau pathology is targeted by both active and passive immunization. As a result, abnormal tau is cleared from the body and decrease the AD symptoms. None of immunotherapies have reached phase III clinical trials yet. Many anti tau agents are in clinical trials. They are not approved yet. So, new targets are investigated and combination therapy brings with a great solution (Vaz & Silvestre, 2020).

1.8 Purpose of the study

The purpose of the study is to investigate and analyze potential risk of developing rhabdomyolysis based on gender variations among AD disease patients who takes donepezil as a medication for the treatment. The breakdown of muscle tissue and the release of muscle cell content into the bloodstream is termed as rhabdomyolysis. By analyzing data from FAERS database, one gender may be more prone to develop rhabdomyolysis than other. The findings from this study will help to provide rational treatment strategy. Moreover, it promotes medical decision making, patient monitoring as well as a better healthcare facility for the patients. This study is also influencing pharmacovigilance practice and create awareness among the patients and healthcare professional. Lastly, the outcome of this study will contribute in further research to ensure patient safety and care.

Chapter 2

Donepezil for Alzheimer's Diseases

2.1 Donepezil

Donepezil is an FDA approved drug for the symptomatic treatment of Alzheimer`s disease and dementia. Its favorable therapeutic profile makes it appropriate drug for the first line treatment of patients with mild to moderate AD. But no evidence suggest that donepezil can alter the disease progression of AD. It blocks acetylcholinesterase enzyme thus inhibiting the degradation of acetylcholine. As a result, the amount of Ach is increased in synaptic cleft, improving cognition, ability of thinking, memory. The oral bioavailability of this drug is approximately 100%. Transdermal delivery system of donepezil is available which include an advantage for the treatment of patients with memory issue. The plasma drug concentration of donepezil at steady state is proportional to dosage. Some studies show that, (S)-donepezil is metabolized slower than the (R)-donepezil (Brewster et al., 2019). FDA recommend the starting dose of donepezil is 5 mg and then gradual increase. Some adverse effects of donepezil exhibit due to some genetic factors and medication related factors. Drug-drug interaction is also noted when donepezil is administered with other drugs. The uses of donepezil can vary each individual’s patient. So, donepezil is only prescribed by the medical practitioners.

2.2 Pharmacodynamics of Donepezil

Donepezil is 1200 times more selective to acetylcholinesterase enzyme rather than butyrylcholinesterase (Sugimoto et al., 1992). It is a reversible AChE inhibitor and it is not related to other cholinesterase inhibitors. It has fewer disadvantages than other drugs that also overcome the side effects of physostigmine and tacrine. Some studies suggest that donepezil dose modification is not required for patients with hepatic or renal failure (Barner, 1998).

In AD patients, amyloid plaques and neurofibrillary tangles can be formed for deficiencies in the cholinergic system. So, the first target is to retain or increase the cholinergic activity. Donepezil increases the ACh in the synaptic cleft of the brain. Thus, improve cognition. In a study, maximum AChE enzyme inhibition was found after 1 week of donepezil administration. A 1-3 mg increase in daily dose has increased the pharmacodynamic effects of donepezil proportionally. There is a strong correlation between the pharmacodynamic effect and the plasma drug concentration of donepezil (Tiseo et al., 1998). The pharmacodynamics of donepezil is discussed further in below: -

2.2.1 Indication

Donepezil is most commonly used for the treatment of Alzheimer's disease. Its FDA-approved indications are mild to moderate dementia, and severe Alzheimer's disease. Evidence from some literature or research suggests the following indications: -

- Mild cognitive impairment
- Vascular dementia
- Lewy body dementia
- Tardive dyskinesia
- Down’s syndrome
- Autism
- Opioid-induced sedation
- Poststroke aphasia
- Migraine prevention
- Parkinson’s disease
- Schizophrenia

2.2.2 Mechanism of Action

Acetylcholine is a neurotransmitter that contributes to brain functions such as memory, cognitive functions, etc. But acetylcholinesterase (AChE) is an enzyme that hydrolysis or breakdown the acetylcholine (Ach) in choline and acetic acid. In AD patients, the Ach level should be increased in the synaptic cleft. Therefore, AChE needs to be inhibited. Donepezil is used to treat Alzheimer's disease. It is a selective, reversible acetylcholinesterase inhibitor that stops the breakdown of acetylcholine. It is called piperidine derivatives. As we know, acetylcholine is broken down by the enzyme acetylcholinesterase, inhibiting the enzyme will increase both the level and duration of acetylcholine (Colovic et al., 2013). Donepezil is called an indirect-acting agonist because it indirectly provides cholinergic action. It also delays the deposition of amyloid plaque which is responsible for Alzheimer's disease.

AD is a neuronal disorder in which misfolding of protein cause neurodegeneration that creates a loss of cholinergic fibers. Therefore, loss of memory or dementia is observed. So, if the cholinergic fibers are restored, loss of memory can be treated and eventually improve the symptoms of AD. To increase Ach levels, AChE inhibitors are used. This inhibitor can prevent the metabolism of Ach thus increasing the level of acetylcholine in the synaptic cleft. Choline is the precursor of acetylcholine. This choline is converted to ACh by choline acetyltransferase. The number of ACh molecules stored in the synaptic vesicle. When the neuro terminal is going to be depolarized, calcium is entered into the membrane resulting the exocytosis. Fusion of synaptic vesicles occurs and release of ACh in the synaptic cleft. Then, the ACh can act on the post synaptic cleft which is equipped with the muscarinic receptor. The M1 receptor is responsible to increase the memory.

Once ACh binds with a muscarinic receptor (GPCR), they stimulate phospholipase C. This converts phosphatidylinositol bisphosphate (PIP2) into inositol trisphosphate (IP3) and Diacylglycerol (DAG). These two mediators are important to increase the calcium level in the

postsynaptic membrane. Increased calcium levels will increase the cellular effect which results in the increase of memory function within the cortex. But the action of ACh is very short. Because, after releasing, it immediately degrades into choline and acetate by acetylcholinesterase enzyme. Donepezil inhibits these AChE, thereby ACh is increased in synaptic cleft which results in more ACh binding with muscarinic receptors. As a result, memory is increased.

