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Alzheimer's Disease: Understanding Risk Factors and Exploring Treatment Options

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ABSTRACT :

Alzheimer's disease is a degenerative neurological condition where memory loss, cognitive decline, and eventually dementia are caused by the death of brain cells. For those 65 years of age and older, it is the most frequent cause of dementia. About 10% of those over 65 and over 50% of people over 85 suffer from the illness. Alzheimer's disease affects about four million people in the US alone, and the annual cost of treatment is close to $100

billion. It is currently the fourth most common cause of death in the United States and is spreading throughout the world. The steady loss of nerve cells and their connections causes the brain's total size to decrease as the condition worsens. Alzheimer's disease currently has no known cure, and brain cell destruction cannot be prevented or undone. As a result, current initiatives concentrate on enhancing treatment and prevention research while bolstering patient and family support networks. Increasing community support, raising public awareness, and improving the quality of care are crucial objectives in the management of the illness.

Keywords: Alzheimer's disease, neuropsychological Testing,cognitive dysfunction,

Introduction

What is now known as Alzheimer's disease was first described by German neuropathologist and psychiatrist Dr. Alois Alzheimer. Alzheimer's disease (AD) is a severe and progressive type of dementia characterised by significant impairments in memory, language, and behaviour.[1,2] In addition to having a significant social impact, Alzheimer's disease is very expensive for healthcare systems worldwide. [3,4] Environmental,
psychological, and vascular factors all affect Alzheimer's disease. As of right now, there are no medications that can stop the disease's neurodegenerative effects. As a result, most current treatments focus more on managing symptoms than on preventing illness.
.[5] Cholinesterase inhibitors are used to enhance neurotransmission in mild to moderate cases of Alzheimer's disease, while memantine helps reduce excitotoxicity in moderate to severe cases. Antidepressants and antipsychotics can also be used to treat related
behavioural and psychological disorders.[6,7] While other cognitive, motor, and sensory functions are unaffected, early symptoms include a minor decline in episodic memory. Independence is preserved and Alzheimer's disease cannot yet be diagnosed.[8] Alzheimer's disease is a degenerative, irreversible brain disorder that gradually impairs memory and thinking, often leading to dementia and other cognitive deficits.[9]
Behavioural abnormalities and a gradual decline in cognitive function are hallmarks of Alzheimer's disease. Neurofibrillary tangles are created when tau protein and beta- amyloid plaques abnormally build up in the brain. These changes damage neurones,
trigger inflammation, and activate immune cells called microglia, all of which worsen the disease.[10,11] The body absorbs riluzole 60% of the time when it is given orally. The greatest blood levels are determined by the dose, however taking it with a high-fat meal may lower these levels. To address this, scientists have developed a sublingual version of riluzole that may be less affected by fatty foods.[12,13]

Risk factors Age

Age is the most unalterable risk factor for Alzheimer's disease. Most incidents involve adults 65 years of age or older. About 5% of people between the ages of 65 and 74 are affected, while the risk rises to 50% for people over 85.[2] **Geneics**:
Sporadic Alzheimer's disease is not linked to any specific inherited genetic pattern. However, the disease is linked to the ApoE gene, which facilitates the movement of cholesterol through the blood. The ApoE4 variation raises the danger, whereas ApoE2
offers protection.[14,15] Alzheimer's disease that appears before the age of 65 is often linked to genetic abnormalities. Mutations in chromosomes 1, 14, or 21 cause familial Alzheimer's disease, a rare type that affects less than 10% of sufferers. If one mutation is inherited, the likelihood of getting the disease is 50%.[16,17]

Educaion:

Research suggests that a lower degree of education may increase the risk of Alzheimer's disease. Higher education may help the brain make up for the loss of neurones as the

disease worsens by creating additional neural connections, or a "synaptic reserve.[1,14] Alzheimer's disease is a degenerative, irreversible brain disorder that gradually impairs daily functioning, thinking, and memory. Over time, it shrinks and kills brain cells. The majority of persons begin to have symptoms in their mid-60s.

