Pharmacogenomics Approaches in Alzheimer's Disease: A Comprehensive Review

Ramdas Bhat[1]*, Varshini[1], Himasvi[1], Ramakrishna Shabaraya[1]

[1]Department of Pharmacology, Srinivas College of Pharmacy, Mangalore, Karnataka, India.

ABSTRACT

Alzheimer's disease (AD) stands as an intricate neurodegenerative condition impacting numerous individuals globally. The present study aimed to comprehensively review pharmacogenomics approaches in AD. In pursuit of enhancing the efficacy and safety of AD treatments, pharmacogenomic strategies have emerged. These methods encompass the identification of genetic variations influencing drug metabolism, the utilization of genetic testing to spot individuals vulnerable to AD, and the pinpointing of potential drug targets grounded in the genetic underpinnings of the ailment. As a demonstration, differences in the genetic variations present within the CYP2D6 gene can mold the processing of donepezil extensively employed cholinesterase inhibitor crucial in the treatment of AD. Identifying these genetic nuances can potentially facilitate personalized dosing or the exploration of alternative drugs. Correspondingly, genetic tests targeting the APOE gene can unmask individuals at a heightened risk of developing AD, enabling early interventions to deter or postpone the onset of the condition. Lastly, leveraging insights into the genetic origins of the disease, pharmaceuticals targeting the beta-amyloid protein, which accumulates in the brains of AD patients, are being crafted. Collectively, pharmacogenomic approaches harbor the potential to refine AD treatment by customizing therapy according to each individual's genetic blueprint.

Key Words: *Alzheimer's disease, Pharmacogenomics, Genetic variations, Apolipoprotein E, Personalized medicine*

eIJPPR 2023; 13(4):7-13

HOW TO CITE THIS ARTICLE: Bhat R, Varshini, Himasvi, Shabaraya R. Pharmacogenomic Approaches in Alzheimer's Disease: A Comprehensive Review. Int J Pharm Phytopharmacol Res. 2023;13(4):7-13. https://doi.org/10.51847/qDMSgl63u7

INTRODUCTION

Alzheimer's disease (AD) is a substantial global health concern owing to its increasing occurrence and the constraints of available treatment alternatives [1, 2]. The intricate genetic landscape of AD has long been acknowledged as a pivotal element in its pathogenesis [3, 4]. Recent strides in the realm of pharmacogenomics have ushered in fresh avenues for delving into the unique ways individuals react to medications within the complex tapestry of this disorder [5, 6]. This section aims to provide a thorough introduction, shedding light on the multifaceted essence of AD, its genetic bedrock, and the compelling rationale for seamlessly integrating pharmacogenomic strategies into its management.

AD, a progressively degenerative affliction of the nervous system, casts a profound impact marked by the gradual erosion of cognitive faculties, dwindling memory, and perturbed behaviors, chiefly afflicting the elder populace [7]. Yet, despite intensive research, the creation of treatments that target the very roots of AD remains an elusive aspiration, with prevailing interventions merely affording temporary respite from symptoms [1]. Extensive research into the genetic aspect of AD has revealed that the Apolipoprotein E (APOE) 4 allele plays a significant role in the development of late-onset AD. This momentous revelation has fundamentally transformed our comprehension of the ailment, and subsequent investigations have unveiled additional genes of susceptibility such as triggering receptor expressed on myeloid cells 2 (TREM2), ATP-binding cassette subfamily a member 7 (ABCA7), and clusterin (CLU), further illuminating the intricate genetic architecture underpinning AD. Concurrently, the domain of pharmacogenomics has gained traction, providing a fresh lens through which to scrutinize the diversity in drug responses amongst AD patients. The convergence of genetic insights and pharmacological avenues presents a

Corresponding author: Ramdas Bhat
Address: Department of Pharmacology, Srinivas College of Pharmacy, Mangalore, Karnataka, India.
E-mail: ✉ Ramdas21@gmail.com
Received: 18 May 2023; **Revised:** 04 August 2023; **Accepted:** 07 August 2023

promising trajectory towards tailored treatment strategies, potentially untangling the complexities of varied drug responses and ultimately enhancing therapeutic outcomes. Decoding the impact of genetic variations on drug metabolism, efficacy, and unfavorable reactions holds the key to crafting interventions that suit the individual patient, heralding a new era of precision medicine for AD [8-12].