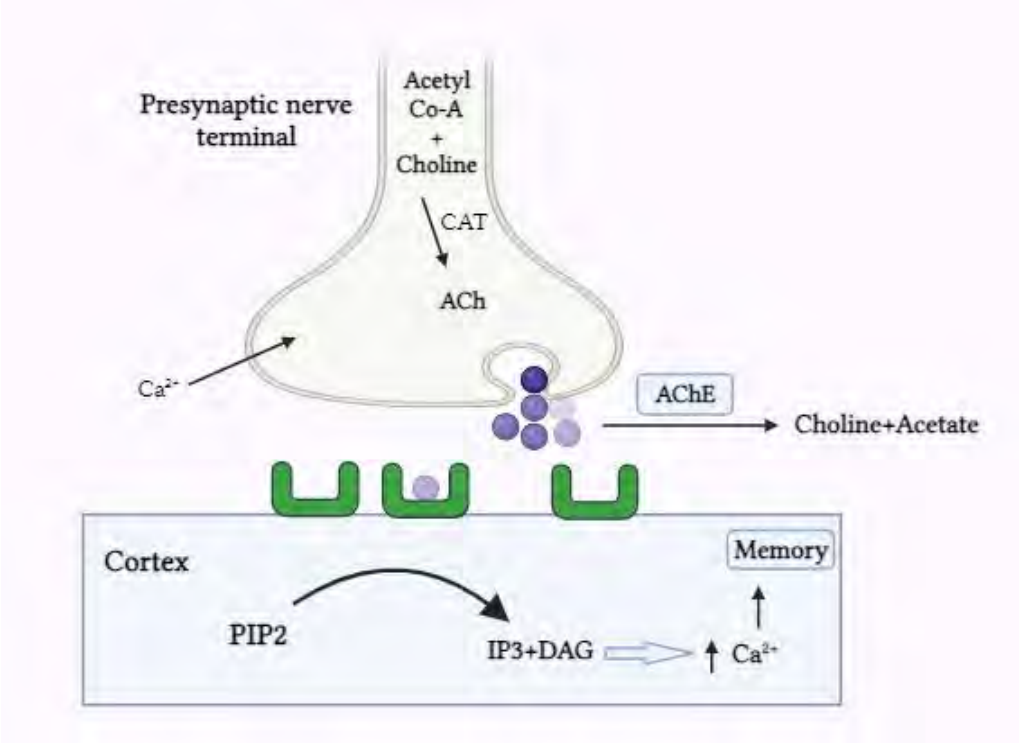

Figure 3: Donepezil Mechanism of action (modified from Moghul & Wilkinson, 2001)

2.2.3 Dosage form and Dosage regimen

Donepezil is available in the form of film coated orally disintegrating tablets for oral administration. (Brewster et al., 2019). The available dosage form and strength is as follows:

- Available routes: Oral
- Available dosage form: Tablets
- Dosage strength: 5, 10, and 23 mg tablets in the package of 30-90 tablets.
- Initial dose: 5 mg tablets once a day at evening.

In Bangladesh, a unit of 10 tablets (blister package) is also available. Some clinical trials suggests that, dosage of 5−10 mg/day is effective as a maintenance dose of mild to moderate AD. On the other hand, 10−23 mg/day is effective for treating moderate to severe AD as a maintenance dose. FDA recommends the dosing of donepezil, 5mg/day as initial dose for 4-6 weeks. Before taking 23mg/day, the dose can be increased 10 mg/day for at least 3 months. The more dosage strength can show more adverse events. Previously, donepezil is recommended to take at evening. Some studies suggest that, taking donepezil immediately after the breakfast and lower dose can be beneficial for the patients who are sensitive to AChEIs (Doty & Heilman, 2013). Overall, the prescriber recommendation based on patient conditions and clinical judgement should be applicable.

2.2.4 Dosage consideration for specific population

A scientific study suggest that donepezil 5 mg and 10 mg was not well tolerated for children (Cubo et al., 2008). Children`s body and brain are in developing stage and react differently with drug or medicines compared to adults. So, donepezil hydrochloride is not recommended or give to the children who are under 18 years old. No indications are approved for pediatric patients. Patients who suffer from liver disease such as liver cirrhosis do not require donepezil dosage adjustment. Donepezil therapy rarely cause clinically apparent liver injury (Erbayraktar et al., 2017). Though donepezil is considered as the safe and effective drug therapy for AD, its uses should be customized for each individual patient. Moreover, the hepatic function should be monitored closely as an extra caution. Patients who have kidney disease or moderate-or-severe renal impaired patient do not required donepezil dosage adjustment (Nagy et al., 2004). The initial dose of this drug is 2.5 mg per day is recommended for patients with hemodialysis. Based on the patient`s clinical condition, the dose can be increased to 5 mg per day (Yiannopoulou et al., 2019). There is not sufficient data for the uses of donepezil in pregnant women and its potential risks. So, the safety of donepezil in pregnant women is under

investigation. Donepezil is also classified Category drug in pregnancy. So, this drug is not recommended during pregnancy. Likewise, donepezil is not recommended for breast feeding mother. In breast milk, the excretion of donepezil is unknown. The elimination half-life of donepezil is approximately 100 hours that means prolonged in older patients. The steady state volume of distribution of donepezil is increased that's why it takes time to eliminate the drug. However, the steady state clearance is similar for all age group patients and dosage adjustment of donepezil is not required for the older patients (Benjamin & Burns, 2007).

2.2.5 Adverse effects and Side effects

As drug is a chemical substance and metabolized by live, eliminated by kidney, can do harm in kidney and liver. Some drug can cause hepatotoxicity and nephrotoxicity. They also show adverse effect commonly known as side effects which are undesirable drug effect. Every drug has some common side effects such as nausea, vomiting, stomach upset, diarrhea etc. Clinically, donepezil gives adverse effects on GI and nervous system. Most common adverse effects observed for donepezil including: -

- loss of appetite
- insomnia
- diarrhea
- headache
- dizziness
- nausea
- lower mean heart rate
- bradycardia
- muscle fatigue
- rashes

- frequent urination
- vivid dreams

Symptoms of donepezil will diminish after several days and also reversible after creasing the treatment (Brewster et al., 2019). All patient will not have the same side effects, it can vary from person to person. Some patients are more totaled with donepezil from others. So, they show fewer side effects. Serious side effects also possible with donepezil. Less than 1 in every 100 people show serious side effects after taking donepezil. Some serious side effects are: -

- Pain in muscle or muscle weakness which was not observed before. These symptoms can observe with kidney and muscle problems, don't confused with it, consult doctors for proper diagnosis.
- Severe heartburn, indigestion or vomiting can be seen as a side effect of donepezil.
- The skin can turn into yellow, but it is less seen in black or brown skin people.
- Increasing the temperature of the body with stiff muscles.
- Trouble in breathing and allergic problems may also occur with donepezil.

Observing this symptoms doesn`t means the adverse or side effects of donepezil. It can be associated with other disease. So, after observing serious side effects, patients need to consult with the physician to confirm about the side effects and get proper advice. On the other hand, when donepezil is taken with psychotropic drugs as a combination, extrapyramidal side effects can occur in the patients (H. C. Li et al., 2020).

