A Review on Donepezil in The Treatment of Dementia

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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

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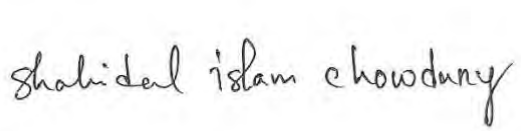

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Approval

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Ethics Statement

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

Abstract

Dementia is a syndrome of acquired deficits in multiple domains of cognition severe enough to interfere with everyday life and not due to impaired consciousness or the effects of a systemic illness. Memory is usually the most severely affected domain initially and gradually it affects other cognition related activity like orientation, language, judgement, perpetual ability and praxis (the ability to carry out complex actions). Alzheimer disease is the most common cause of dementia, and may be involved majority of the cases. It is a primary degenerative disease which leads to dementia of insidious onset, most commonly in later life. Donepezil a second-generation cholinesterase inhibitor used in the treatment of dementia due to Alzheimer disease which helps to improve cognition and behavior.

Keywords: Dementia, Alzheimer's disease, Cholinesterase Inhibitor, Donepezil

Dedication

Dedicated to my faculty members, family and friends.

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Chapter 1 Introduction

1.1 Dementia

Dementia is a disease that can be brought on by a number of illnesses including Alzheimer's disease which over time damage the brain and kill nerve cells, impairing cognitive function (i.e., the capacity for thought processing) in ways that go above and beyond what is generally expected as a result of biological aging (American Psychiatric Association, 2000). Furthermore, International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) recognizes that cognitive impairments in dementia frequently precede and accompany losses in emotional regulation, social conduct, or motivation. (World Health Organization, 2010) dementia was reclassified as a major neurocognitive disorder (NCD) in the ICD-10 Classification of Mental and Behavioral Disorders (American Psychiatric Association, 2013), a less severe form of cognitive impairment called minor NCD, which is equivalent to mild cognitive impairment (MCI) and prodromal dementia. By definition, it is arbitrary to distinguish between a small NCD and a big NCD. To underline that these illnesses are brought on by brain diseases and impaired brain function, resulting in cognitive symptoms, these disorders are increasingly referred to as "neurocognitive" disorders (DSM-5) (American Psychiatric Association, 2013). The DSM-5 has also provided a list of six cognitive domains that may be impacted by both mild and major NCDs. These domains are learning and memory (free recall, cued recall, recognition memory, semantic and autobiographical memory), executive function including planning, decision-making, working memory, responding to feedback, inhibition, and mental flexibility), complex attention (which includes sustained attention, divided attention, selective attention, and information processing speed), and mental flexibility. The DSM-5 categorizes minor and major NCD according to the condition that caused the cognitive deficits. These conditions include Alzheimer's disease (AD), frontotemporal dementia, dementia with Lewy bodies, vascular dementia, dementia due to Parkinson's disease, dementia brought on by Huntington's disease, dementia due to another

medical condition, and NCD. Between 60 and 80 percent of all instances of dementia are assumed to be AD, which is regarded as the prototype for irreversible dementia. (Alzheimer's Association,2014). The prevalence of irreversible dementias is thought to range from 0 to 23% of all dementia cases, according to several clinic-based research (Clarifield, 1988; Weytingh et al., 1995; Clarifield, 2003). This is despite the fact that there are a growing number of potential causes of irreversible dementia. The most frequent causes of reversible dementia have been the subject of debate among researchers. Some claim that depression is the most frequent cause (Djukic et al., 2015), while others argue that benign tumors, normal pressure hydrocephalus, and subdural hematomas are neurosurgical causes that account for the majority of cases (Michel & Sellal, 2011).

1.2 Etiology of Dementia

The various irreversible and reversible causes of dementia are shown in Table 1 (American Psychiatric Association, 2000; World Health Organization, 1992; American Psychiatric Association, 2013; Ioannidis & Karacostas, 2011; Trivedi & Narang, 2008; Tripathi & Vibha, 2009).

Table 1: Etiology of Dementia

Causes of Dementia	
Neurosurgical conditions	Subdural hematoma Normal pressure hydrocephalus Intracranial tumors Intracranial empyema or abscess

Infections	Meningitis (tubercular, fungal, malignant) HIV dementia Neurosyphilis Lyme's disease Whipple's disease Fungal/protozoal Intracranial abscess Neurocysticercosis
Inflammatory/autoimmune cause	Sarcoidosis Multiple sclerosis