As we plunge deeper into the complexities of AD and its genetic substratum, pharmacogenomic approaches furnish a unique vantage point for unraveling the intricate interplay of genetics, drug targets, and the course of the ailment. This exposition seeks to scrutinize the present terrain of pharmacogenomic inquiry in AD, underscoring the latent potential of personalized medicine to revolutionize strategies of treatment, casting a ray of hope upon patients and their close ones.

RESULTS AND DISCUSSION

Mechanism underlying pathogenesis of AD

The development of AD arises from an imbalance in the generation and removal of amyloid-beta (A-beta) peptides. This disbalance triggers the buildup of A-beta clusters, setting off a sequence of repercussions affecting both glial cells and neurons [13, 14]. Specific A aggregates, known as A oligomers, engage receptors on neuron surfaces, impairing regular synaptic function. Simultaneously, the overall neuroinflammatory environment escalates due to astrocytes releasing pro-inflammatory agents in response to this disarray [15, 16].

Concurrently, tau, a pivotal protein in upholding neuron microtubules, undergoes abnormal chemical changes. These alterations lead to the emergence of tau oligomers and larger aggregations, disrupting synaptic communication. Additionally, brain microglia, the immune cells, internalize these anomalous tau forms. This interaction prompts microglia to produce pro-inflammatory cytokines, intensifying neuroinflammation [17].

The intricate interplay between Aβ and tau disruption forms the bedrock of AD's advancement. The breakdown of synaptic functionality, coupled with the accumulation of neurotoxic variants and ensuing neuroinflammation, contributes to the cognitive deterioration witnessed in individuals with AD.

Genetic variants associated with AD

AD shows dual variants: early-onset AD (EOAD) and late-onset AD (LOAD), contingent on the symptom debut age. Genetic factors play a substantial role in shaping the paths of both EOAD and LOAD [18]. EOAD arises from genetic changes in genes such as amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2), adhering to Mendelian inheritance guidelines. Conversely, LOAD vulnerability encompasses a collection of genes illuminated by genome-wide association studies (GWAS). While APP, PSEN1, and PSEN2 illuminate a substantial portion of EOAD narratives, LOAD's vulnerability dances to a distinct tune, one that doesn't solely adhere to Mendelian symphony. The presence of a first-degree relative affected by AD amplifies LOAD's vigilance in their kin, with monozygotic twins resonating more intensely compared to dizygotic counterparts, accentuating the genetic orchestration [19, 20]. APOE ε4, a well-recognized protagonist in the realm of risk, exerts its influence across both EOAD and LOAD [21]. Yet, within the realm of genetics' enduring legacy, AD's tapestry is also woven with non-genetic accents. This mosaic encompasses occupational nuances (pesticides, electromagnetic fields), lifestyle choices (alcohol, smoking, cognitive engagement), antecedent medical histories (head trauma, hypertension), and the interplay with metals such as aluminum, zinc, and lead [22].

The genetic architecture of LOAD spans like a constellation. APOE ε4 guides the choreography of amyloid-beta, while variants of the TREM2 gene delicately influence microglial dynamics and the clearance of toxins. ABCA7 mutations alter the processing of amyloid, and CLU gene variations direct the aggregation and dissolution of amyloid. Alongside these, susceptibility genes interweave within lipid metabolism (B1N1), the tapestry of inflammation (INPP5D), and the whispers of synaptic function (PICALM), collectively composing the mosaic of AD risk [23-26]. The amalgamation of these genetic constituents, intricately entwined with their synergies and the interplay of environmental elements, fashions the grand tableau of AD risk. It is crucial to recognize that while these genetic markers elevate the likelihood of AD, they do not definitively foretell its manifestation. Beyond genetics, a symphony of factors plays a role in the multifaceted landscape of Alzheimer's. Notably, broad genetic testing for AD risk is seldom endorsed due to the intricate and multifaceted nature of the condition, as well as the limited predictive strength of genetic assessments alone.

Pharmacogenomics in drug metabolism and efficacy for AD

Pharmacogenomics is increasingly crucial in AD treatment, introducing genetic variations that impact medication metabolism and effectiveness. Patient genetics significantly influence drug metabolism, particularly through enzymes like cytochrome P450 (CYP). Genetic variants modify enzyme activity, resulting in diverse drug metabolic kinetics, affecting medication efficacy and safety. Genetic diversity in CYP enzymes categorizes

ISSN (Online) 2249-6084 (Print) 2250-1029

individuals as extensive (EM), intermediate (IM), or poor metabolizers (PM), influencing drug journeys in the body [27, 28].

