Journal of Advanced Zoology
ISSN: 0253-7214
Volume 45 Issue 2 Year 2024 Page 306-314

Aspirin Therapy In Neurological Disorder Such As Migraine And Alzhemeirs Disease

Ajith kumar K[1], Ajithkumar K[2] , Dr. Aswin Sarath.[3*]

[1,2]*Pharm.D, Department of Pharmacy Practice, J.K.K.Nattraja College of Pharmacy, Kumarapalayam – 638183.*
[3*]*Assistant Professor, Department of Pharmacy Practice, J.K.K.Nattraja College of Pharmacy, Kumarapalayam – 638183.*

***Corresponding Author**:Dr. Aswin Sarath, Pharm.D.,*
**Assistant Professor, Department of Pharmacy Practice,J.K.K.Nattraja college of Pharmacy, Kumarapalayam – 638183.Contact No. : 9496574157 Email: aswinsarath95@gmail.com*

Abstract

Aspirin, a widely used nonsteroidal anti-inflammatory medication, has a long history of therapeutic applications in pain relief, fever reduction, and inflammation management. Recent research has expanded its potential utility in treating neurological conditions such as migraines and Alzheimer's disease. For migraine management, aspirin's mechanism of action involves the suppressing the production of prostaglandins, a key factor in migraine-related inflammation and pain. Clinical trials have demonstrated its effectiveness in reducing the intensity and frequency of migraine attacks. Aspirin, especially when combined with metoclopramide, has proven to be a valuable treatment option for acute migraine episodes. In the case of Alzheimer's disease, which exhibits neurodegeneration, aspirin's anti-inflammatory and antioxidant properties have generated interest in its potential as a preventive and therapeutic agent. While epidemiological studies and biological processes have suggested aspirin's potential benefits, randomized studies have raised concerns about the risks of bleeding, outweighing the potential advantages. This review article examines the latest research on aspirin's role in managing and preventing migraines and Alzheimer's disease. It also discusses the clinical research regarding aspirin's effectiveness, safety profile, and possible side effects in these neurological conditions. Finally, the article explores the directions for future research involving aspirin in relation to migraines and Alzheimer's disease.

Keywords:- Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), migraine, Alzheimer's disease, prostaglandin synthesis, neurodegeneration.

Introduction:

An extremely well-liked nonsteroidal anti-inflammatory medications (NSAIDs), aspirin has been used to treat pain, fever, and inflammation for more than a century. Numerous studies have been conducted on the

pharmacological properties of aspirin, which have demonstrated its value in the management of a number of illnesses, including cancer, cardiovascular diseases, and neurological disorders [1]. Aspirin may be used to treat and prevent neurological conditions like migraine and Alzheimer's disease, according to recent studies.
Recurrent headaches that can linger for hours or days are an indication of the common neurologic condition known as migraine. Millions of individuals suffer from migraines, a severe illness whose pathogenesis is poorly understood. According to recent studies, aspirin may be a useful migraine treatment option. Aspirin suppresses prostaglandin production, which are essential to the inflammatory process that causes migraine-related pain and inflammation. Aspirin has demonstrated effective in lowering the intensity and frequency of migraine attacks in several clinical trials [2].
Cognitive function, memory, and behavior are all disrupted by the progressive neurodegenerative condition known as Alzheimer's disease. It is the most prevalent type of dementia and a significant public health issue. Although its specific causes are still unknown, infection and oxidative stress are thought to be important contributors to the pathogenesis of Alzheimer's disease. Anti-inflammatory and antioxidant effects of aspirin have been demonstrated, and these features may be helpful in the prevention and management of Alzheimer's disease. Aspirin use in treating Alzheimer's disease has been the subject of numerous studies, and the findings are encouraging[3-5].
We will examine the most recent research articles on aspirin's usage in the management and prevention of migraines and Alzheimer's disease in this review article. We will also go over the clinical research on aspirin's effectiveness, safety, and potential side effects in treating migraines and Alzheimer's disease. Finally, this article will discuss the directions for future aspirin research in these illnesses.