	Systemic lupus erythematosus Sjogren's syndrome Autoimmune limbic encephalitis

Metabolic conditions	Hypo and hyperthyroidism Hashimotos encephalitis Hypo – and hyper - parathyroidism Pituitary insufficiency Hypercalcemia Cushing's disease Addison's disease Hypoglycemia Wilson's disease Accidental hypothermia Electrolyte imbalance
Organ failure	Chronic liver failure Hepatic encephalopathy Chronic respiratory failure Pulmonary insufficiency Chronic renal failure Uremic encephalopathy
Nutritional deficiencies	Vitamin deficiencies (A, B1, B6, B12, and folate) Iron deficiency
Psychiatric disorders	Depression
Substance use	Alcohol abuse

Toxins/toxicity with metals	Arsenic, Mercury, Aluminum Lithium Lead Manganese Bismuth

1.3 Diseases Related to Dementia

1.3.1 Alzheimer Disease

The most prevalent cause of dementia, which is characterized by a slow loss of memory, thinking, behavior, and social abilities, is Alzheimer's disease. The ability to function is impacted by these changes. Acetylcholinesterase inhibitors, such as donepezil, galantamine and rivastigmine, as well as N-methyl Daspartate receptor antagonists, such as memantine, are some of the therapies for the condition that are available (Kumar et al., 2015). Alzheimer's disease has historically been thought of as an illness characterized by a progressive loss of neurons and synapses in various anatomical sites, leading to various symptoms. By analyzing the distribution, number, and location of distinctive brain lesions, AD may be diagnosed (Kumar et al., 2015).

1.3.2 Vascular Dementia

The second highest prevalent kind of dementia is vascular dementia (VaD). Binswanger's disease or multi-infarct dementia were its previous names. Clinical symptoms and indicators of VaD depend on the size of the clogged blood artery. Memory loss and cognitive abnormalities may coexist in this condition, or they may not, according to O'Brien and Thomas (2015), who found that the location of the damaged brain has a significant impact on this. Due to its abrupt start and progressive degeneration, VaD can be distinguished from other types of degenerative dementia. The patient usually has visual loss, confusion,

disorientation, trouble speaking or understanding speech, and other symptoms after a stroke. The cognitive symptoms and localized neurological symptoms and signs may coexist (Alzheimer's Society, 2015). Some studies divide VaD into three categories: subcortical VaD, and combined AD: poststroke dementia and VaD (AD + VaD).(Wallin et al., 2003). Cerebrovascular insult causes pathological brain alterations in people with VaD that impair cognition. Though it is challenging to determine exactly how these modifications contributed. There are microinfarcts, small vessel infarcts, and big vessel atherosclerotic alterations. These modifications also coincide with those observed in AD patients. Thus, massive infarcts may be the only way to define cases with pure VaD. Vascular alterations in the brain are more frequent as people age. (Grinberg et al., 2010; Thal et al., 2012). Strokes and transient ischemic attacks (TIAs) are risk factors for VaD. Any factors that increase the risk of atherosclerosis are therefore considered to be risk factors for VaD. These include the prevalence of smoking, metabolic syndrome, diabetes mellitus, dyslipidemia, postmenopausal women using estrogen, and hypertension. family history of cardiovascular disease, becoming older, being a man, cardiovascular disease, having had sleep apnea in the past, having had depression in the past, and having a history of cardiovascular disease are additional risk factors for vaD (Kirshner, 2009). According to studies, those with a history of stroke had a 9-fold higher chance of developing VaD than people without a history of stroke (Kokmen et al., 1996). In the six to twelve months following a stroke, around 30% of patients develop dementia, according to follow-up studies (Tatemichi et al., 1994). The management of vascular disease risk factors requires taking consideration of the significance of cardiometabolic risk factors. (O'Brien &Thomas, 2015).

1.3.3 Lewy Body Dementia

Lewy body dementia (LBD) which makes up 0-30.5% of cases of dementia. Further, the prevalence of LBD in the general population varies from 0% to 5% depending on how a case is characterized (Zaccai et al., 2005; Vann &, O'Brien, 2014). Parkinson's disease