Beyond metabolism, pharmacogenomics also affects AD medication efficacy. Cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and memantine (an N-methyl-D-aspartate receptor antagonist) constitute standard treatments. However, these interventions lack universal efficacy and may lead to adverse reactions. Pharmacogenomic studies decode genetic factors influencing individual responses [29].

Genetic variations, like those in the butyrylcholinesterase (BCHE) and NMDA receptor gene (GRIN2B), impact responses to cholinesterase inhibitors and memantine. Pharmacogenomic insights empower clinicians to tailor treatments based on genetic information, optimizing outcomes while minimizing side effects. This precision medicine approach promises improved AD management [30, 31].

Pharmacogenomic products for the treatment of AD

AD treatment encompasses five FDA-approved drugs: acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine), memantine, and aducanumab. The latter, stirring controversy due to concerns about efficacy and safety, targets amyloid beta plaques [32]. Personalizing AD treatment involves a genetic panel that includes APOE4, CYP2D6, and BChEK genes. APOE4 variations amplify AD risk and modulate treatment response, CYP2D6 gene variants impact drug metabolism, while BChEK gene alterations influence acetylcholine levels, thereby influencing AD symptoms [33, 34]. This genetic understanding steers gene-focused therapies (like gantenerumab), companion diagnostics (as seen in aducanumab), BAN2401, ALZ-801, and personalized medicine paradigms, fostering more efficient and individualized AD treatment [35].

Pharmacogenomic offerings, such as ApoE4 and CYP2D6 tests, provide clinicians with tools to gauge AD risk and optimize medication choices. By integrating pharmacogenomics, AD treatment attains greater precision, potentially enhancing outcomes and curtailing side effects [36]. The realm of pharmacogenomics is ever-evolving, carrying the potential to redefine AD treatment by tailoring medication choices to individuals' genetic profiles, thus enhancing therapeutic results and mitigating unfavorable effects. Pharmacogenomics is a swiftly progressing domain, and it's conceivable that more such tests will arise for AD treatment in the future. These evaluations possess the potential to empower physicians to select the most fitting medications for individual patients, possibly leading to an enriched quality of life and a slower AD progression [37].

In conjunction with pharmacogenomic assessments, a multitude of other individualized medicine approaches are under exploration for AD treatment. For instance, researchers are crafting fresh drugs that focus on precise genetic mutations linked to AD. They're also devising novel delivery techniques for existing medications to boost their effectiveness. Personalized medicine emerges as a promising avenue for AD treatment. By considering an individual's unique genetic blueprint, physicians can decide on treatments most likely to yield efficacy while curbing side effects [38, 39]. This could translate into an ameliorated quality of life and a more gradual AD advancement for those affected [40].

Personalized treatment approaches in AD

The approach to treating AD is shifting towards personalization, driven by enhanced comprehension of its intricate nature and individualized variations [41]. This multifaceted neurodegenerative condition, characterized by cognitive decay and memory disturbances, is being tackled through a spectrum of tailored methodologies [42]. These encompass early identification and diagnosis, where precise detection at initial stages facilitates focused interventions utilizing biomarkers, genetics, and advanced imaging modalities [43, 44].

Genetic profiling assumes a pivotal role by uncovering distinct variants such as APOE ε4, aiding in risk prognosis, and guiding therapeutic determinations [45]. Personalized dosing strategies consider an individual's genetic makeup, medical history, and stage of disease, tailoring medications such as cholinesterase inhibitors and memantine to control cognitive symptoms [46]. Precision nutrition schemes, like the Mediterranean diet, are formulated to synchronize with individual dietary inclinations and needs, potentially influencing cerebral health and ailment progression [47]. Tailored lifestyle adjustments encompass bespoke plans for physical exercise, cognitive drills, social interaction, and stress alleviation, fostering the conservation of cognitive function and general wellness [48].