1.Aspirin:

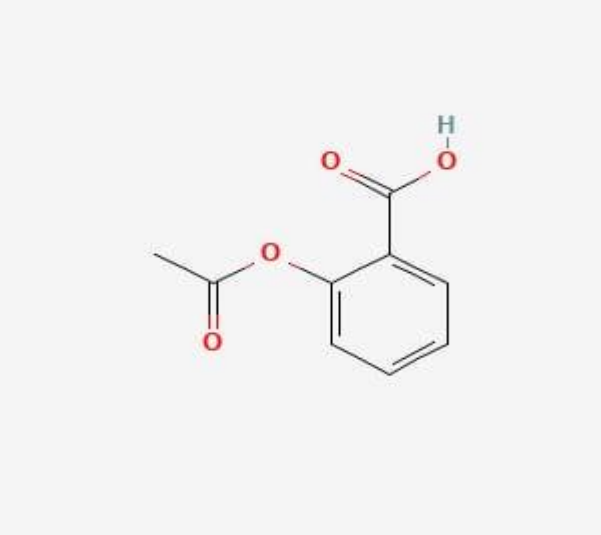


Fig 1: Chemical Structure of Aspirin[6]

The process of esterification is used to create aspirin, an ester, from salicylic acid and a compound called acetic anhydride. Aspirin's chemical structure involves the attachment of an acetyl group to the hydroxyl group located at the second position of the benzene ring in salicylic acid, which generates a carboxylic acid functional group[7].
Aspirin's molecular weight is 180.16 g/mol and the compound's molecular formula is C9H8O4. It is a white crystalline solid with a melting point of 136°C and a boiling point of 140°C. Aspirin is dissolve in chemical solvents like ethanol and acetone but only weakly soluble in water[8].
Aspirin exhibits several important pharmacological properties. It works by inhibiting the activity of cyclooxygenase (COX) enzymes, which are accountable for production of prostaglandins, thromboxane's, and other mediators of inflammation. By inhibiting COX, aspirin reduces the production of these inflammatory molecules, resulting in pain relief, fever reduction, and anti-inflammatory effects[9].
Apart from its analgesic properties, it is antipyretic, and anti-inflammatory effects, aspirin also exhibits antithrombotic properties. It functions by permanently reducing platelet cyclooxygenase activity, which reduces the synthesis of thromboxane A2, a potent platelet aggregator. This antiplatelet effect of aspirin makes it useful in the prevention of heart attacks and strokes[10].

Despite its beneficial effects, aspirin can cause several side effects, including gastrointestinal irritation, bleeding, and in rare cases, Reye's syndrome. When taking aspirin, people who have previously experienced bleeding problems or stomach ulcers should use careful[7].

1.2 Pharmacokinetics

Aspirin's absorption from the digestive system (Gastrointestional tract) is influenced by its formulation state. Compared to tablets, it is quickly absorbed when taken as a liquid preparation. Salicylic acid is produced during its hydrolysis. The therapeutic window for salicylic acid is quite small. It has the right anti-inflammatory effect if kept within that small range.

The small intestine is where aspirin absorption is pH sensitive. For the same pH range, absorption via the small intestine is greater than that through the stomach. Aspirin is more readily absorbed through the intestines than through the stomach when the pH is either 3.5 or 6.5. Aspirin is not absorbed by the stomach at pH 6.5.

By producing 2-hydroxybenzoylglycine and 2-Carboxyphenyl β-D-Glucopyranosiduronic Acid, there are two methods by which salicylate is eliminated. Urinary pH can be raised to increase the renal clearance of salicylic acid. Predicting higher urine pH, medications such as antacids can enhance renal clearance. The placental-blood barrier is not impervious to it. In breast milk, it is also expressed.

1.3 Pharmacodynamics

It is possible to achieve about 90% COX inhibition by giving 160–325 mg of acetyl salicylic acid. These results typically last seven to ten days, which is how long platelets typically last. Higher doses can be used to achieve prostacyclin inhibition. This inhibition takes place in blood vessel of endothelial cells[10].