dementia and dementia with Lewy Bodies are two related forms of dementia that are together referred to as LBD. Dementia with Lewy bodies is defined as dementia that initially manifests within a year after the start of those symptoms, whereas dementia with Parkinson's disease manifests more than a year after the onset of the disease's motor symptoms (Walker et al., 2015). There are four categories for the clinical characteristics of LBD: central, core, suggestive, and supportive. The defining characteristic is significantly influenced by cognitive deficits, which frequently impede executive and attentional functions. It's likely that memory loss does not exist in the early stages of dementia, but that it becomes so when the condition worsens. The primary signs of LBD are the existence of parkinsonian motor symptoms, frequent, well-defined visual hallucinations, and erratic attention and focus. REM sleep behavior disorder, severe neuroleptic sensitivity, and low basal ganglia dopamine transporter uptake as shown by single-photon emission computed tomography or positron emission method imaging are a few of the clinical characteristics that are regarded to be diagnostic of LBD. Some of the supporting characteristics of LBD include the existence of autonomic dysfunction, hallucinations in other modalities, visuospatial abnormalities, and other mental problems such systematized delusions, aggressiveness, and sadness. Other supporting aspects are the occurrence of recurring falls and syncope (fainting), as well as brief, inexplicable loss of consciousness. When a patient has dementia and at least one of the core symptoms, or if they have dementia and at least a few of the suggestive symptoms, a probable diagnosis is taken into account. (McKeith et al., 2005). Neuronal inclusions of α-synuclein, commonly known as Lewy bodies, along with neuronal degeneration are the pathological hallmark of LBD. However, postmortem examples of LBD that show substantial α-synuclein pathology but no illness symptoms are thought to be multifactorial in origin (Goerge et al.,2013; Parkkinen,2008). Since most occurrences of LBD are sporadic, more people with LBD have been discovered to have higher frequencies of the APOE ε4 gene, which is strongly linked to AD (Walker et al., 2015; Hyun et al., 2013). Ageing and being a man are risk factors for LBD.

According to previous studies, a history of depression, anxiety, stroke, adult attention deficit hyperactivity disorder, and a family history of Parkinson's disease is linked to an increased risk of LBD compared to healthy controls. Additionally, those with the APOE 4 allele are especially vulnerable (Boot et al., 2013; Golimstok et al., 2011).

1.3.4 Frontotemporal Dementia

Pick's disease, commonly known as frontotemporal dementia (FTD), is a neurodegenerative ailment that is characterized by abnormalities in behavior, language, and executive processes that come before the onset of memory difficulties. Additionally, the frontal and temporal lobes selectively atrophy, and the structural and functional abnormalities don't become obvious until late in the disease process (Bang et al., 2015). According to Bang et al. (2015), frontal lobe, anterior temporal, anterior cingulate, and insular cortex loss of neurons, gliosis, and microvascular alterations are the hallmarks of FTD. Behavioral variation FTD (bvFTD) and primary progressive aphasia (PPA), two separate types of FTD that may possibly be related to motor neuron disease, are characterized clinically. Characteristic of the bvFTD is personality change, which frequently results in social difficulties. Atrophied behavior, judgment, empathy, and foresight-related brain regions are a hallmark of this subtype. Language, speaking, writing, and understanding issues define the PPA subtype of FTD. Even though it could start later, it frequently starts before the age of 65 (Boxer & Miller, 2005; Neary et al., 1990; Kirshner, 2014).

1.3.5 Prion Related Dementia

Prions are a class of severe neurodegenerative disorders that include diseases like Creutzfeldt-Jakob disease (CJD) and Gerstmann-Sträussler-Scheinker (GSS) in humans. There are various different kinds of CJD, each with different potential etiologies, including acquired, genetic, and sporadic. In 85% of instances, posttranslational modification of the native cellular prion protein results in the production of the pathogenic scrapie prion protein (World Health

Organization, 1993) The sporadic form of CJD often starts to show symptoms between 60 and 65 years of age. Familial CJD, which is caused by genetic changes in the PRNP gene, produces the prion protein and accounts for 10-15% of cases of the disease. Point mutations in the autosomal dominant gene account for the majority of familial CJD cases. According to Will (2003), exposure to an external source of aberrant PRNP causes the third form of acquired CJD, which accounts for 1% of all CJD cases. [GSS is caused by PRNP mutations and is characterized by a lengthy sickness course, as opposed to CJD's brief course of illness (Shrestha et al., 2015). According to Shrestha et al. (2015), the disease CJD causes gliosis, neuronal death, and the distinctive spongiform alteration in the gray matter. Cognitive impairment is the most prevalent neuropsychiatric symptom of all prion diseases. Affective symptoms are frequently found in patients with young-onset sporadic CJD. The electroencephalogram, cerebrospinal fluid studies, and brain MRI all reveal signs of CJD (Shrestha et al., 2015).

1.3.6 Reversible Dementias

Reversibility of the cognitive symptoms is a distinguishing feature of reversible dementia in comparison to degenerative dementias, provided the root cause is treated effectively. It is crucial to keep in mind that the severity of any concurrent medical conditions and the timing of the diagnosis both affect the reversibility of cognitive symptoms (Ioannidis & Karacoatas, 2011). Reversible dementia has an expanding variety of etiological causes. According to Ioannidis and Karacoatas (2011), determining the origin of dementia and making an accurate diagnosis of reversible dementia frequently need detailed clinical history, examination, and investigations. For the purpose of making a diagnosis, it is crucial to seek for the traditional symptoms of a certain condition. Additionally, it's crucial to keep in mind that while assessing dementia patients, some reversible factors such as heavy metal toxicity must always be taken into account. Similar to this, while examining a patient's medical history, attention should be paid to any specific drugs they may have taken. For instance, some antihypertensives may cause cognitive problems. In light of the underlying condition, the

patient may receive a false diagnosis of VaD if these are not taken into account (Ioannidis & Karacoatas, 2011).