Personalized cognitive stimulation programs challenge and engage an individual's cognitive strengths and weaknesses, potentially reducing the rate of cognitive decline [49]. Acknowledging the indispensable role of caregivers, personalized education, and backing mitigate their burdens. Participation in pertinent clinical trials provides access to avant-garde treatments and interventions that align with an individual's profile. Adaptations to the home environment enhance safety and autonomy by introducing modifications that cater to individual requirements. Capitalizing on cutting-edge technologies such as wearable gadgets and digital applications enables personalized monitoring of cognitive and physical transformations, facilitating disease

management and intervention evaluation. Lastly, individualized psychological support and therapy tackle the emotional ramifications of AD for patients and their families [50]. These bespoke strategies collectively epitomize the evolving panorama of Alzheimer's treatment, aiming for more potent, focused, and individualized care paradigms.

Challenges and limitations of using pharmacogenomics in AD treatment

Applying pharmacogenomics to tailor treatments for AD holds intriguing potential, but it comes with intricate hurdles and multifaceted contemplations. One primary obstacle lies in the limited empirical substantiation [51]. While various pharmacogenomic investigations have been conducted in AD, the modest scale of many studies and their potential lack of universal applicability hinder the robust evidence needed to confidently shape clinical decisions [52-54].

Furthermore, the intricate complexity of AD, shaped by an interplay of genetic and environmental elements, adds a dimension of intricacy to the realm of pharmacogenomics Though pharmacogenomics furnishes valuable insights into potential medication responses, it's unable to encompass the full scope of influences that contribute to treatment outcomes. Augmenting these intricacies are practical and ethical dimensions [55]. These encompass conceivable cost and access barriers linked to pharmacogenomic testing, with concerns about insurance coverage and availability across diverse geographical locales and healthcare settings. Also, pharmacogenomics' current scope is confined to existing drugs, rendering limited guidance for emerging therapies under development. Ethical questions also come to the fore, spanning matters of privacy, potential bias, and the risk that genetic data might fuel stigmatization [56].

Steering through these multifaceted hurdles necessitates a cautious and holistic approach to incorporating pharmacogenomic testing into AD treatment strategies. It demands further research to formulate evidence-based guidelines for pragmatic implementation, all while fostering comprehensive discourse on the wider ethical and societal implications. Ensuring that patients gain a comprehensive understanding of the potential benefits and drawbacks of undergoing pharmacogenomic testing remains central within this evolving realm of tailored medical approaches [57].

Future directions and potential impact of pharmacogenomics in AD treatment

Amidst the challenges and constraints associated with pharmacogenomics in AD treatment, there is a burgeoning interest in its prospective impact. The envisioned directions and potential implications are noteworthy. Firstly, it can pave the way for targeted therapies by unraveling genetic variations that influence drug reactions, thus enabling the creation of precision treatments that surpass prevailing options in effectiveness and minimizing side effects. Moreover, the integration of pharmacogenomic data into clinical determinations holds the promise of tailored Alzheimer's treatment strategies, meticulously tailored to an individual's genetic composition [38, 58].

Furthermore, the realm of drug development stands to gain from pharmacogenomics, as it offers insights into the genetic facets steering the course of AD. This knowledge not only opens avenues for identifying novel drug targets but also for formulating treatments that outshine current therapies [59]. The far-reaching impact extends to healthcare economics, where individualized treatment plans derived from pharmacogenomics may optimize the allocation of resources, thus potentially curtailing costs. Most notably, patient outcomes could undergo a paradigm shift. The optimization of drug regimens based on intricate genetic cues has the potential to substantially elevate patient well-being and overall quality of life. Realizing this transformative potential necessitates a concerted effort in two key domains. Firstly, there's an imperative for deeper research into the intricate genetic underpinnings of drug responses, to comprehensively exploit pharmacogenomics' potential. Simultaneously, the establishment and seamless integration of evidence-backed protocols for integrating genetic insights into clinical decisions is paramount [36, 40].

Through a dedicated resolve to address these challenges, pharmacogenomics stands poised to usher in a new era in AD treatment, one characterized by enhanced efficacy, individualized approaches, and improved patient outcomes.

CONCLUSION

Pharmacogenomics offers personalized Alzheimer's treatment using genetic insights on drug response. Challenges include limited evidence, complex genetics, cost, drug options, and ethics. Yet, benefits like targeted therapies and patient outcomes are substantial. Future practice needs provider education, guidelines, and patient access to testing. Research is crucial for realizing pharmacogenomics' potential in Alzheimer's treatment.