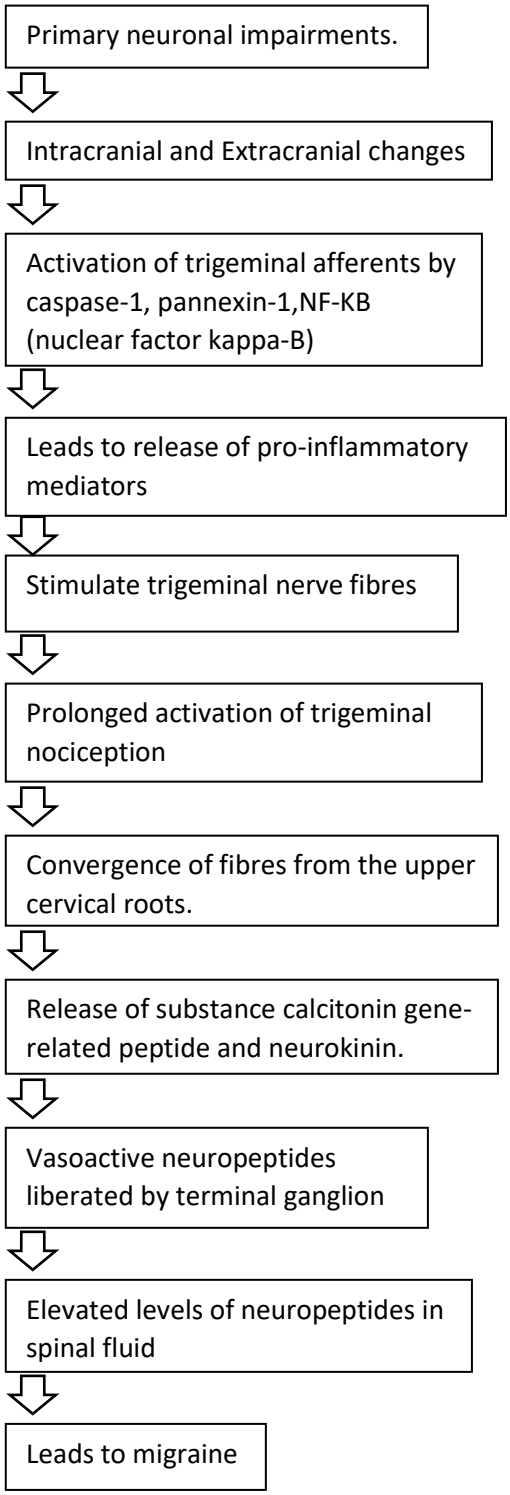
2.Migraine:

A complex disorder with genetic influences, migraine is typified by episodes of moderate-to-severe headache, usually unilateral, and is typically accompanied by nausea and increased light and sound sensitivity[11].

2.1 Pathophysiology

The past theory of migraine vascular origin states that vasoconstriction causes the aura and vasodilation causes the headache, however there is currently no evidence to support this theory[12]. According to the theories, a number of primary neuronal impairments trigger a cascade changes in the brain that occur both inside and outside the skull that cause migraines [13]. Neuronal pannexin-1 mega channel opening and caspase-1 activation trigger the release of proinflammatory mediators, activate NF-kB (nuclear factor kappa-B), and propagate this inflammatory signal to trigeminal nerve fibres surrounding piamater vessels, thereby activating trigeminal afferents[14]. This sets off a sequence of meningeal, cortical, and brainstem events that lead to inflammation in the pain-sensitive meninges and, via central and peripheral mechanisms, headaches[15-16]. Thus, this pathway can account for both the later, Trigeminal nociception sustained activation (which causes headaches) and the cortical depression that creates the aura[17].

According to theories, cortical depression in migraine without aura may happen in regions like the cerebellum where depolarization is not consciously felt[18]. The trigeminal nerve's ophthalmic division innervates the anterior structures primarily, which may account for the pain in the anterior part of the head.. There is a convergence of fibers from the upper cervical roots, which originate from trigeminal nerve neurons along with the trigeminal ganglion and the trigeminal nerve at the trigeminal nucleus caudalis, which can explain the anterior to the posterior distribution of pain, from where the fibers ascend to the thalamus and the sensory cortex[19]. Based on vasodilation, edema, and plasma protein extravasation, neurogenic inflammation results from nociceptor activation, in this case, the trigeminal system. It is linked to the release of vasoactive neuropeptides released by the trigeminal ganglion being stimulated, including substance P, calcitonin gene-related peptide, and neurokinin A[20]. The spinal fluid of patients with persistent migraines contains greater concentrations of these neuropeptides[21,22]. Sensitization, or the tendency for neurons to become more responsive to stimulation, is a process that can result from neurogenic inflammation. This explains why some clinical signs of the suffering and the shift from episodic to chronic migraines can occur[23].



2.2 Treatment

The goal of acute treatment is to halt a headache's progression. It needs to be treated right away with a big dose in one treatment. When a patient has stomach stasis brought on by a migraine, oral medications may not work. Parenteral medication may therefore be the standard for certain patients, particularly those who are experiencing nausea or vomiting[24-25]. NSAIDs (nonsteroidal anti-inflammatory drugs**):** Ibuprofen (400 to 600 mg), naproxen (275 to 825 mg), diclofenac (65 mg), aspirin (900 to 1000 mg), or acetaminophen (1000 mg)[26]. Trimethoptan (10 mg per 24 hours; nasal 2.5 to 5 mg as a single dose and oral 2.5 mg as a single dose), eletriptan, rizatriptan, and almotriptan are the first line of treatment for patients with allodynia. It is possible to inject sumatriptan subcutaneously of 6 mg, a nasal spray of 20 to 40 mg over 24 hours, a nasal powder of 10 to 30 mg over 24 hours, or orally 50 to 100 mg once. From mild to extreme attacks, they can be used with or without naproxen [27]. Antiemetics**:** Metoclopramide, chlorpromazine, or prochlorperazine. In order to reduce nausea and vomiting, they are typically used as adjunctive therapy with NSAIDs or triptans, particularly

in the emergency room. To stop dystonic reactions, diphenhydramine can also be added (mostly metoclopramide)[28].Selective serotonin 1F receptor agonist**:** In October 2019, the Food and Drug Administration in the US (FDA) authorised lasmiditan oral tablets for the adult acute treatment of migraines. Lasmiditan may be especially beneficial for people whose cardiovascular risks prevent them from taking triptans. The first dosage is either 50 or 100 mg. [29].Dexamethasone can reduce the recurrence of early headaches but does not provide immediate relief[30,31].