Chapter 2

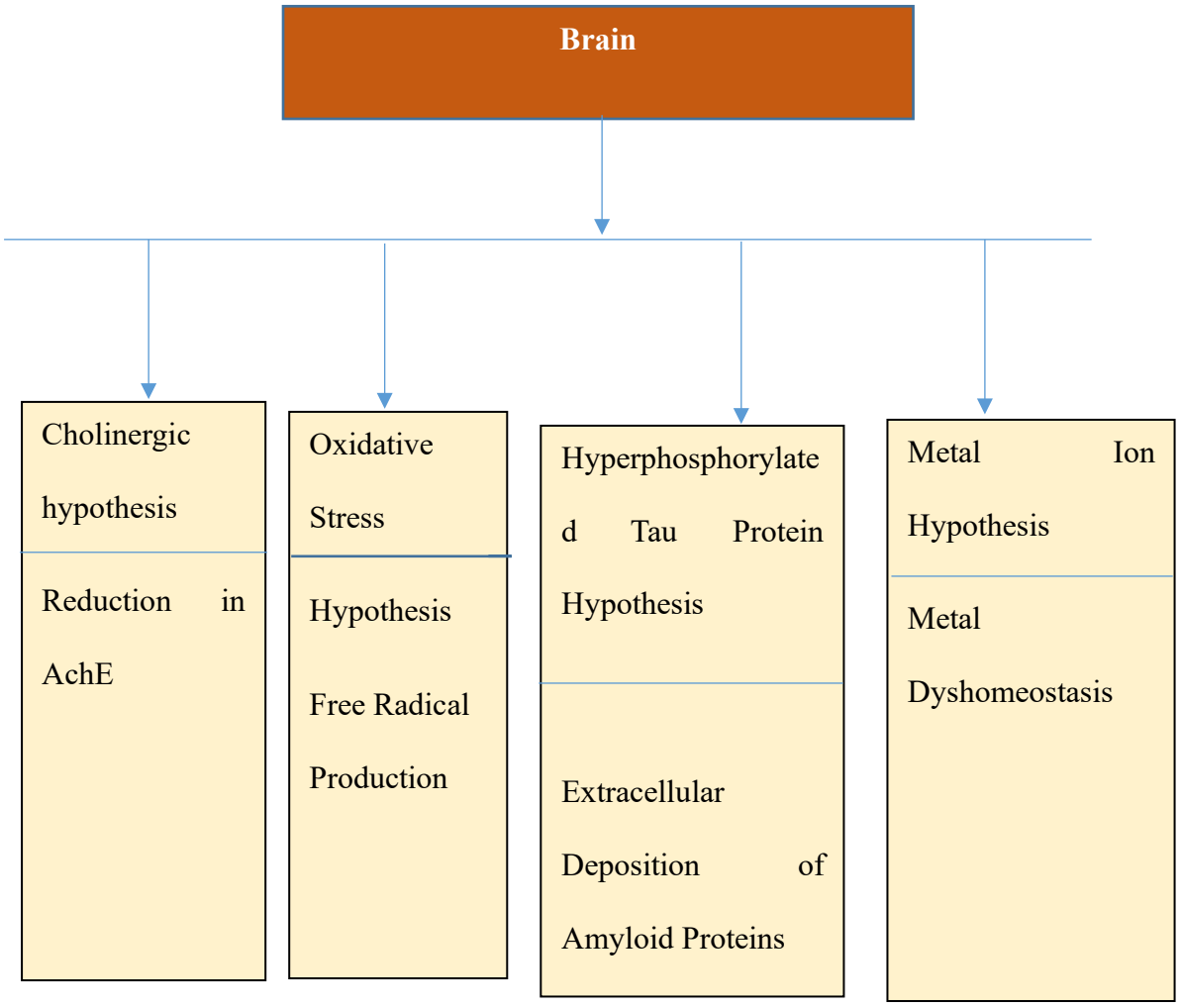
2.1 Alzheimer Disease

In the initial phases of Alzheimer's disease, memory loss worsens over time. Language, executive function, visuospatial skills, and memory loss are some of the other cognitive processes that may be impacted (American Psychiatric Association, 2013). Cognitive problems may be followed by behavioral signs as the illness gets worse. Patients who are in the most severe stage could require help with routine everyday tasks including showering, dressing, and using the bathroom. They might also lose their ability to speak, fail to recognize their loved ones, and become bedridden (Alzheimer's Association, 2014). Alzheimer's disease has historically been thought of as an illness characterized by a progressive loss of neurons and synapses in various anatomical sites, leading to various symptoms. By analyzing the distribution, number, and location of distinctive brain lesions, AD may be diagnosed (Kumar et al., 2015).