Acknowledgments: I would like to thank Staffs and Management of Srinivas College of Pharmacy for their Support.

Conflict of interest: None

Financial support: None

Ethics statement: None

REFERENCES

[1] Yiannopoulou KG, Papageorgiou SG. Current and future treatments for Alzheimer's disease. Ther Adv Neurol Disord. 2012;6(1):19-33.
[2] Lalthanpuii K, Kaur J, Saini S, Bhatti K, Nain P. Strengthen the monitoring and reporting of adverse drug reaction at a tertiary teaching hospital. Arch Pharm Pract. 2022;13(1):61-7.
[3] Hassan F, Hatah E. A thematic analysis of non-pharmacological intervention strategies in the management of diabetic patients in Malaysia. Arch Pharm Pract. 2022;13(3):62-9.
[4] Van Cauwenberghe C, Van Broeckhoven C, Sleegers K. The genetic landscape of Alzheimer disease: clinical implications and perspectives. Genet Med. 2016;18(5):421-30.
[5] Roden DM, Wilke RA, Kroemer HK, Stein CM. Pharmacogenomics. Circulation. 2011;123(15):1661-70.
[6] AlMogbel MS. First report of escherichia coli sequence type 1193 a multidrug-resistant clone isolated in Ha'il, Saudi Arabia. Int J Pharm Res Allied Sci. 2022;11(2):24-8.
[7] DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. Mol Neurodegener. 2019;14(1):1-8.
[8] Rosenthal SL, Kamboh MI. Late-Onset Alzheimer's disease genes and the potentially implicated pathways. Curr Genet Med Rep. 2014;2(2):85-101.
[9] Walter J. The triggering receptor expressed on myeloid cells 2: a molecular link of neuroinflammation and neurodegenerative diseases. J Biol Chem. 2016;291(9):4334-41.
[10] Quan M, Cao S, Wang Q, Wang S, Jia J. Genetic phenotypes of Alzheimer's disease: mechanisms and potential therapy. Phenomics. 2023:1-7.
[11] Andrade-Guerrero J, Santiago-Balmaseda A, Jeronimo-Aguilar P, Vargas-Rodríguez I, Cadena-Suárez AR, Sánchez-Garibay C, et al. Alzheimer's disease: an updated overview of its genetics. Int J Mol Sci. 2023;24(4):3754.
[12] Liang X, Wu H, Colt M, Guo X, Pluimer B, Zeng J, et al. Microglia and its genetics in Alzheimer's disease. Curr Alzheimer Res. 2021;18(9):676-88.
[13] Murphy MP, LeVine H. Alzheimer's disease and the Amyloid-β peptide. Lovell MA, editor. J Alzheimer's Dis. 2010;19(1):311-23.
[14] Hampel H, Hardy J, Blennow K, Chen C, Perry G, Kim SH, et al. The Amyloid-β pathway in Alzheimer's disease. Mol Psychiatry. 2021;26(10):5481-503.
[15] Javanmehr N, Saleki K, Alijanizadeh P, Rezaei N. Microglia dynamics in aging-related neurobehavioral and neuroinflammatory diseases. J Neuroinflammation. 2022;19(1):1-20.
[16] Osman AS, Gad MH, Hareedy AA, Mishriki AA, Rasheed EA. Sitagliptin attenuates cognitive impairment in the rat model of Aluminum-induced Alzheimer's disease. J Adv Pharm Educ Res. 2019;9(3):53-61.
[17] Kapoor M, Chinnathambi S. TGF-β1 signalling in Alzheimer's pathology and cytoskeletal reorganization: a specialized Tau perspective. J Neuroinflammation. 2023;20(1):72.
[18] Bekris LM, Yu CE, Bird TD, Tsuang DW. Review article: genetics of Alzheimer disease. J Geriat Psychiatry Neurol. 2010;23(4):213-27.
[19] Lanoiselée HM, Nicolas G, Wallon D, Rovelet-Lecrux A, Lacour M, Rousseau S, et al. APP, PSEN1, and PSEN2 mutations in early-onset Alzheimer disease: a genetic screening study of familial and sporadic cases. Miller BL, editor. PLOS Med. 2017;14(3):e1002270.
[20] Giri M, Lü Y, Zhang M. Genes associated with Alzheimer's disease: an overview and current status. Clin Interv Aging. 2016;11:665-81.
[21] M Di Battista A, M Heinsinger N, William Rebeck G. Alzheimer's disease genetic risk factor APOE-ε4 also affects normal brain function. Curr Alzheimer Res. 2016;13(11):1200-7.
[22] Jiang T, Yu JT, Tian Y, Tan L. Epidemiology and etiology of Alzheimer's disease: from genetic to non-genetic factors. Curr Alzheimer Res. 2013;10(8):852-67.
[23] Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat Rev Neurol. 2013;9(2):106-18.
[24] Deming Y, Li Z, Benitez BA, Cruchaga C. Triggering receptor expressed on myeloid cells 2 (TREM2): a potential therapeutic target for Alzheimer disease? Expert Opin Ther Targets. 2018;22(7):587-98.
[25] Foster EM, Dangla-Valls A, Lovestone S, Ribe EM, Buckley NJ. Clusterin in Alzheimer's disease: mechanisms, genetics, and lessons from other pathologies. Front Neurosci. 2019;13:164.
[26] Karch CM, Goate AM. Alzheimer's disease risk genes and mechanisms of disease pathogenesis. Biol Psychiatry. 2015;77(1):43-51.
[27] Cacabelos R. Pharmacogenomics in Alzheimer's disease. Pharmacogenomics Drug Discov Dev. 2008;448:213-357.
[28] Ahmed S, Zhou Z, Zhou J, Chen SQ. Pharmacogenomics of drug metabolizing enzymes