2.3 Effect of aspirin in migraine

In a study conducted by Ingledue VF, Mounsey A, Stevermer JJ et al, Aspirin alone or aspirin plus the antiemetic metoclopramide were used to treat a total of 5261 occurrences of mild to extreme migraine[33]. The study participants' symptoms were categorized by the International Headache Society. as migraines with or without aura, with ages ranging from 18 to 65 (mean age: 37–44)[34]. Prior to the study period, all patients had experienced migraine symptoms for an average of 12 months, with one to six attacks of mild to extreme intensity per month. In six trials (n=2027), researchers contrasted aspirin dosages of 900 and 1000 mg. By itself with a placebo for both primary outcomes, aspirin alone performed better than placebo; the number needed to treat (NNT) was 8.1 for pain-free status after two hours and 4.9 for headache relief after two hours. Aspirin was found to be superior to a placebo in three trials (n=1142) for providing headache relief for a full 24-hour period. Aspirin plus metoclopramide also outperformed placebo for primary and secondary outcomes, with NNTs of 8.8, 3.3, and 6.2 for 2-hour headache relief, 2-hour pain-free status, and 24-hour headache relief, respectively. Subgroup analysis showed that Metoclopramide plus acetyl salicylic acid was just as helpful for twenty four-hour headache relief and 2-hour pain-free status, however, for a two-hour headache remedy, it worked better than aspirin alone (P=.0131). When combined with aspirin, metoclopramide significantly reduced vomiting (P =.006) and nausea (P =.002In two trials (n = 726), aspirin by itself was comparable to sumatriptan 50 mg for achieving pain-free and headache-relieving status at two hours. In two more research studies (n = 523), aspirin plus metoclopramide and 100 mg of sumatriptan were tested and found to be equivalent for relieving headaches for two hours; however, the acetyl salicylic acid combination was not as effective as triptan for achieving a pain-free state after two hours (n = 528)[35]. The cyclo-oxygenase enzymes required for prostaglandin and thromboxane synthesis are irreversibly inhibited by aspirin. Numerous physiological processes, including the preservation of the intestinal mucosal barrier, regulation of renal blood flow, and regulation of endothelial tone, are mediated by prostaglandins. They are essential nociceptive and inflammatory process mediators. Aspirin is thought to have analgesic properties through preventing the synthesis of prostaglandins[36,37]. Adults between the ages of 18 and 65 who suffer from migraine headaches can effectively treat them with high-dose aspirin (900–1000 mg). Metoclopramide is added to minimise nausea and vomiting, although it has little to no effect on relieving pain or headaches[38]. Insufficient data were available to evaluate the efficacy of aspirin in relation to zolmitriptan, other stand-alone nonsteroidal anti-inflammatory drugs, or acetaminophen plus codeine[35].

3.Alzhemeir's disease:

In those who are sixty-five years of age or older, Alzheimer's disease (AD) accounts for at least two-thirds of dementia cases. AD is the most prevalent type of dementia. A neurodegenerative condition known as Alzheimer's disease slowly impairs behavioural and cognitive abilities such as memory, comprehension, language, attention, reasoning, and judgement[39-41].