Causes The most noticeable signs of early-stage Alzheimer's disease may be occasional disorientation or mild forgetfulness. But over time, your memory steadily deteriorates
more, particularly for recent events. Age often has an impact on the rate of worsening symptoms, which may vary from person to person. To understand the causes, three ideas can be applied.

Cholinergic hypothesis:

The cholinergic hypothesis suggests that reduced acetylcholine and cholinergic neurone death may contribute to memory and cognitive impairment in Alzheimer's disease, albeit a direct cause-and- effect relationship hasn't been proven. [18,19].Additionally, more than half of Alzheimer's patients do not respond well to cholinesterase inhibitors (Cis),
suggesting that the disease's progression is likely influenced by other important factors.[18]

Amyloid hypothesis:

Amyloidosis causes insoluble amyloid proteins to build up in tissues. In Alzheimer's disease, APP breaks down into amyloid-β, which leads to neuritic plaques in the brain and worsens the condition. [20] Although Alzheimer's disease is linked to amyloid-β (Aβ) fibrils, soluble Aβ1-42 oligomers, or ADDLs, may be more detrimental because they target synapses, disrupt plasticity, and affect cognition through cell-surface toxin receptors and Fyn kinase..[21,22]

Tau hypothesis:

The Tau theory states that excessive phosphorylation of Tau in Alzheimer's causes it to
detach from microtubules, increasing free Tau and disrupting microtubule function, which impacts neuronal transport, structure, and overall cell health.[23] Phosphorylated tau subunits called paired helical filaments (PHFs) make up NFTs. Damaged microtubules
affect the axonal transport of proteins, which eventually leads to neuronal death.[24]

Treatments

Drug Therapy:

Alzheimer's disease is treated with two types of drugs: N-methyl D-aspartate antagonists and acetylcholinesterase inhibitors. The two types function in distinct ways.

Cholinesterase Inhibitors:

Alzheimer's disease causes a decrease in acetylcholine, a neurotransmitter that helps nerve cells communicate. Cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) improve memory in mild to severe cases by raising acetylcholine.[18] While galantamine blocks both acetylcholine and butyrylcholinesterase, donepezil and
rivastigmine selectively inhibit acetylcholine. While a metaanalysis of 13 trials found no change in behaviour or daily activities, all three drugs demonstrated similar effects on cognition and overall benefits.[25] Cholinesterase inhibitors (CIs) can be helpful for a long time even if they cannot stop Alzheimer's disease from progressing. In a randomised,
double-blind study, patients on long-term donepezil treatment sustained improvements for up to two years.[26] The minor adverse effects of CIs are frequently limited to digestive issues such nausea, vomiting, and diarrhoea.[27]

NMDA Receptor Antagonists:

Memantine is a non-competitive NMDA receptor antagonist that effectively treats
moderate-to-severe Alzheimer's disease by reducing glutamate-induced excitotoxicity.
Studies show that it lessens the burden on caretakers, enhances behaviour, reduces agitation, slows cognitive decline, and eases the behavioural and psychological symptoms of dementia (BPSD).[28]

Anidepressants and Anipsychoics:

BPSD affects carers and is prevalent in Alzheimer's disease. Memantine and cholinesterase inhibitors offer only modest alleviation. Antidepressants, such as SSRIs, tricyclics, and SNRIs, are helpful in treating depression; stopping them exacerbates
depressive symptoms.[29] Olanzapine, quetiapine, and risperidone are common
antipsychotics used to treat agitation and psychosis in Alzheimer's patients. Their utility is debatable, nevertheless, because patients frequently experience a marked loss in cognitive function when compared to those who get a placebo.[30]

Disease modifying treatments:

Even though symptomatic treatments are beneficial, finding a cure is crucial. Anti-amyloid therapies target excessive Aβ synthesis, aggregation, and deposition from APP breakdown in order to reduce Aβ levels, enhance its clearance, and prevent the formation of amyloid plaque. [31, 32] Immunotherapy is another interesting tactic that helps eliminate Aβ
peptides, which may either directly or indirectly lessen the cognitive decline linked to Alzheimer's disease. [33]

BRIEF OVERVIEW OF RILUZOLE

1. Chemistry of riluzole

High-fat meals lower the blood levels of riluzole, which are dependent on the dosage. It has a 60% oral bioavailability. Regardless of the type of meal, a sublingual form might offer
more consistent absorption by avoiding this effect.[34,35] After being absorbed, riluzole is converted by the liver's CYP1A2 enzyme into N-hydroxyl riluzole, which is then removed by glucuronidation. [36] Roughly 10% of the dose is lost in faeces, and less than 1% of the
dose appears unaltered in urine. The body generally breaks down riluzole, and the kidneys are principally responsible for excreting its metabolites. [37, 38]

2. Adverse effects

Riluzole is generally safe; no serious side effects have been reported. Weakness and nausea are the most common issues. Because it may potentially raise liver enzymes, liver function should be regularly evaluated. [39] Furthermore, studies have shown that riluzole has a typically benign profile and does not cause birth issues or genetic abnormalities. [41, 42]

3. Mechanism of action

In several neurodegenerative diseases (NDs), including AD, riluzole may diffuse across the blood-brain barrier and exhibit its neuroprotective benefits through a variety of routes. [43]

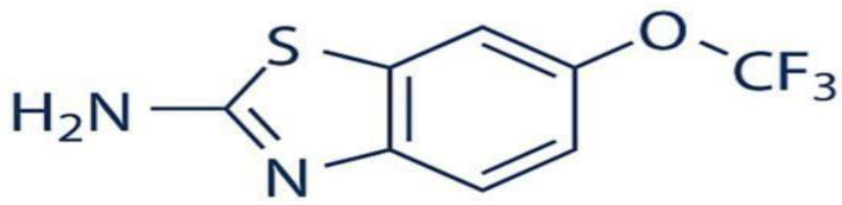

FIGURE .1: Molecular structure of riluzole.

CONCLUSION :

Numerous environmental, behavioural, and genetic factors influence Alzheimer's disease, a complex and degenerative neurological disorder. Age and heredity remain the greatest
risk factors, even though lifestyle and cardiovascular health have a major impact on the onset and progression of disease. Even though there is currently no cure, a combination of pharmaceutical treatments, nonpharmacological interventions, and lifestyle
modifications can help manage symptoms, improve quality of life, and potentially slow the disease's course.Because to early discovery, preventive measures, and ongoing research into new medicines, there is hope for improved management in the future. Ultimately, a
multidisciplinary strategy involving patients, carers, medical professionals, and researchers is necessary to address the challenges of Alzheimer's disease and assist those affected by it.

REFERENCE

1) Alzheimer's Disease Facts and igures. Rep. Vol 6. Chicago: Al- zheimer's Associaion. 2010.

2) Alzheimer's Associaion. 2010.

3) Santana I, Farinha F, Freitas S, et al. The epidemiology of demen- ia and Alzheimer's disease in Portugal: esimaions of preva- lence and treatment costs. ActaMédica Portuguesa. 2015; 28: 182-188.

4) Chiang K, Koo EH. Emerging therapeuics for Alzheimer's dis- ease. Annual Review of Pharmacology and Toxicology. 2014; 54: 381-405

5) Yiannopoulou KG and Papageorgiou SG. Current and future treatments for Alzheimer's disease. There Adv Neurol Disord. 2013; 6: 19-33.

6) Lukiw WJ. Amyloid beta (Aß) pepide modulators and other cur- rent treatment strategies for Alzheimer's disease (AD). Expert

OpinEmerg Drugs. 2012

7) Ballard C and Corbet A Management of neuropsychiatric symp- toms in people with demenia. CNS Drugs. 2010; 24: 729-739.