2.2.6 Drug-Drug interaction

Several drug-drug interactions occur with donepezil. When donepezil is prescribed with risperidone, extrapyramidal effects have been reported due to the imbalance of the cholinergic and dopaminergic systems. But the concurrent administration of donepezil and risperidone is also considered as safe (Reyes et al., 2004). Synergistic effects have been reported when

donepezil is combined with neostigmine and physostigmine. Concurrent administration of donepezil with tiapride exhibits parkinsonism. Moreover, it increases the risk of bradycardia when donepezil concurrently administered with propranolol, carvedilol, metoprolol and atenolol (Kho et al., 2021). During anesthesia, prolonged neuromuscular blockade can occur by coadministration of donepezil and neostigmine. Metabolite enzyme CYP2D6 and CYP3A4 inducers can reduce donepezil levels in the body. Because CYP2D6 and CYP3A4 inducers such as phenobarbital, rifampin can increase the elimination rate of donepezil from the body (Levy & Collins, 2007). On the other hand, inhibitors of CYP3A4 and CYP2D6 can increase the donepezil level in the body. Ketoconazole and quinidine are the inhibitors of this metabolite enzyme and inhibits the metabolism of donepezil thus increasing donepezil plasma drug concentration (Pasqualetti et al., 2015). Paroxetine and other SSRIs inhibit CYP2D6 enzyme that increases donepezil plasma drug concentration levels and increase the risk of adverse effect. So, donepezil should not prescribe with Paroxetine and other SSRIs (Brewster et al., 2019). This drug-drug interaction is noted in some patients, further study is ongoing to find out more drug-drug interactions of donepezil. So, donepezil is only recommended or prescribed by professional physicians.

2.3 Pharmacokinetics of Donepezil

Pharmacokinetics means what the body does to the drug including absorption, distribution, metabolism, and excretion. Donepezil is administered orally and absorbed from the intestine, eventually going to the blood circulation. It is metabolized by hepatic isoenzymes and excreted by the kidney. Most pharmacokinetics parameter of donepezil is not significantly different between a healthy person and a patient with liver and renal impairment. The pharmacokinetic properties of donepezil are discussion in below:

2.3.1 Absorption

Donepezil is available as a tablet and it is taken by oral route of drug administration. After taking the drug and swallowed, it enters the Gi tract/ stomach. Then it disintegrates which means the breakdown of the drug. After disintegration, the drug is absorbed from the administration side and enters the bloodstream. The Oral bioavailability of donepezil is approximately 100%, indicating all drug reaches systemic circulation. After 3-4 hours of oral administration of donepezil, the peak plasma concentration is obtained. Donepezil shows a linear pharmacokinetics relationship within its dose. Food doesn`t affect the bioavailability or rate and extent of the absorption of donepezil (Barner, 1998).

2.3.2 Distribution

After a single dose, 93% of donepezil is bound with serum protein. Furthermore, Donepezil binds 96% plasma protein after multiple doses, mostly with albumin (75%). It also binds with alpha-glycoprotein (21%). So, 4% of the drug is unbound in the bloodstream. For a 5 mg dose, the volume of distribution (Vd) is 11.8 ± 1.7 L/kg, and for a 10 mg dose, Vd is 11.6 ± 1.91 L/kg. After 15 days of administration of multiple doses of donepezil, a steady state is achieved. After 24 hours of donepezil administration, the drug concentration in cerebrospinal fluids is higher compared to 12 hours after administration (Valis et al., 2017).

2.3.3 Metabolism

As we know, the maximum drug is metabolized by the liver and converted into inactive metabolites. Donepezil is largely metabolized by the liver with hepatic enzymes including CYP2D6 and CYP3A4. It produces four metabolites including two active and several minor metabolites. Donepezil has approximately 70 hours of elimination half-life.

2.3.4 Excretion

Donepezil and its metabolite substance are eliminated by kidney/renal excretion. 79% of the total administered donepezil is found in urine. 21% of donepezil is excreted in feces. The unchanged drug is also eliminated by the kidney. For patients with hepatic and renal complications, a customized dose is required with prescriber advice.

Chapter 3

Methodology

3.1 Data Source

The pharmacovigilance statistical data analysis was conducted based on FDA Adverse Event Reporting System Database (FAERS). It is the most remarkable database to support post marketing surveillance program which is conducted by US Food and Drug Administration. This database was opened in 2004. The healthcare professionals, patients or the consumers reports the adverse events voluntarily related to medications, vaccinations, biologics, medical device. The CDER and CBER monitor the safety of FDA approval drug by using this database (Ali et al., 2015). FAERS include the real time data of suspected adverse drug reactions (ADRs) reported by patients, doctors, companies or other healthcare professionals via Medical Dictionary for Regulatory Activities (MedDRA) keywords. This database have over 20 million reports and consist of demographic, findings, outcomes, reporter type (patients, doctors etc.) and suspected drugs information (Kvist et al., 2021). FAERS database creates awareness about adverse drug events among people for promotion safe, effective and rational drug therapy. As it is a voluntary work to submit adverse drug reaction reports, people may submit incomplete information. When collecting data, sometime duplicate data can include. So, minimizing the duplication data was considered during the analysis. According to MedDRA terminology, all the reported adverse events are recorded. Now, there are 27,096,432 reports in total in FAERS database. For this study, the data search was performed on July, 2023 and gathering the data from January 2016 to June 2023 for statistical analysis. FDA approved drug for symptomatic treatment of AD such donepezil, memantine, rivastigmine, galantamine associated adverse events were searched. More specifically, donepezil associated adverse events are taken considered. Moreover, MedDRA terminology is chosen to define the adverse events.

3.2 Inclusion and Exclusion Criteria

The adverse events associated with donepezil was searched. Cases and non-cases data can find out by using FAERS Public Dashboard. The data was gathered from January 2016 to June 2023. All side effects associated with the medication known by generic name donepezil was present in the database. Data on adverse event “Rhabdomyolysis” was collected and documented according to MedDRA terminology. Our drug donepezil was the sole medicine suspected for reported adverse events. CI 95% and reporting odds ratio was performed to finds or detect the signal that helps to interpret the association between donepezil and the adverse event “Rhabdomyolysis”. We exclude the duplicate report of age, sex, event date by using the case number and cross-referencing. Similar side effects of non-cases reports are not included in this study.

3.3 Statistical Analysis

The Data extraction from FAERS database and statistical analysis of this study was carried out on July,2023. The interpretation of the relation or association between our desired drug (donepezil) and adverse events “Rhabdomyolysis” was measured. We determined the odds ratio (OR) along with 95% Confidence Interval (CI) to performed a disproportionality analysis. For detecting medication safety signal’s, ROR is used as it is one of the most widely used techniques for calculating the disproportionality measures. The ROR was measured by using 2 by 2 contingency table that employed on R 4.2.1 statistical tool. The lower bound of confidence interval 95% is used as signal identifying parameter in pharmacovigilance or drug safety research. If the lower bound of 95% confidence interval (CI) is less than 1or equal to 1, then the signal is not detected. Moreover, the adverse events are not associated with the drug. On the other hand, 95% confidence interval cutoff value is greater than 1 represents that the signal is detected or accepted. That means the adverse events are associated with the drug. A higher precision of the ROR can achieve from a small CI, oppositely, a large CI value represents a

low level of precision. Thus 95% confidence interval determines the precision of the ROR (Sedgwick & Marston, 2010).