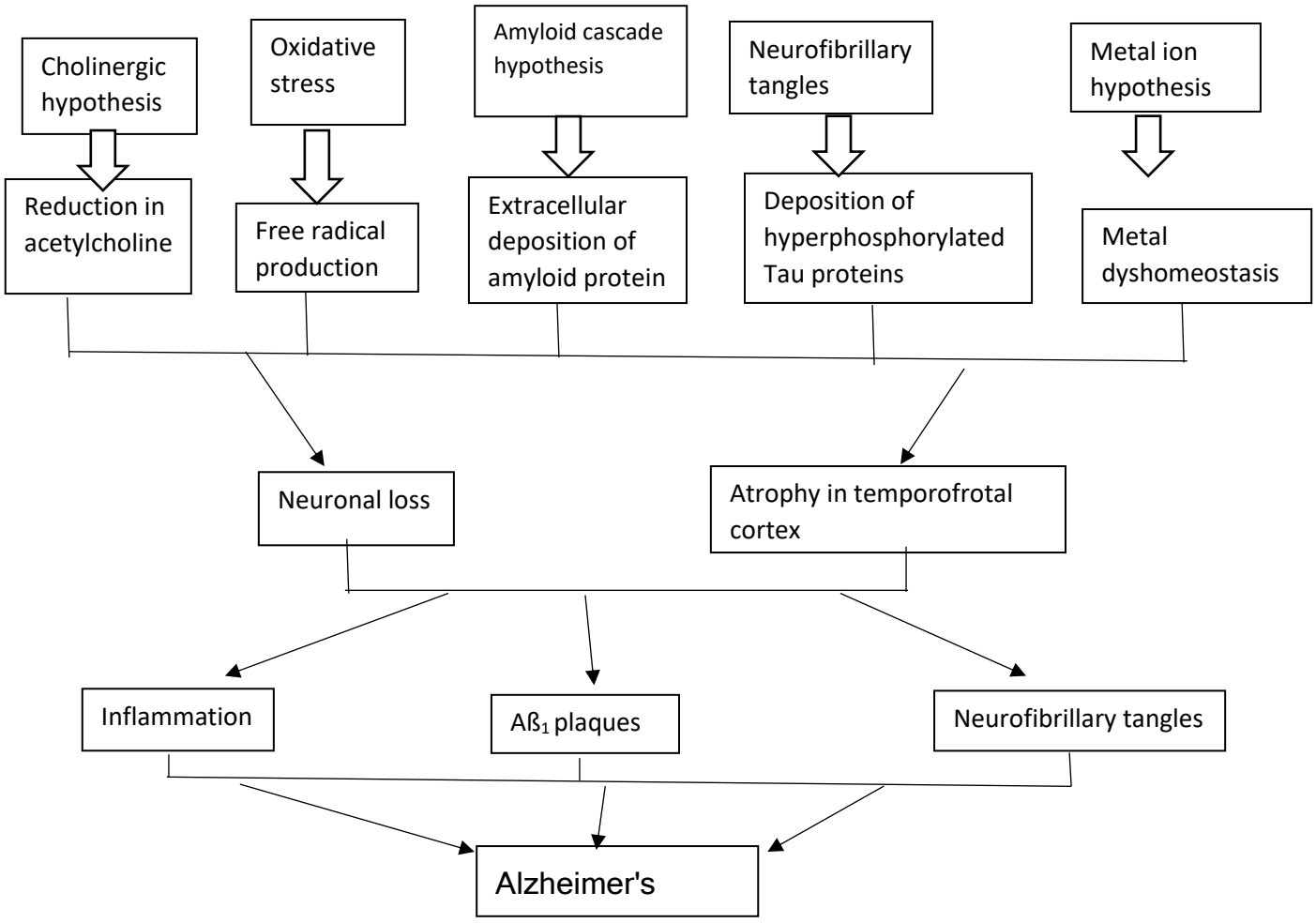
3.1 Pathophysiology

An accumulation of abnormal neurofibrillary tangles and neuritic plaques is a hallmark of Alzheimer's disease. Enlarged axonal endings encircle an extracellular amyloid beta-peptide core in spherical microscopic lesions known as plaques. The transmembrane protein called as Anti-Amyloid β (A4) Precursor Protein-Binding (APP) is the source of beta-amyloid peptide. Beta, beta, and gamma-secretase are the proteases that separate the beta-amyloid peptide from APP. Alpha-or beta-secretase can typically cleave APP, and the resulting small fragments don't harm neurons. However, 42 amino acid peptides (beta-amyloid 42) are produced by the sequential cleavage of beta and then gamma-secretase. Increased beta-amyloid 42 levels trigger amyloid aggregation, which is harmful to neurons. Aggregated fibrillary amyloid protein is preferred over normal APP degradation by beta-amyloid 42. One of the chromosomes connected to Alzheimer's disease in families is chromosome 21, which contains the APP gene. Alzheimer's disease is characterised by amyloid buildup around the meningeal, cerebral, and grey matter vessels. Multifocal grey matter deposits combine to make the

millenary structures called plaques.. In neurons, tau protein forms fibrillary intracytoplasmic structures known as neurofibrillary tangles. The stabilisation of axonal microtubules is the main job of the tau protein.