and transporters: relevance to precision medicine. Genom Proteom Bioinform. 2016;14(5):298-313.
[29] Li DD, Zhang YH, Zhang W, Zhao P. Meta-analysis of randomized controlled trials on the efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease. Front Neurosci. 2019;13:472.
[30] Lockridge O, Norgren RB, Johnson RC, Blake TA. Naturally occurring genetic variants of human acetylcholinesterase and butyrylcholinesterase and their potential impact on the risk of toxicity from cholinesterase inhibitors. Chem Res Toxicol. 2016;29(9):1381-92.
[31] Andreoli V, De Marco EV, Trecroci F, Cittadella R, Di Palma G, Gambardella A. Potential involvement of GRIN2B encoding the NMDA receptor subunit NR2B in the spectrum of Alzheimer's disease. J Neural Transm. 2014;121:533-42.
[32] Alhazmi HA, Albratty M. An update on the novel and approved drugs for Alzheimer disease. Saudi Pharm J. 2022;30(12):1755-64.
[33] Cacabelos R, Martínez R, Fernández-Novoa L, Carril JC, Lombardi V, Carrera I, et al. Genomics of dementia: APOE- and CYP2D6-related pharmacogenetics. Int J Alzheimer's Dis. 2012;2012:1-37.
[34] Wang J. Butyrylcholinesterase K Variant and Alzheimer's disease risk: a meta-analysis. Med Sci Monit. 2015;21:1408-13.
[35] Tolar M, Abushakra S, Hey JA, Porsteinsson A, Sabbagh M. Aducanumab, gantenerumab, BAN2401, and ALZ-801—the first wave of amyloid-targeting drugs for Alzheimer's disease with potential for near term approval. Alzheimer's Res Ther. 2020;12(1):95.
[36] Ventola CL. Pharmacogenomics in clinical practice: reality and expectations. Pharm Ther. 2011;36(7):412.
[37] Aneesh TP, Sekhar S, Jose A, Chandran L, Zachariah SM. Pharmacogenomics: the right drug to the right person. J Clin Med Res. 2009;1(4):191.
[38] Beera AM, Seethamraju SM, Nori LP. Alzheimer's disease: perspective on therapeutic options and recent hallmarks in clinical research. Int J Pharm Res Allied Sci. 2021;10(4):110-20.
[39] Raevskaya AI, Belyalova AA, Shevchenko PP, Karpov SM, Mishvelov AE, Simonov AN, et al. Cognitive impairments in a range of somatic diseases. diagnostics, modern approach to therapy. Pharmacophore. 2020;11(1):136-41.
[40] Crews KR, Hicks JK, Pui CH, Relling MV, Evans WE. Pharmacogenomics and individualized medicine: translating science into practice. Clin Pharmacol Ther. 2012;92(4):467-75.
[41] Svob Strac D, Konjevod M, Sagud M, Nikolac Perkovic M, Nedic Erjavec G, Vuic B, et al. Personalizing the care and treatment of Alzheimer's disease: an overview. Pharmacogenomics Pers Med. 2021;14:631-53.
[42] Vrahatis AG, Skolariki K, Krokidis MG, Lazaros K, Exarchos TP, Vlamos P. Revolutionizing the early detection of Alzheimer's disease through non-invasive biomarkers: the role of artificial intelligence and deep learning. Sensors. 2023;23(9):4184.
[43] Hampel H, Au R, Mattke S, van der Flier WM, Aisen P, Apostolova L, et al. Designing the next-generation clinical care pathway for Alzheimer's disease. Nat Aging. 2022;2(8):692-703.
[44] Nisar S, Haris M. Neuroimaging genetics approaches to identify new biomarkers for the early diagnosis of autism spectrum disorder. Mol Psychiatry. 2023:1-4.
[45] Raulin AC, Doss SV, Trottier ZA, Ikezu TC, Bu G, Liu CC. ApoE in Alzheimer's disease: pathophysiology and therapeutic strategies. Mol Neurodegener. 2022;17(1):1-26.
[46] Rountree SD, Chan W, Pavlik VN, Darby EJ, Siddiqui S, Doody RS. Persistent treatment with cholinesterase inhibitors and/or memantine slows clinical progression of Alzheimer disease. Alzheimer's Res Ther. 2009;1(2):7.
[47] de Toro-Martín J, Arsenault BJ, Després JP, Vohl MC. Precision nutrition: a review of personalized nutritional approaches for the prevention and management of metabolic syndrome. Nutrients. 2017;9(8):913.
[48] Küster OC, Fissler P, Laptinskaya D, Thurm F, Scharpf A, Woll A, et al. Cognitive change is more positively associated with an active lifestyle than with training interventions in older adults at risk of dementia: a controlled interventional clinical trial. BMC Psychiatry. 2016;16(1):1-2.
[49] Irazoki E, Contreras-Somoza LM, Toribio-Guzmán JM, Jenaro-Río C, van der Roest H, Franco-Martín MA. Technologies for cognitive training and cognitive rehabilitation for people with mild cognitive impairment and dementia. a systematic review. Front Psychol. 2020;11:648.
[50] Chaudhuri JD, Das S. The role of caregivers in the management of Alzheimer's disease: examples from Asian Countries. Sultan Qaboos Univ Med J. 2006;6(2):11.
[51] Argueta N, Notari E, Szigeti K. Role of pharmacogenomics in individualizing treatment for Alzheimer's disease. CNS Drugs. 2022;36(4):365-76.