The reporting odds ratio is widely used to measure the relationship between two dichotomous variables. In association with 95% confidence interval, the reporting odds ratio evaluates the reports or data and find out the relation between the drug (donepezil) and its adverse effect (Rhabdomyolysis). Memantine, Rivastigmine, Galantamine data analysis were also considered. This statistical analysis gives an interpretation or comparison with other drugs of same class regarding the side effects. The ROR with 95% confidence interval can identify the same side effects of others drug. Thus, appropriate medications can advise for rational treatment strategies. For graphical representation, a forest plot was drowned for both class comparator and whole database. The forest plot visualized the association of all studies and heterogenicity in one figure. All statistical analysis was done very carefully to conclude with an accurate result.

Chapter 4

Result & Discussions

4.1 Result

Table 1: Whole database as a comparator(male)

WHOLE DATABASE AS A COMPARATOR (Male)		
2016-2023		
	Cases	ROR (CI)
Donepezil	11	10.97 (6.04 - 19.92)
Other drugs	8780	

Table 2: Class as a comparator(male)

CLASS AS A COMPARATOR (Male)		
2016-2023		
	Cases	ROR (CI)
Donepezil	11	4.93 (1.90 - 12.76)
Other drugs	7	

Table 3: Whole database as a comparator (Female)

WHOLE DATABASE AS A COMPARATOR (Female)		
2016-2023		
	Cases	ROR (CI)
Donepezil	4	5.71 (2.14 - 15.26)
Other drugs	5463	

Table 4: Class as a comparator (Female)

CLASS AS A COMPARATOR (Female)		
2016-2023		
	Cases	ROR (CI)
Donepezil	4	1.82 (0.51 - 6.46)
Other drugs	6	

Using R statistical software, the collected data from January 2016 to July 2023 was analyzed and calculated the odds ratio (ROR) along with 95% confidence interval. Adverse events report of our interest is called cases and others drug is called non-cases. We observed 11 cases of Rhabdomyolysis associated with donepezil in male patients while consider the whole database as a comparator (Table 1). On the other hand, 8780 cases of Rhabdomyolysis associated with other drugs (memantine, rivastigmine, galantamine) in case of male. The ROR along with 95% CI vale is 10.97 (6.04 - 19.92). When considering class (AChEIs) as a comparator (Table 2) in case of male, 11 cases of Rhabdomyolysis associated with donepezil whereas 7 cases associated with other drugs. The ROR (95%CI) value is 4.93 (1.90 - 12.76). Furthermore, considering the whole database as a comparator in case of female (Table 3), 4 cases of Rhabdomyolysis due to donepezil and 5467 cases for other drugs (memantine, rivastigmine, galantamine). The ROR (95% CI) have found to be 5.71 (2.14 - 15.26). In addition, 4 cases of Rhabdomyolysis due to donepezil whereas 6 cases for other drugs while considering class (AChEIs) as a comparator in case of female patients (Table 4). 1.82 (0.51 - 6.46) is the ROR value in this situation. The forest plot gives a clear representation of our result.

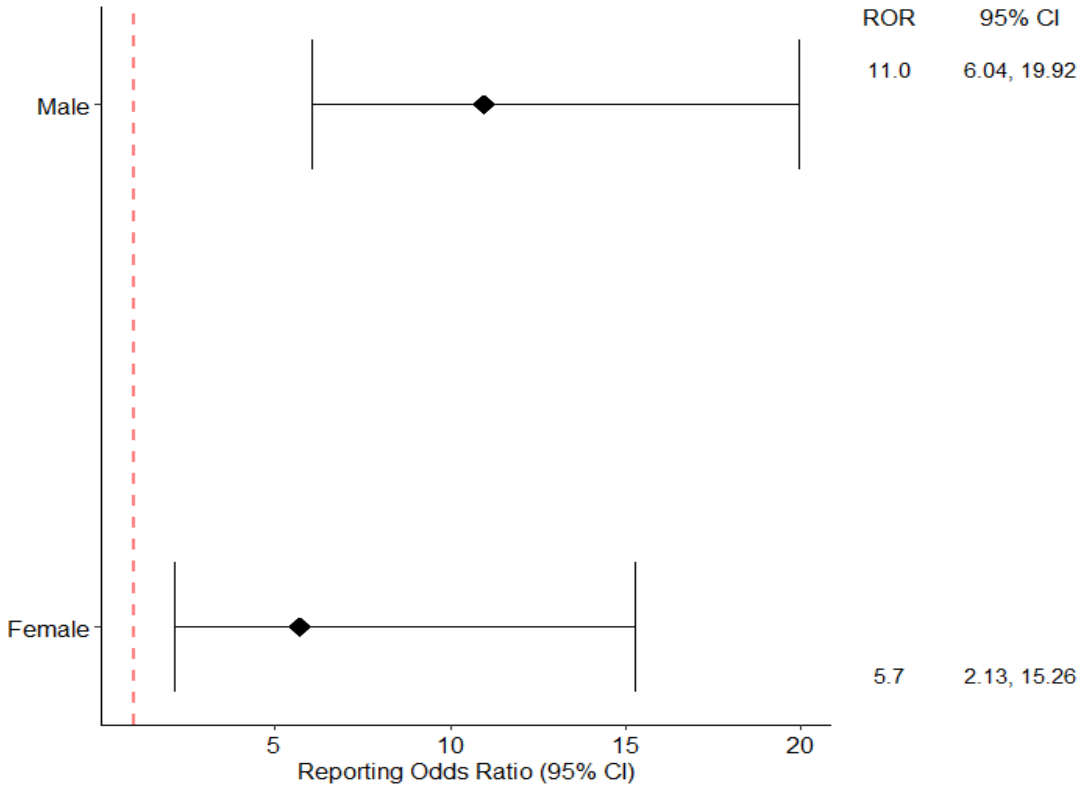

Figure 4: Forest Plot (whole database)