Microtubules are necessary for intracellular transport and travel along neuronal axons. Tau protein holds the assembly of microtubules together. Hyperphosphorylation of tau leads to the formation of tau aggregates in Alzheimer's disease as a result of extracellular beta-amyloid aggregation. Neurofibrillary tangles are twisted paired helical filaments that are formed by tau aggregates. They have the ability to spread from the hippocampus to other areas of the cerebral cortex. Within the neurons are deposits of tau-aggregates. The topographical staging of neurofibrillary tangles into six stages, developed by Braak and Braak, forms the basis of the Braak staging system, which is heavily relied upon by the National Institute on Ageing and Reagan Institute neuropathological criteria for the diagnosis of Alzheimer disease[41]. In severe cases, Aβ is also present in the cerebellar cortex, lower brain stem, and the whole mesencephalon. In the locus coeruleus, transentorhinal, and entorhinal regions of the brain, there is a concentration of Aβ that causes -tangle formation. It spreads to the hippocampus and neocortex at the crucial stage[42] .

Alzheimer's disease has almost complete penetrance and is inherited as an autosomal dominant disorder. There are three genes: Presenilin 1 (PSEN1) on chromosome 14, Presenilin 2 (PSEN2) on chromosome 1, and the AAP gene on chromosome 21—are mutated in the autosomal dominant form of the disease. Increased production and aggregation of beta-amyloid peptide may result from APP mutations. Because PSEN1 and PSEN2 mutations obstruct gamma-secretase processing, beta-amyloid aggregates as a result. Most cases of early-onset Alzheimer's disease and approximately 5–10% of all cases are caused through changes made to these three genes. Both familial and sporadic forms of Alzheimer disease have been linked to variations in the sortilin receptor gene, SORT1, which is necessary for moving APP (Apolipoprotein) from the cell surface to the Golgi-endoplasmic reticulum complex[41].



3.2 Treatment

Acetylcholine is a chemical that nerve cells exchange signals with one another and is necessary for cognitive functions like learning and memory. Cholinesterase inhibitors work by raising the amount of this chemical in the body. Three medications from this class have FDA clearance for the medication of Alzheimer's disease: galantamine, rivastigmine, and donepezil. Alzheimer's disease can be treated at any stage with donepezil. It is

approved to address mild cognitive decline (MCD) and dementia stages with galantamine and rivastigmine. Acetylcholinesterase is quickly and reversibly inhibited by donepezil and galantamine. Memantine, a partial NMDA antagonist, inhibits NMDA receptors and reduces the amount of calcium that builds up inside cells. The FDA has given it approval to treat moderate-to-severe Alzheimer's disease. Constipation, headaches, body aches, and dizziness are typical side effects. It is possible to take it along with cholinesterase inhibitors[43].

3.3 Effect of aspirin in alzheimer's disease

In a study conducted by Bentham P, Gray R, et al, The median age of the participants was 75 years; 156 had mild AD, 154 had moderate AD, and 18 had concurrent vascular dementia. The mean BADLS score was 062 points lower (-137 to 013; p=011) and the mean MMSE score was 010 points higher (95% CI -037 to 057; p=07) in patients who took aspirin over the three years following randomization than in individuals randomised to aspirin avoidance. Other outcome metrics showed no overt distinctions between the groups. Three (2%) of the aspirin group's patients experienced fatal cerebral bleeding, compared to two (1%) of the control group's patients, who experienced 13 (8%) hospital admission-related bleeds. Thus, the direct evidence from this randomized study reveals that the hazards outweigh any benefits[44] despite the evidence from epidemiological studies and many extremely plausible biological processes to imply that aspirin treatment might reduce the progression of AD. In none of these investigations was there a discernible cognitive improvement in the aspirin-treated group. In contrast to the aspirin avoidance group, there were significant bleedings from multiple sites (RR 7.90, 95% CI 2.43 to 25.69; Analysis 1.1), but there was no difference in the death rate (RR 1.01, 95% CI 0.70 to 1.46; Analysis 1.2) or institutionalisation rate (RR 0.93, 95% CI 0.50 to 1.74; Analysis 1.3)[45].

Conclusion:

In conclusion, aspirin, a widely used nonsteroidal anti-inflammatory medication, has shown promise in the treatment of both migraines and Alzheimer's disease. For migraines, aspirin's ability to inhibit the synthesis of prostaglandins, which contribute to the inflammatory process causing migraine-related pain, has made it an effective option in reducing the intensity and frequency of migraine attacks. It can be particularly beneficial when combined with antiemetics to manage associated symptoms like nausea.

In the case of Alzheimer's disease, while there were hopes that aspirin's anti-inflammatory and antioxidant properties potentially inhibit the disease's progression, evidence from randomized studies suggests that the risks of bleeding associated with aspirin may outweigh any potential benefits in terms of cognitive improvement or disease progression.

It's important to note that the effectiveness and safety of aspirin can vary from person to person, and these findings highlight the complexity of using aspirin as a treatment for neurological conditions. Further investigations are essential to elucidate the full extent of its benefits and risks in these complex neurological conditions.