2.2 Pathophysiology of Alzheimer Disease

Beta-amyloid (Aβ) plaques and neurofibrillary tangles, which are gradually disseminated throughout the brain, are two degenerative lesions that define Alzheimer's disease (AD). The disruption of neural communication routes, neuronal aging, brain atrophy, and functional loss are all factors linked with these lesions. In a specific order, tangles develop in the trans-entorhinal cortex, entorhinal cortex, the CA1 region of the hippocampus, and ultimately the cortical association regions, which are most affected by the frontal, parietal, and temporal lobes. The tau proteins build up inside the neuron and create neurofibrillary tangles, obstructing nutrition transfer and impair communication. As a result of the neuron's toxicity from these tangles, neurons eventually start to die. (Kumar et al., 2015).

Tau protein buildup has a strong correlation with cognitive decline and brain shrinkage, particularly hippocampal atrophy. The symptoms of Alzheimer's disease include swelling, amyloid plaque buildup, neuronal death, atrophy of the temporofrontal cortex, abnormal protein fragment clusters, and twisted fiber bundles. As a result, the cerebral cortex develops more monocytes and macrophages and the parenchymal microglia become active. (Mishra & Palanivelu, 2008). Summary of pathophysiology of AD are shown in Figure 1.



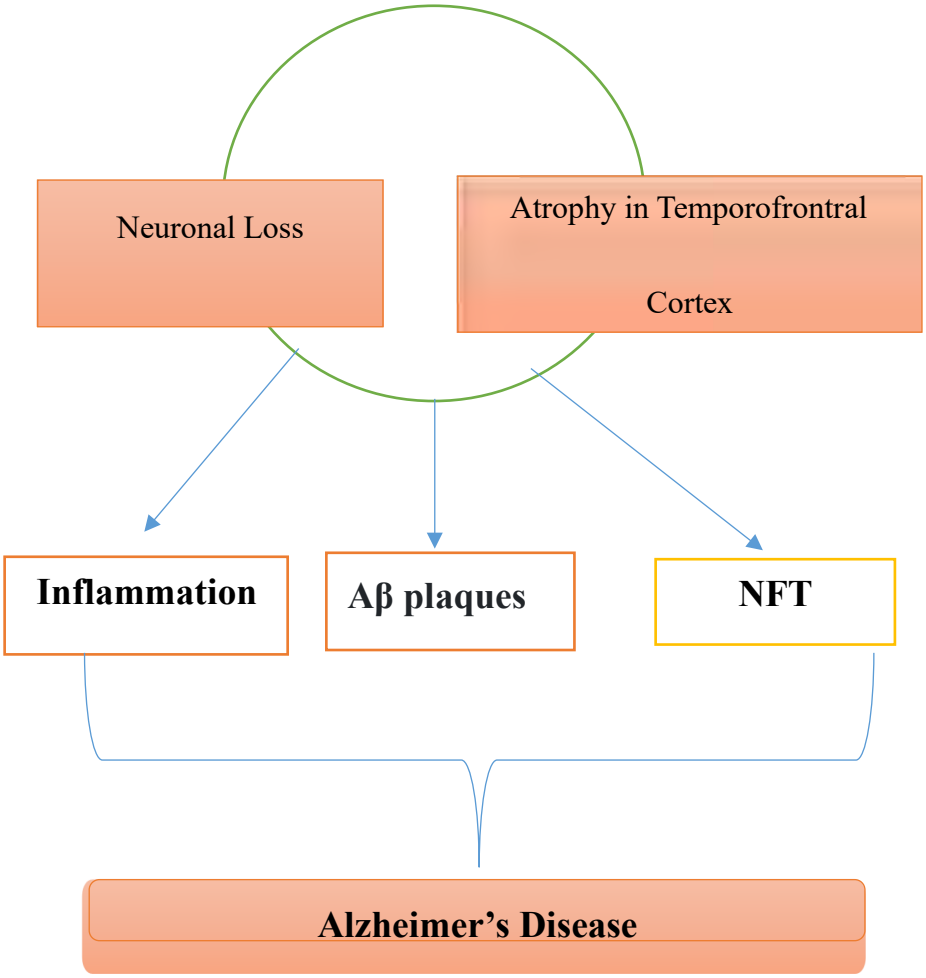


Figure 1: Pathophysiology of Alzheimer's Disease

2.2.1 Hyperphosphorylated Tau Protein and Amyloid B Hypothesis

One of the main pathogenic characteristics of AD is the emergence of senile plaques (SP), which are brought on by the accumulation of amyloid beta (Aβ). Aβ are generally soluble short peptides that are produced when the amyloid precursor protein (APP) is broken down by the enzymes -secretase, -secretase, and -secretase, according to Thakur et al. (2018). The imbalance between β -amyloid (Aβ) synthesis and clearance lead to protofibrils, fibrils, and plaques, three distinct types of dangerous oligomers, depending on the degree of oligomerization. The exact reason for Aβ generation is still unknown, despite the fact that the order, concentration, and circumstances of Aβ stability are significant variables. (Liu et al., 2017). There are a variety of factors that are hypothesized to have a role in the etiology of