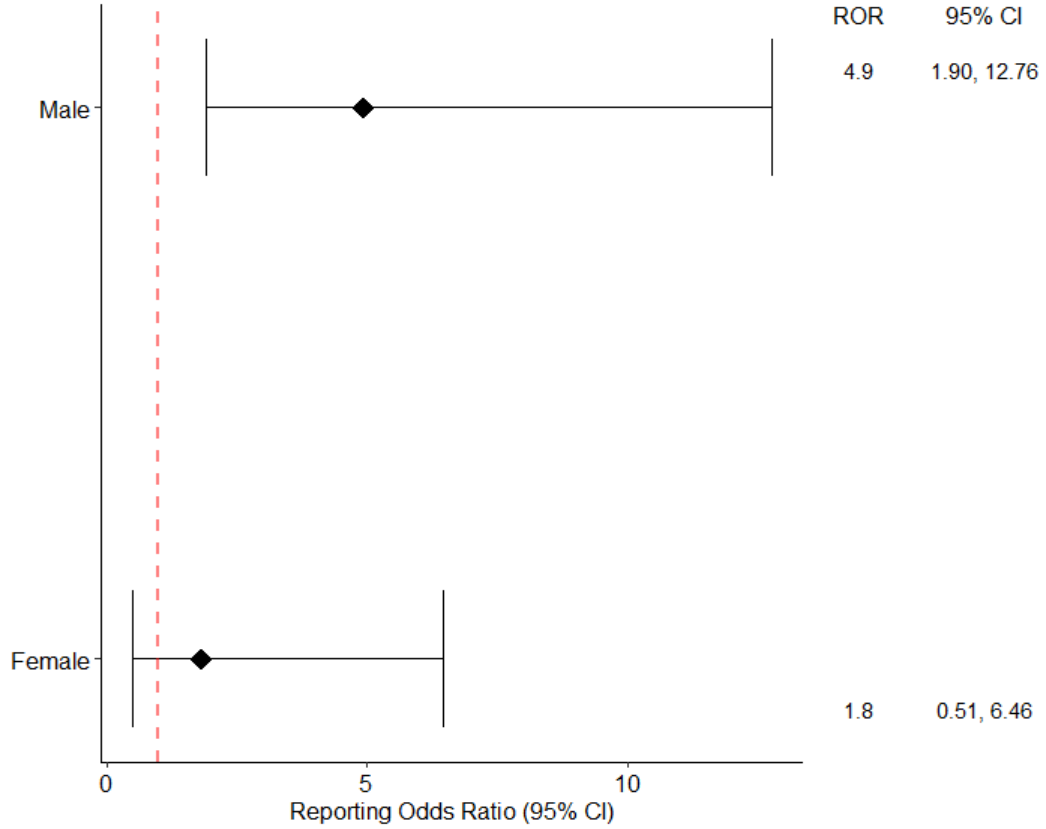

Figure 5:Forest Plot (class comparator)

4.2 Discussion

The R 4.2.1 version tool is used to calculate the ROR along with 95% CI with the arranged data from FAERS database (January 2016-June2023). The analysis has performed in July 2023. According to the result from FAERS database reporting odds ratio, signal is detected when the whole database considers as comparator in case of male. It means rhabdomyolysis adverse events is associated with donepezil in male case when considered the whole database as a comparator. Considering AChEIs class as a comparator, lower bound of 95% CI is 1.90 which indicates signal is present. So, rhabdomyolysis associated with donepezil for both considerations. On the other hand, lower bound of 95% CI value is 2.14 when considering the whole database as comparator for female cases. The lower bound of 95% CI is greater than 1 indicates signal is present. But lower bound of 95% CI value is lower than 1 when considering AChEIs class as a comparator. This has not given any signal for female cases. To sum up, Donepezil shows greater cases of rhabdomyolysis in male cases.

The reason behind more rhabdomyolysis cases in male patients with donepezil compared to female is may be due to the increase of creatine kinase (CK) level after administering donepezil. CK is found more in male compared to female (Cook et al., n.d.). A study suggest that donepezil increase creatine kinase level in the blood (Adlimoghaddam et al., 2018). CK is also called creatine phosphokinase (CPK) which is found in various tissue throughout the body including muscle tissue. The main role of creatine kinase in the muscle is to add a phosphate group to creatine which ultimately helps muscles to produce energy. So, CK needs to be found in muscle. Donepezil increases the levels of CK in the bloodstream. It leaks out creatine kinase from the muscle into the bloodstream. So, increase creatine kinase in blood is associated with rhabdomyolysis. On the other hand, higher CK levels can cause severe electrolyte abnormalities and also acid base disturbance (Luckoor et al., 2017). This can result muscle

weakness, spasms and crams (Balance & Pressure, 2017). So, we can state that donepezil is more associated with rhabdomyolysis in male compare to female patients.

Another reason for more rhabdomyolysis cases in male patients with donepezil can be due to the hormone differences in males and females. When it comes to males, testosterone is a widely researched androgen that plays a role in muscle mass distribution. The effect of testosterone is associated with an increased levels of muscle mass in males as compared to females (Haizlip et al., 2015). On average, baseline muscle mass in men is 36% greater than in women (Janssen et al., 2000). Moreover, women have less upper body muscle mass than man. Hence due to the greater muscle mass and women bas greater fat mass, rhabdomyolysis can be commonly observed more in men who are on treatment with Donepezil drug. On the other hand, testosterone can decrease the metabolism of donepezil when combined with it. Donepezil is mainly metabolized by CYP2D6 enzyme in the liver (Chamnanphon et al., 2020). On the other hand, CYP2D6 catalytic function can be decreased by testosterone (J. Li et al., 2015). Less metabolism of donepezil results higher concentration of donepezil in plasma and eventually increased activity of drug leading to increased side effect such as muscle cramps. So, male patients can experience this side effects more than female due to having testosterone hormone.

Further reason is may be due to more physical activities, exercise and lifestyle. A study showed female participants are in significantly less minutes of vigorous physical activities compared to male (McCarthy & Warne, 2022). Donepezil is an acetylcholinesterase inhibitor that inhibits the breakdown of ACh. Thus, ACh is increased in the synaptic cleft. As we know acetylcholine plays a major role in voluntary muscle movement in our body (Jones, 2009). It also binds to the receptors on muscle, allowing movement and physical activities. When there is more ACh, the body will be more physically active. Physical activities are associated with muscle movement. In addition, a study stated that males are more physically active than females (Hands & Parker, 2016). Donepezil can improve the daily activities of AD patients (Meguro et

al., 2014). As a result, when male takes donepezil, they are more physically active compared to female. Sometimes, extensive movement of muscle can cause injury. Eventually, rhabdomyolysis occurs. So, male patients can be more prone to develop rhabdomyolysis compared to females when donepezil is administered. On the other hand, according to CDC, males are more habituated to take smoke and alcohol than females. Consumption of alcohol makes the symptoms of dementia worsen. So, long-term therapy with donepezil can be required. Alcohol consumption also leads the muscle weakness and atrophy (Steiner et al., 2015). So, male habited with alcohol drinking are more associated with rhabdomyolysis when taking donepezil drug.