8) Almkvist O Neuropsychological features of early Alzheimer's disease: preclinical and clinical stages. ActaNeurolScandSuppl. 1996; 165:63-71.

9) Bronzuoli MR, Iacomino A, Steardo L, Scuderi C. Targeting neuroinfammation in Alzheimer"s disease. J Infamm Res, 2016; 9: 199–208.

10) Huynh RA, Mohan C Alzheimer"s disease: biomarkers in the genome, blood, and cerebrospinal fluid. Front Neurol, 2017; 8: 102

11) Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S et al Alzheimer"s disease. Lancet, 2016; 388: 505–517.

12) Qureshi I, Lovegren M, Wirtz V, et al. A pharmacokinetic bio- equivalence study comparing sublingual riluzole (BHV-0223) and oral tablet formulation of riluzole in healthy volunteers. Clin

Pharmacol Drug Dev. 2020;9(4):476-485. doi:10.1002/cpdd.747

13) Le Liboux A, Lefebvre P, Le Roux Y, et al. Single- and multiple- dose pharmacokinetics of riluzole in white subjects. J Clin Phar- macol. 1997;37(9):820-827. doi:10.1002/j.1552-4604.1997.

tb05630.x

14) Mayo Clinic Medical Informaion and Tools for Healthy Living. Mayo Foundaion for Medical Educaion and Research. 2010.

15) American Health Assistance Foundaion (AHAF): Alzheimer's disease, Macular Degeneraion and Glaucoma. Web. 2010.

16) American Psychiatric Associaion; Diagnosic and Staisical Manual of Mental Disorders. 1980; 111-112.

17) Emilien and Grard, et al. Alzheimer Disease: Neuropsychology and Pharmacology. Basel: Birkhauser. 2004.

18) Thies W and Bleiler L Alzheimer's disease facts and igures. Al- zheimer Dement.2013; 9: 208-245.

19) Francis PT, Palmer AM, Snape M et al. The cholinergic hypothesis of Alzheimer's disease: a review of progress. J NeurolNeurosurg Psychiatry. 1999; 66: 137-147.

20) Corbet A, Williams G and Ballart C. Drug reposiioning: an op- portunity to develop novel treatments for Alzheimer's disease.

Pharmaceuicals. 2013; 6: 1304-1321.

21) Lacor PN, Buniel MC, Furlow PW, et al. Abeta oligomer-induced aberraions in synapse composiion, shape, and density provide a molecular basis for loss of connecivity in Alzheimer's disease.

J Neurosis. 2007; 27: 796-807.

22) Lambert MP, Barlow AK, Chromy BA, et al. Difusible, nonibrillar ligands derived from Abeta1-42 are potent central nervous sys-tem neurotoxins. ProcNatlAcadSci USA. 1998; 95: 6448- 6453.

23) Mudher A, Lovestone S. Alzheimer's disease-do tauists and bap- ists inally shake hands? Trends Neurosis. 2002; 25: 22-26.

24) Trojanowski JQ and Lee VMY. The Alzheimer's brain: inding out what's broken tells us how to ix it. Rous-Whipple Award Lec- ture. 2005; 167: 1183-1188.

25) Birks J Cholinesterase inhibitors for Alzheimer's disease. Co- chrane Database Syst Rev (1): CD005593. 2006

26) Courtney C, Farrell D, Gray R, et al. Long-term donepezil treat- ment in 565 paients with Alzheimer's disease: randomized dou- ble-blind trial. Lancet. 2000; 363: 2105-2115.

27) Blennow K, de Leon MJ and Zeterberg H. Alzheimer's disease. Lancet. 2006; 29: 387-403.

28) Maidment ID, Fox CG, Boustani M, et al. Eicacy of Memanine on behavioral and psychological symptoms related to demenia: a systemaic meta-analysis. Ann Pharmacother. 2008; 42: 32-38.