Acknowledgement:

We would like to express our deepest gratitude to our guide, Dr. Aswin Sarath, Pharm.D., Assistant Professor, Department of Pharmacy Practice, for their invaluable guidance, unwavering support, and insightful feedback throughout the completion of this review article. Their expertise and mentorship have been instrumental in shaping our understanding of ALS treatment strategies. We would also like to extend our thanks to Dr N. Venkateshwaramurthy, M.Pharm, Ph.D., Head of the Department, and the staff members for their assistants and cooperation in providing the necessary resources and creating a conducive learning environment. Their dedication to fostering academic excellence has been truly inspiring. We are indebted to their collective efforts in making this review endeavour possible.

Reference:

1. Ong CK, Lirk P, Tan CH, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. *Clinical Medicine* & Research. 2007;5(1):19-34.
2. Schürks M, Diener HC, Goadsby P. Update on the prophylaxis of migraine. *Current Treatment Options Neurology*. 2008;10(1):20-29
3. Wang J, Tan L, Wang HF, et al. Anti-inflammatory drugs and risk of Alzheimer's disease: an updated systematic review and meta-analysis. Journal of Alzheimer's Disease. 2015;44(2):385-396

4. Rehman SU, Shah SA, Ali T, Chung JI, Kim MO. Anthocyanins Reversed D-Galactose-Induced Oxidative Stress and Neuroinflammation Mediated Cognitive Impairment in Adult Rats. *Molecular Neurobiology* 2017;54(1):255-271.
5. Ng TP, Feng L, Yap KB, et al. Long-term usage of non-steroidal anti-inflammatory drugs and risk of cognitive impairment in older women. Alzheimer's & Dementia. 2013;9(4):5312-5418
6. PubChem. Aspirin. Nih.gov. Accessed September 19, 2023.
7. Rainsford KD. Aspirin and its related analgesic and anti-inflammatory compounds. Inflammop harmacology. 2018;26(4):1109-1130.
8. Bhatt DL, Grosser T, Dong JF, et al. Aspirin's mechanisms of action and clinical application *Arteriosclerosis*, *Thrombosis*, and *Vascular Biology*. 2019;39(3):22-32.
9. Patrono C. Aspirin: new cardiovascular uses for an old drug. Am J Med. 2016;129(12):319-325.
10. Christiansen M, Grove EL, Hvas AM. Contemporary Clinical Use of Aspirin: Mechanisms of Action, Current Concepts, Unresolved Questions, and Future Perspectives, *Seminars* in *Thrombosis* and *Hemostasis*. 2021;47(7):800-814.
11. Rose FC. The history of migraine from Mesopotamian to Medieval times. *Cephalalgia*. 1995;15 Suppl 15:1-3.
12. Amin FM, Asghar MS, Hougaard A, et al. Magnetic resonance angiography of intracranial and extracranial arteries in patients with spontaneous migraine without aura: a cross-sectional study *Lancet Neurology*. 2013;12(5):454-461
13. Burstein R, Noseda R, Borsook D. Migraine: multiple processes, complex pathophysiology. The *Journal of Neuroscience*. 2015;35(17):6619-6629.
14. Karatas H, Erdener SE, Gursoy-Ozdemir Y, et al. Spreading depression triggers headache by activating neuronal Panx1 channels [published correction appears in Science. 2015 Oct 2;350(6256):aad5166] [published correction appears in Science. 2015 Nov 20;350(6263):921]. *Science*. 2013;339(6123):1092-1095.
15. Andreou AP, Edvinsson L. Mechanisms of migraine as a chronic evolutive conditione Journal of *Headache* and *Pain*. 2019;20(1):117. Published 2019 Dec 23.
16. Bolay H, Reuter U, Dunn AK, Huang Z, Boas DA, Moskowitz MA. Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model.journal of natural medicine 2002;8(2):136-142.
17. Gursoy-Ozdemir Y, Qiu J, Matsuoka N, et al. Cortical spreading depression activates and upregulates MMP-9. The Journal of Clinical Investigation. 2004;113(10):1447-1455.
18. Takano T, Nedergaard M. Deciphering migraine. *J Clin Invest*. 2009;119(1):16-19.
19. Pritlove-Carson S, Palmer RM, Morgan PR, Floyd PD. Immunohistochemical analysis of cells attached to teflon membranes following guided tissue regeneration. Journal of *Periodontology*. 1992;63(12):969-973.
20. Matsuda M, Huh Y, Ji RR. Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain. The Journal of *Anesthesia*. 2019;33(1):131-139
21. Riesco N, Cernuda-Morollón E, Pascual J. Neuropeptides as a Marker for Chronic Headache. Current Pain and Headache Reports. 2017;21(4):18
22. Anapindi KDB, Yang N, Romanova EV, et al. PACAP and Other Neuropeptide Targets Link Chronic Migraine and Opioid-induced Hyperalgesia in Mouse Models. *Molecular* and *Cellular Proteomics*. 2019;18(12):2447-2458.
23. Su M, Yu S. Chronic migraine: A process of dysmodulation and sensitizationMolecular Pain. 2018;14:1744806918767697.
24. Hsu YC, Lin KC, Taiwan Headache Society TGSOTHS. Medical Treatment Guidelines for Acute Migraine Attacks. *Acta Neurologica Taiwanica*. 2017;26(2):78-96.
25. Cameron C, Kelly S, Hsieh SC, et al. Triptans in the Acute Treatment of Migraine: A Systematic Review and Network Meta-Analysis. *Headache*. 2015;55 Suppl 4:221-235.
26. Becker WJ. Acute Migraine Treatment in Adults. *Headache*. 2015;55(6):778-793.
27. Biglione B, Gitin A, Gorelick PB, Hennekens C. Aspirin in the Treatment and Prevention of Migraine Headaches: Possible Additional Clinical Options for Primary Healthcare Providers. *American Journal* of *Medicine*. 2020;133(4):412-416.
28. Brandes JL, Kudrow D, Stark SR, et al. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. The Journal of the American Medical Association . 2007;297(13):1443-1454.
29. Dodick DW, Lipton RB, Ailani J, et al. Ubrogepant for the Treatment of MigraineThe *New England Journal of Medicine* . 2019;381(23):2230-2241.
30. Kuca B, Silberstein SD, Wietecha L, et al. Lasmiditan is an effective acute treatment for migraine: A phase 3 randomized study. *Neurology*. 2018;91(24):e2222-e2232.