Chapter 5

Conclusion

This study shows pharmacovigilance investigation of rhabdomyolysis associated with donepezil between male and female patients. Male have more rhabdomyolysis cases compared to female when donepezil is administered. But we do not sum up with an exact conclusion regarding this result due to lack of enough information. We found fewer cases and less information in FDA Adverse Event Reporting System (FAERS) database. We have found 11 cases of male and 4 cases of female associated with rhabdomyolysis. Therefore, the findings of this study can be arguable. So, further investigation and longer time period is required to find out the exact reason and to reach a clear conclusion. Moreover, future studies can be performed on that topic to get more clear view of donepezil adverse effect with gender variations.

References

Adlimoghaddam, A., Neuendorff, M., Roy, B., & Albensi, B. C. (2018). A review of clinical treatment considerations of donepezil in severe Alzheimer's disease. *CNS Neuroscience and Therapeutics*, *24*(10), 876–888. https://doi.org/10.1111/cns.13035

Aisen, P. S., Cummings, J., Jack, C. R., Morris, J. C., Sperling, R., Frölich, L., Jones, R. W., Dowsett, S. A., Matthews, B. R., Raskin, J., Scheltens, P., & Dubois, B. (2017). On the path to 2025: Understanding the Alzheimer's disease continuum. *Alzheimer's Research and Therapy*, *9*(1), 1–10. https://doi.org/10.1186/s13195-017-0283-5

Ali, T. B., Schleret, T. R., Reilly, B. M., Chen, W. Y., & Abagyan, R. (2015). Adverse effects of cholinesterase inhibitors in dementia, according to the pharmacovigilance databases of the United-States and Canada. *PLoS ONE*, *10*(12), 1–10. https://doi.org/10.1371/journal.pone.0144337

Balance, A., & Pressure, O. (2017). Disturbances of Free Water, Electrolytes, Acid-Base Balance, and Oncotic Pressure. *Veterinary Medicine*, 113–152. https://doi.org/10.1016/b978-0-7020-5246-0.00005-x

Barner. (1998). Donepezil for Alzheimer disease [Alzheimer's]. *The Annals of Pharmacotherapy*, *32*(4), 70.

Bature, F., Guinn, B. A., Pang, D., & Pappas, Y. (2017). Signs and symptoms preceding the diagnosis of Alzheimer's disease: A systematic scoping review of literature from 1937 to 2016. *BMJ Open*, *7*(8). https://doi.org/10.1136/bmjopen-2016-015746

Benjamin, B., & Burns, A. (2007). Donepezil for Alzheimer's disease. *Expert Review of Neurotherapeutics*, *7*(10), 1243–1249. https://doi.org/10.1586/14737175.7.10.1243

Bittar, A., Bhatt, N., & Kayed, R. (2020). Advances and considerations in AD tau-targeted

immunotherapy. *Neurobiology of Disease*, *134*(July 2019), 104707. https://doi.org/10.1016/j.nbd.2019.104707

Breijyeh, Z., & Karaman, R. (2020). *Comprehensive Review on Alzheimer ' s Disease :*

Breijyeh, Z., Karaman, R., Muñoz-Torrero, D., & Dembinski, R. (n.d.). *molecules Comprehensive Review on Alzheimer's Disease: Causes and Treatment*. https://doi.org/10.3390/molecules25245789

Brewster, J. T., Dell'Acqua, S., Thach, D. Q., & Sessler, J. L. (2019). Classics in Chemical Neuroscience: Donepezil. *ACS Chemical Neuroscience*, *10*(1), 155–167. https://doi.org/10.1021/acschemneuro.8b00517

Budd Haeberlein, S., Aisen, P. S., Barkhof, F., Chalkias, S., Chen, T., Cohen, S., Dent, G., Hansson, O., Harrison, K., von Hehn, C., Iwatsubo, T., Mallinckrodt, C., Mummery, C. J., Muralidharan, K. K., Nestorov, I., Nisenbaum, L., Rajagovindan, R., Skordos, L., Tian, Y., … Sandrock, A. (2022). Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. *Journal of Prevention of Alzheimer's Disease*, *9*(2), 197–210. https://doi.org/10.14283/jpad.2022.30

Castellani, R. J., Peclovits, A., & Perry, G. (2014). Neuropathology of Alzheimer's Disease. In *Pathobiology of Human Disease: A Dynamic Encyclopedia of Disease Mechanisms*. Elsevier Inc. https://doi.org/10.1016/B978-0-12-386456-7.04604-9

Chamnanphon, M., Wainipitapong, S., Wiwattarangkul, T., Chuchuen, P., Nissaipan, K., Phaisal, W., Tangwongchai, S., Sukasem, C., Wittayalertpanya, S., Gaedigk, A., Aniwattanapong, D., & Chariyavilaskul, P. (2020). Cyp2d6 predicts plasma donepezil concentrations in a cohort of thai patients with mild to moderate dementia. *Pharmacogenomics and Personalized Medicine*, *13*, 543–551. https://doi.org/10.2147/PGPM.S276230

Chen, G. F., Xu, T. H., Yan, Y., Zhou, Y. R., Jiang, Y., Melcher, K., & Xu, H. E. (2017). Amyloid beta: Structure, biology and structure-based therapeutic development. *Acta Pharmacologica Sinica*, *38*(9), 1205–1235. https://doi.org/10.1038/aps.2017.28

Colovic, M. B., Krstic, D. Z., Lazarevic-Pasti, T. D., Bondzic, A. M., & Vasic, V. M. (2013). Acetylcholinesterase Inhibitors: Pharmacology and Toxicology. *Current Neuropharmacology*, *11*(3), 315–335. https://doi.org/10.2174/1570159x11311030006

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

Cook, J. C., Wong, E., & Haywood, L. J. (n.d.). *ORIGINAL COMMUNICATIONS CREATINE KINASE : RACE GENDER DIFFERENCES IN PATIENTS HOSPITALIZED FOR SUSPECTED*. 249–254.

Cubo, E., Fernndez Jaén, A., Moreno, C., Anaya, B., Gonzlez, M., & Kompoliti, K. (2008). Donepezil use in children and adolescents with tics and attention-deficit/hyperactivity disorder: An 18-week, single-center, dose-escalating, prospective, open-label study. *Clinical Therapeutics*, *30*(1), 182–189. https://doi.org/10.1016/j.clinthera.2008.01.010

Cummings, J. L., Tong, G., & Ballard, C. (2019). Treatment Combinations for Alzheimer's Disease: Current and Future Pharmacotherapy Options. *Journal of Alzheimer's Disease*, *67*(3), 779–794. https://doi.org/10.3233/JAD-180766

Davis, K. L. (2000). *Alzheimer ' s Disease*.