29) Zec RF and Burket NR. Non-pharmacological and pharmacologi- cal treatment of the cogniive and behavioural symptoms of Al- zheimer disease.NeuroRehabilitaion. 2008; 23: 425-438. 30)Vigen CL, Mack WJ, Keefe RS, Sano M, et al. Cogniive efects of atypical anipsychoic medicaions in paients with Alzheimer's disease: outcomes from CATIE-AD. Am J Psychiatry. 2011; 168: 831-839

31) Corbet A, Williams G and Ballart C. Drug reposiioning: an op- portunity to develop novel treatments for Alzheimer's disease. Pharmaceuicals. 2013; 6: 1304-1321.

32) Van Marum RJ Current and future therapy in Alzheimer's dis- ease. FundamClinPharmacol. 2008; 22: 265-274.

33) Weksler ME. The immunotherapy of Alzheimer's disease. Im- mun Ageing. 2004; 1: 2.

34) Qureshi I, Lovegren M, Wirtz V, et al. A pharmacokinetic bio- equivalence study comparing sublingual riluzole (BHV-0223) and oral tablet formulation of riluzole in healthy volunteers. Clin Pharmacol Drug Dev. 2020;9(4):476-485. doi:10.1002/cpdd.747

35) Le Liboux A, Lefebvre P, Le Roux Y, et al. Single- and multiple- dose pharmacokinetics of riluzole in white subjects. J Clin Phar- macol. 1997;37(9):820-827. doi:10.1002/j.1552-4604.1997. tb05630.x

36) Sanderink GJ, Bournique B, Stevens J, Petry M, Martinet M. Involvement of human CYP1A isoenzymes in the metabolism and drug interactions of riluzole in vitro. J Pharmacol Exp Ther. 1997;282(3):1465-1472.

37) Malgouris C, Bardot F, Daniel M, et al. Riluzole, a novel antiglu- tamate, prevents memory loss and hippocampal neuronal dam- age in ischemic gerbils. J Neurosci. 1989;9(11):3720-3727. doi: 10.1523/JNEUROSCI.09-11-03720.1989

38) Grossman RG, Fehlings MG, Frankowski RF, et al. A prospec- tive, multicenter, phase I matched-comparison group trial of safety, pharmacokinetics, and preliminary efficacy of riluzole in patients with traumatic spinal cord injury. J Neurotrauma. 2014; 31(3):239-255. doi:10.1089/neu.2013.2969

39) Miller RG, Mitchell JD, Moore DH. Riluzole for amyotrophic lat- eral sclerosis (ALS)/motor neuron disease (MND). Cochrane Database Syst Rev. 2012;2012(3):CD001447. doi:10.1002/ 14651858.CD001447.pub3

40) Grossman RG, Fehlings MG, Frankowski RF, et al. A prospec- tive, multicenter, phase I matched-comparison group trial of safety, pharmacokinetics, and preliminary efficacy of riluzole in patients with traumatic spinal cord injury. J Neurotrauma. 2014; 31(3):239-255. doi:10.1089/neu.2013.2969

41) Grossman RG, Fehlings MG, Frankowski RF, et al. A prospec- tive, multicenter, phase I matched-

comparison group trial of safety, pharmacokinetics, and preliminary efficacy of riluzole in patients with traumatic spinal cord injury. J Neurotrauma. 2014;

31(3):239-255. doi:10.1089/neu.2013.2969

42) Stefan H, Feuerstein TJ. Novel anticonvulsant drugs. Pharmacol Ther. 2007;113(1):165-183. doi:10.1016/j.pharmthera.2006.

07.005

43) Benavides J, Camelin JC, Mitrani N, et al. 2-Amino- 6- trifluoromethoxy benzothiazole, a possible antagonist of excit- atory amino acid neurotransmission—II. Biochemical properties. Neuropharmacology. 1985;24(11):1085-1092. doi:10.1016/

0028-3908(85)90196-0