Alzheimer's disease, such as cholinergic dysfunction, amyloid/tau toxicity, and oxidative stress/mitochondrial dysfunctions (Mohamed et al.,2016).

2.2.2 Oxidative Stress Hypothesis

In humans, a variety of physiological and pathological processes result in the production of reactive oxygen and nitrogen radicals (RONs). Liu et al. (2017) claim that they have a dichotomous nature, serving as both harmful compounds that can disrupt cellular components such the cell membrane, lipids, proteins, and DNA and as crucial biological signaling molecules. Due to its higher oxygen consumption (20% more than other tissues with mitochondrial respiration), the brain is particularly susceptible to oxidative stress (Liu et al., 2017). A significant number of polyunsaturated fatty acids are found in the neuron, the brain's main functional unit (Liu et al., 2017). As a result, it may interact with ROS, leading to lipid peroxidation and molecular death. Lack of glutathione in neurons is another factor that causes oxidative stress damage (Liu et al., 2017).

2.2.3 Metal ion hypothesis

Metal dyshomeostasis is essential for the onset and progression of many illnesses, including cancer and neurological diseases. Ionophores and metal chelators, which have been proven successful in clinical studies, can be used to control transition metal homeostasis. But metal binding agents are not the only medications that target transition metal homeostasis (Weekley & He, 2017). Redox transition metals, in particular copper (Cu), iron (Fe), and other trace metals, may have a role in the etiology of various disorders, according to recent studies. While other neurodegenerative illnesses are linked to abnormalities in copper, manganese, aluminum, and zinc, high quantities of these metals have been found in the brains of Alzheimer's disease patients (Prakash et al., 2017).

2.2.4 Cholinergic Hypothesis

Researchers are looking at how the APOE genotype affects the positive effects of AChEIs in Alzheimer's patients. Treatment for AD must include AChEI medications, and the main factor affecting AD is the APOE genotype. In light of the "Cholinergic Hypothesis" of AD, which has been around since 1976, the importance of APOE is being assessed. It is acknowledged by this theory that cholinergic neurons are not AD's main target.

In particular regions of the brain, mild to moderate AD sufferers might be seen to have decreased cholinergic receptor binding, which is associated with neuropsychiatric symptoms. In elderly adults who are healthy, lower receptor binding may be linked to slower processing speed. A potential biological target for therapy could be revealed by in vivo cholinergic receptor binding, which may also provide linkages to other significant changes in the brain associated with aging and AD (Sultzer & Marder, 2017). A considerable loss of cholinergic neurons in the medial forebrain nuclei is associated with clinical decline, and this loss is also accompanied by a decline in acetylcholine-mediated neurotransmission. The cornerstone of symptomatic therapy for AD has been donepezil and cholinesterase inhibitors (ChEIs) for more than 20 years (Chase et al., 2017).

2.2.5 Current Treatment of Alzheimer Disease

Drug therapy for Alzheimer disease is still in its early stages and there is no known cure for the disorder. While drugs that are likely to be used to treat AD can help control symptoms, they cannot stop the illness from progressing or turn it around. The "cholinergic hypothesis" of memory failure led to the first focus of pharmaceutical treatments for AD on improving cholinergic transmission in the brain. Acetylcholinesterase (AChE) inhibition and preventing the breakdown of acetylcholine (ACh) have shown to be the most effective up to this point among the different methods employed to raise synaptic levels of ACh. Cholinergic transmission may potentially be enhanced by inhibiting the enzyme butyrylcholinesterase