Doty, L., & Heilman, K. M. (2013). Recommendations for the safe administration of donepezil. *Neurology: Clinical Practice*, *3*(6), 458. https://doi.org/10.1212/01.CPJ.0000440993.45670.4A

Eratne, D., Loi, S. M., Farrand, S., Kelso, W., Velakoulis, D., & Looi, J. C. L. (2018).

Alzheimer's disease: clinical update on epidemiology, pathophysiology and diagnosis. *Australasian Psychiatry*, *26*(4), 347–357. https://doi.org/10.1177/1039856218762308

Erbayraktar, Z., Evlice, A., Yener, G., & Ulusu, N. N. (2017). Effects of donepezil on liver and kidney functions for the treatment of Alzheimer's disease. *Journal of Integrative Neuroscience*, *16*(3), 335–346. https://doi.org/10.3233/JIN-170020

Forchetti, C. M. (2005). Treating patients with moderate to severe Alzheimer's Disease: Implications of recent pharmacologic studies. *Primary Care Companion to the Journal of Clinical Psychiatry*, *7*(4), 155–161. https://doi.org/10.4088/pcc.v07n0403

Haizlip, K. M., Harrison, B. C., & Leinwand, L. A. (2015). Sex-based differences in skeletal muscle kinetics and fiber-type composition. *Physiology*, *30*(1), 30–39. https://doi.org/10.1152/physiol.00024.2014

Hands, B., & Parker, H. (2016). Male and Female Differences in Health Benefits Derived from Physical Activity: Implications for Exercise Prescription. *Journal of Womens Health, Issues and Care*, *5*(4). https://doi.org/10.4172/2325-9795.1000238

Janssen, I., Heymsfield, S. B., Wang, Z. M., & Ross, R. (2000). Skeletal muscle mass and distribution in 468 men and women aged 18-88 yr. *Journal of Applied Physiology*, *89*(1), 81–88. https://doi.org/10.1152/jappl.2000.89.1.81

Jellinger, K. A. (2006). Alzheimer's disease. *Neurobiology of Disease*, 69–82. https://doi.org/10.1016/B978-012088592-3/50008-6

Jia, J., Wei, C., Jia, L., Tang, Y., Liang, J., Zhou, A., Li, F., Shi, L., & Doody, R. S. (2017). Efficacy and Safety of Donepezil in Chinese Patients with Severe Alzheimer's Disease: A Randomized Controlled Trial. *Journal of Alzheimer's Disease*, *56*(4), 1495–1504. https://doi.org/10.3233/JAD-161117

Jones, R. (2009). An acetylcholine receptor keeps muscles in balance. *PLoS Biology*, *7*(12), 1–2. https://doi.org/10.1371/journal.pbio.1000268

Kho, J., Ioannou, A., Mandal, A. K. J., Cox, A., Nasim, A., Metaxa, S., & Missouris, C. G. (2021). Long term use of donepezil and QTc prolongation. *Clinical Toxicology*, *59*(3), 208–214. https://doi.org/10.1080/15563650.2020.1788054

Kishi, T., Matsunaga, S., Oya, K., Nomura, I., Ikuta, T., & Iwata, N. (2017). Memantine for Alzheimer's Disease: An Updated Systematic Review and Meta-analysis. *Journal of Alzheimer's Disease*, *60*(2), 401–425. https://doi.org/10.3233/JAD-170424

Kvist, A. V., Faruque, J., Vallejo-Yagüe, 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). *Journal of Clinical Medicine*, *10*(8), 1–14. https://doi.org/10.3390/jcm10081660

Levy, R. H., & Collins, C. (2007). Risk and Predictability of Drug Interactions in the Elderly. *International Review of Neurobiology*, *81*(06), 235–251. https://doi.org/10.1016/S0074-7742(06)81015-9

Li, D. D., Zhang, Y. H., Zhang, W., & Zhao, P. (2019). Meta-analysis of randomized controlled trials on the efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease. *Frontiers in Neuroscience*, *13*(MAY). https://doi.org/10.3389/fnins.2019.00472

Li, H. C., Luo, K. X., Wang, J. S., & Wang, Q. X. (2020). Extrapyramidal side effect of donepezil hydrochloride in an elderly patient: A case report. *Medicine*, *99*(11), e19443. https://doi.org/10.1097/MD.0000000000019443

Li, J., Xie, M., Wang, X., Ouyang, X., Wan, Y., Dong, G., Yang, Z., Yang, J., & Yue, J. (2015).

Sex hormones regulate cerebral drug metabolism via brain miRNAs: Down-regulation of brain CYP2D by androgens reduces the analgesic effects of tramadol. *British Journal of Pharmacology*, *172*(19), 4619–4634. https://doi.org/10.1111/bph.13206

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

Luckoor, P., Salehi, M., & Kunadu, A. (2017). Exceptionally high creatine kinase (CK) levels in multicausal and complicated rhabdomyolysis: A case report. *American Journal of Case Reports*, *18*, 746–749. https://doi.org/10.12659/AJCR.905089

Matsunaga, S., Fujishiro, H., & Takechi, H. (2019). Efficacy and safety of glycogen synthase kinase 3 inhibitors for Alzheimer's disease: A systematic review and meta-analysis. *Journal of Alzheimer's Disease*, *69*(4), 1031–1039. https://doi.org/10.3233/JAD-190256

Matsunaga, S., Kishi, T., Nomura, I., Sakuma, K., Okuya, M., Ikuta, T., & Iwata, N. (2018). The efficacy and safety of memantine for the treatment of Alzheimer's disease. *Expert Opinion on Drug Safety*, *17*(10), 1053–1061. https://doi.org/10.1080/14740338.2018.1524870

McCarthy, C., & Warne, J. P. (2022). Gender differences in physical activity status and knowledge of Irish University staff and students. *Sport Sciences for Health*, *18*(4), 1283–1291. https://doi.org/10.1007/s11332-022-00898-0

Medeiros, R., Baglietto-Vargas, D., & Laferla, F. M. (2011). The Role of Tau in Alzheimer's Disease and Related Disorders. *CNS Neuroscience and Therapeutics*, *17*(5), 514–524. https://doi.org/10.1111/j.1755-5949.2010.00177.x

Meguro, K., Ouchi, Y., Akanuma, K., Meguro, M., & Kasai, M. (2014). Donepezil can improve

daily activities and promote rehabilitation for severe Alzheimer's patients in long-term care health facilities. *BMC Neurology*, *14*(1), 1–7. https://doi.org/10.1186/s12883-014-0243-7

Mimica, N., & Presečki, P. (2009). Side effects of approved antidementives. *Psychiatria Danubina*, *21*(1), 108–113.