31. Giamberardino MA, Affaitati G, Costantini R, Guglielmetti M, Martelletti P. Acute headache management in emergency department. A narrative review International Journal of Internal and *Emergency Medicine*2020;15(1):109-117.
32. Mirbaha S, Delavar-Kasmaei H, Erfan E. Effectiveness of the concurrent intravenous injection of dexamethasone and metoclopramide for pain management in patients with primary headaches presenting to emergency department. Adv J Emerg Med. 2017;1(1):e6.
33. Kirthi V, Derry S, Moore RA. Aspirin with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev*. 2013;(4): CD008041.
34. The international classification of headache disorders. 2nd ed.*Cephalalgia.* 2004;24(suppl1):S9-S160.
35. Ingledue VF, Mounsey A, StevermerJJ. Priority updates from the research. literature from the family Physicians inquiries network PURLs ®. Nih.gov Accessed July 25, 2023.
36. Vane 1971 . Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nature: New Biology. 1971; 231(25):232–5.
37. Volans 1974 . Volans GN. Absorption of effervescent aspirin during migraine. British Medical Journal. 1974; 4(5939):265–8. [PubMed: 4425854]
38. Buring JE, Peto R, Hennekens CH. Low-dose aspirin for migraine prophylaxis. The Journal of the American Medical Association . 1990;264(13):1711-1713.
39. Tang Y, Lutz MW, Xing Y. A systems-based model of Alzheimer's disease. *Alzheimers Dementia*. 2019;15(1):168-171.
40. Zilberzwige-Tal S, Gazit E. Go with the Flow-Microfluidics Approaches for Amyloid Research. *Asian Journal* of *Chemistry*2018;13(22):3437-3447.
41. Khoury R, Grysman N, Gold J, Patel K, Grossberg GT. The role of 5 HT6-receptor antagonists in Alzheimer's disease: an update. Expert Opinion on Investigational Drugs2018;27(6):523-533.
42. Goedert M. Alzheimer’s and Parkinson’s diseases: the prion concept in relation to assembled Aβ, tau, and α-synuclein. Science. 2015;349(6248):1255555. doi:10.1126/science.1255555
43. Yasojima K, Schwab C, McGeer EG and McGeer PL: Distri- bution of cyclooxygenase-1 and cyclooxygenase-2 mRNAs and proteins in human brain and peripheral organs. Brain Res 830, 226-236 (1999)
44. AD2000 Collaborative Group, Bentham P, Gray R, et al. Aspirin in Alzheimer’s disease (AD2000): a randomised open-label trial. *Lancet Neurol*. 2008;7(1):41-49.
45. Bentham P, Gray R, Sellwood E, Hills R, Crome P, Raftery J. Aspirin in Alzheimer’s disease (AD2000): a randomised open-label trial. *Lancet Neurology* 2008;**7**(1):41–9.