(BuChE). The central nervous system's (CNS) cholinergic pathways are the focus of three drugs: donepezil, galantamine, and rivastigmine. In addition to its allosteric modulatory activity at nicotinic acetylcholine receptors, galantamine, which is produced from a natural product, has anticholinesterase capabilities like the other two medicines. These drugs are available in generic form and are approved for the treatment of moderate to severe dementia, however they are frequently given to patients with predementia who demonstrate growing memory deterioration according to the results of cognitive tests. (Graham et al., 2017). Memantine, the treatment most recently approved for AD in the US, is notable since it is the first AD medication to target both glutaminergic and N-methyl-d-aspartate (NMDA) receptor pathways. Glutamatergic modulation impacts the clustering of dendritic spines in a mouse model of AD. More recently, a pathophysiological explanation for AD has been proposed that involves excessive glutamate at excitatory synapses and accompanying cytotoxicity, which may be brought on by defective microglial glutamate absorption. This has led to the use of riluzole, a glutamate antagonist. As a result, less Aβ is generated. Donepezil and memantine have been approved for the treatment of AD symptoms in monotherapy in addition to their approved uses (Ito et al., 2017). Given together, the effects of memantine and donepezil, which each have distinctive and complementary modes of action, are more advantageous to the patient. The first line of evidence that memantine and donepezil may be taken together safely came from the findings of a clinical study in healthy volunteers. In combination with ongoing ChEI therapy, memantine shows a favorable safety profile in AD patients (Ito et al., 2017).

Chapter 3

3.1 Parkinson's Disease

Parkinson disease is a neurological disease. stiffness, and bradykinesia and tremor are the hallmarks of Parkinson's disease (PD). As the condition worsens, postural instability may also develop in certain people. Our understanding of Parkinson's disease (PD) is constantly growing. James Parkinson originally defined it in 1817, and Jean-Martin Charcot went on to characterize it. According to Kalia and Lang (2015), PD is the second most prevalent neurodegenerative illness after Alzheimer's disease (AD), with prevalence rates ranging from 0.5% to 1% for those 65 to 69 years old to 1-3% for people 80 years of age and beyond (Tanner & Goldman, 1996; Nussbaum & Ellis, 2003). By 2030, it is anticipated that the prevalence and incidence of PD will have risen by more than 30% due to an aging population (Chen et al., 2001).

3.2 Pathology of Parkinson's Disease

In the substantia nigra pars compacta (SNpc), which experiences loss or degeneration of dopaminergic neurons in Parkinson's disease (PD), Lewy bodies, aberrant intracellular aggregates comprising proteins such alpha-synuclein (aSyn) and ubiquitin, accumulate (Dickson et al., 2009; Goedert et al., 2012). The SNpc loses 60–70% of its neurons prior to any symptoms appearing, according to Postuma et al. (2009). Studies have revealed that the pathogenic process in PD affects both the peripheral and central nervous systems in addition to the SNpc's dopaminergic neurons. Lewy body pathology, which initially impacts cholinergic and monoaminergic brainstem neurons as well as olfactory system neurons, affects limbic and neocortical brain regions as the disease develops (Halliday & McCann, 2010; Dijkstra et al., 2014). Dopaminergic neuron loss becomes more widespread when the disease reaches its terminal stage (Damier et al., 1999; Fearnley & Lees, 1991).

Chapter 4

Donepezil

The benzylpiperidine portion of the donepezil molecule is joined to the dimethoxy indanone by a methylene group (Figure 1). It serves as a racemic mixture.

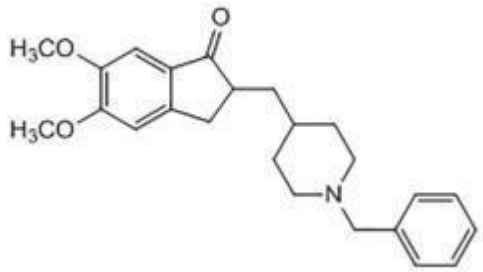


Figure 2: Structure of Donepezil

4.1 Mechanism of action

A centrally acting, quick-acting, reversible acetylcholinesterase inhibitor, donepezil hydrochloride is a piperidine derivative. Following release from the presynapse, the enzyme acetylcholinesterase breaks down the acetylcholine. The reversible acetylcholinesterase binding property of donepezil prevents acetylcholine from being hydrolyzed, increasing its availability at synapses and promoting cholinergic transmission. The anticholinesterase action of donepezil may be rather selective to the acetylcholinesterase in the brain, according to certain in vitro findings. Other anticholinesterase medications like tacrine and physostigmine are structurally unrelated to it (Seltzer, 2005).

Some theories postulate the existence of noncholinergic processes as well. Its ability to act as a neuroprotective is enhanced by donepezil's stimulation of the nicotinic receptors in the cortical neurons. This activity has the potential to delay rectifier potassium currents, slow rapid

transient potassium currents, and reversibly decrease voltage-activated sodium currents. However, it is unlikely to offer any therapeutic benefits (Seltzer, 2005; Seltzer, 2007)

4.2 Adverse Effects

The gastrointestinal side effects are the most typical. Nausea, diarrhea, and vomiting are examples of these symptoms. Along with this, greater dosages are more likely to cause anorexia, tiredness, muscular cramps, and sleeplessness. Even with sustained treatment, most patients only have minimal side effects that last up to three weeks (Seltzer 2007; Kumar et al.,2015) Hypertension, edema, irregular EKGs, and hypotension are other, less frequent cardiovascular adverse effects (Seltzer 2007; Kumar et al., 2015). About 5% of patients using donepezil experience weight loss. With larger dosages, the incidence is increased. Due to increased activity of the visual association cortex during REM sleep, donepezil can contribute to nightmares, just as other cholinesterase inhibitors. But the frequency of nightmares can be decreased by taking donepezil first thing in the morning (Seltzer 2007; Kumar et al., 2015). A very small number of reports link donepezil to the neuroleptic malignant syndrome. Rarely, rhabdomyolysis has been linked to the usage of donepezil (Seltzer 2007; Kumar et al., 2015).