Moghul, S., & Wilkinson, D. (2001). Use of acetylcholinesterase inhibitors in Alzheimer's disease. *Expert Review of Neurotherapeutics*, *1*(1), 61–69. https://doi.org/10.1586/14737175.1.1.61

Nagy, C. F., Kumar, D., Cullen, E. I., Bolton, W. K., Marbury, T. C., Gutierrez, M. J., Hutman, H. W., & Pratt, R. D. (2004). Steady-state pharmacokinetics and safety of donepezil HCl in subjects with moderately impaired renal function. *British Journal of Clinical Pharmacology, Supplement*, *58*(1), 18–24. https://doi.org/10.1111/j.1365-2125.2004.01803.x

Nguyen, K., Hoffman, H., Chakkamparambil, B., & Grossberg, G. T. (2021). Evaluation of rivastigmine in Alzheimer's disease. *Neurodegenerative Disease Management*, *11*(1), 35–48. https://doi.org/10.2217/nmt-2020-0052

Olivares, D., Deshpande, V. K., Shi, Y., Lahiri, D. K., Greig, N. H., Rogers, J. T., & Huang, X. (2012). N-Methyl D-Aspartate (NMDA) Receptor Antagonists and Memantine Treatment for Alzheimer's Disease, Vascular Dementia and Parkinson's Disease HHS Public Access. *Curr Alzheimer Res*, *9*(6), 746–758.

Pardo-Moreno, T., González-Acedo, A., Rivas-Domínguez, A., García-Morales, V., García-Cozar, F. J., Ramos-Rodríguez, J. J., & Melguizo-Rodríguez, L. (2022). Therapeutic Approach to Alzheimer's Disease: Current Treatments and New Perspectives. *Pharmaceutics*, *14*(6), 1–20. https://doi.org/10.3390/pharmaceutics14061117

Pasqualetti, G., Tognini, S., Calsolaro, V., Polini, A., & Monzani, F. (2015). Potential drug–drug interactions in alzheimer patients with behavioral symptoms. *Clinical Interventions in Aging*, *10*, 1457–1466. https://doi.org/10.2147/CIA.S87466

Ph, D., Tan, J., Ph, D., Shytle, R. D., & Ph, D. (2010). for the Treatment of Alzheimer ' s Disease. *International Journal Pharmacology*, *389*, 207–212.

Plotkin, S. S., & Cashman, N. R. (2020). Passive immunotherapies targeting Aβ and tau in Alzheimer's disease. *Neurobiology of Disease*, *144*(July), 105010. https://doi.org/10.1016/j.nbd.2020.105010

Qiu, C., Kivipelto, M., & Von Strauss, E. (2009). Epidemiology of Alzheimer's disease: Occurrence, determinants, and strategies toward intervention. *Dialogues in Clinical Neuroscience*, *11*(2), 111–128. https://doi.org/10.31887/dcns.2009.11.2/cqiu

Rafii, M. S., Skotko, B. G., Mcdonough, M. E., Pulsifer, M., Evans, C., Doran, E., Muranevici, G., Kesslak, P., & Abushakra, S. (2018). *Syndrome without Dementia*. *58*(2), 401–411. https://doi.org/10.3233/JAD-160965.A

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

Reyes, J. F., Preskora, S. H., Khan, A., Kumar, D., Cullen, E. I., Perdomo, C. A., & Pratt, R. D. (2004). Concurrent administration of donezepil HCl and risperidone in patients with schizophrenia: Assessment of pharmacokinetic changes and safety following multiple oral doses. *British Journal of Clinical Pharmacology, Supplement*, *58*(1), 50–57. https://doi.org/10.1111/j.1365-2125.2004.01817.x

Sedgwick, P., & Marston, L. (2010). Statistical question: Odds ratios. *BMJ (Online)*, *341*(7769), 407. https://doi.org/10.1136/bmj.c4414

Selkoe, D. J., & Hardy, J. (2016). The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Molecular Medicine*, *8*(6), 595–608. https://doi.org/10.15252/emmm.201606210

Sheppard, O., & Coleman, M. (2020). Enfermedad de Alzheimer: etiología, neuropatología y patogenia. *Enfermedad de Alzheimer: Descubrimiento de Fármacos*, 1–22.

Steiner, J. L., Gordon, B. S., & Lang, C. H. (2015). Moderate alcohol consumption does not impair overloadinduced muscle hypertrophy and protein synthesis. *Physiological Reports*, *3*(3), 1–10. https://doi.org/10.14814/phy2.12333

Sugimoto, H., Iimura, Y., Yamanishi, Y., & Yamatsu, K. (1992). Synthesis and anti-acetylcholinesterase activity of 1-benzyl-4-[(5,6-dimethoxy-1-indanon-2-yl)methyl]piperidine hydrochloride (E2020) and related compounds. *Bioorganic and Medicinal Chemistry Letters*, *2*(8), 871–876. https://doi.org/10.1016/S0960-894X(00)80547-8

Tiseo, P. J., Rogers, S. L., & Friedhoff, L. T. (1998). Pharmacokinetic and pharmacodynamic profile of donepezil HCl following evening administration. *British Journal of Clinical Pharmacology, Supplement*, *46*(1), 13–18. https://doi.org/10.1046/j.1365-2125.1998.0460s1013.x

Valis, M., Masopust, J., Vysata, O., Hort, J., Dolezal, R., Tomek, J., Misik, J., Kuca, K., & Karasova, J. Z. (2017). Concentration of Donepezil in the Cerebrospinal Fluid of AD Patients: Evaluation of Dosage Sufficiency in Standard Treatment Strategy. *Neurotoxicity Research*, *31*(1), 162–168. https://doi.org/10.1007/s12640-016-9672-y

Vaz, M., & Silvestre, S. (2020). Alzheimer's disease: Recent treatment strategies. *European Journal of Pharmacology*, *887*(May), 173554. https://doi.org/10.1016/j.ejphar.2020.173554

Xiao, Q. yue, Ye, T. yuan, Wang, X. long, Han, L., Wang, T. xing, Qi, D. mei, Cheng, X. rui, & Wang, S. qi. (2021). A network pharmacology-based study on key pharmacological pathways and targets of Qi Fu Yin acting on Alzheimer's disease. *Experimental Gerontology*, *149*, 101–115. https://doi.org/10.1016/j.exger.2021.111336

Y.Y. Szeto, J., & J.G. Lewis, S. (2016). Current Treatment Options for Alzheimer's Disease and Parkinson's Disease Dementia. *Current Neuropharmacology*, *14*(4), 326–338. https://doi.org/10.2174/1570159x14666151208112754

Yiannopoulou, K. G., Anastasiou, A. I., Kyrozis, A., & Anastasiou, I. P. (2019). Donepezil Treatment for Alzheimer's Disease in Chronic Dialysis Patients. *Case Reports in Nephrology and Dialysis*, *9*(3), 126–136. https://doi.org/10.1159/000502682

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