4.3 Drug interactions

Synergic effects can be seen while combination of donepezil and other cholinergic drugs. Depolarizing neuromuscular blocking medications like suxamethonium may have their effects prolonged by donepezil (Heath, 1997).In combination with beta blockers donepezil may increase the risk of bradycardia (Kho et al., 2021).By accelerating the rate of elimination, CYP2D6 and CYP3A4 inducers such as rifampin, phenytoin, phenobarbital, may lower levels of donepezil (Levy & Collins, 2007).The clinical importance of this is uncertain (Levy & Collins, 2007), however CYP3A4 and CYP2D6 inhibitors like quinidine and ketoconazole theoretically have the potential to decrease donepezil metabolism.

4.4 Contraindication

Patients who have a history of donepezil hydrochloride or piperidine derivative hypersensitivity are not advised to take donepezil.

4.5 Warnings/Precautions

Given that donepezil can extend QT intervals, it should be administered with caution to people who are at risk for prolonged cardiac repolarization. Due to the possibility of bradycardia and/or heart blocks, patients with sick sinus syndrome, abnormal cardiac conduction, and symptomatic bradycardia should use caution when using this medication (Kho et al., 2021). Use of cholinesterase inhibitors may lead to increased production of stomach acid. As a result, those at risk for ulcer disease should be cautious, and any indicators of GI bleeding should be monitored (Kho et al., 2021). In patients who have a history of seizure disorder, doctors should use caution when administering donepezil or other cholinomimetic medications since they might cause seizures (Kho et al., 2021). If a patient has a history of prostatic hyperplasia, they should take caution while using cholinomimetic drugs like donepezil since they might induce or exacerbate bladder outflow blockage (Kho et al., 2021). During anesthesia, it may intensify the muscular relaxation caused by succinylcholine (Kho et al., 2021). When treating patients who have a history of asthma or chronic obstructive pulmonary disease, due to its cholinomimetic effects, it should be prescribed with caution. (Kho et al., 2021). Patients who are susceptible to rhabdomyolysis should use donepezil with care. Muscular problems in the past, untreated hypothyroidism, and concurrent usage of rhabdomyolysis-related drugs are all risk factors (Kho et al., 2021).

4.6 Toxicity

The doctor should consult poison control and take general supportive measures in the case of a donepezil overdose. An overdose of donepezil may cause a cholinergic crisis.

Overdose symptoms include persistent nausea, vomiting, increased sweating, and increased salivation. . Furthermore, bradycardia, hypotension, respiratory depression, collapse, and convulsions may occur. If respiratory muscles are involved, a donepezil overdose could aggravate muscular weakness and result in death. Hepatotoxicity has been noted in a rare overdose event. As with other toxicities caused by anticholinesterase inhibitors, atropine, a tertiary anticholinergic, can be used to treat donepezil overdose. Atropine IV dosage modifications are required depending on the patient's reaction. Removal of donepezil or its metabolites may be accomplished using hemofiltration, hemodialysis, or peritoneal dialysis (Seltzer, 2007;

Chapter 5

Conclusion

Dementia patients may acquire new personas and lose the ability to manage their emotions due to impaired cognitive skills. The mildest stage of dementia starts with affecting the person's daily functioning which gradually changes to the most severe stage, when basic daily tasks are completely dependent on support from the others, such feeding. In case of dementia, certain brain regions have experienced changes that make it impossible for neurons (nerve cells) and the connections that connect them to function correctly. Complex abnormalities in the brain that follow cell injury are what cause degenerative disorder known as Alzheimer's. It ultimately results in dementia symptoms that progressively worsen. Memory loss is the most common early symptom of Alzheimer's disease because it often impacts the learning related portion of the brain first. Among movement disorder Parkinson's disease one. As a result, the muscles could become tighten and contract. This makes walking and others day tasks challenging. Tremors, dementia and memory loss are among the cognitive issues that Parkinson's disease patients might suffer from. There are four drugs available to manage the symptoms of dementia, which are donepezil, rivastigmine, galantamine and memantine. To get synergistic effect, a physician might prescribe a combination of donepezil and memantine.

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