[52] Cacabelos R, Fernández-Novoa L, Martínez-Bouza R, McKay A, Carril JC, Lombardi V, et al. Future trends in the pharmacogenomics of brain disorders and dementia: influence of APOE and CYP2D6 variants. Pharmaceuticals. 2010;3(10):3040-100.

[53] Zúñiga Santamaría T, Yescas Gómez P, Fricke Galindo I, González González M, Ortega Vázquez A, López López M. Pharmacogenetic studies in Alzheimer disease. Neurología (English Edition). 2022;37(4):287-303.

[54] Cacabelos R. Donepezil in Alzheimer's disease: from conventional trials to pharmacogenetics. Neuropsychiatr Dis Treat. 2007;3(3):303-33.

[55] Cacabelos R, Torrellas C, Carrera I. Opportunities in pharmacogenomics for the treatment of Alzheimer's disease. Future Neurol. 2015;10(3):229-52.

[56] Virelli CR, Mohiuddin AG, Kennedy JL. Barriers to clinical adoption of pharmacogenomic testing in psychiatry: a critical analysis. Transl Psychiatry. 2021;11(1):509.

[57] Shineman DW, Basi GS, Bizon JL, Colton CA, Greenberg BD, Hollister BA, et al. Accelerating drug discovery for Alzheimer's disease: best practices for preclinical animal studies. Alzheimer's Res Ther. 2011;3(5):28.

[58] Frozza RL, Lourenco MV, De Felice FG. Challenges for Alzheimer's disease therapy: insights from novel mechanisms beyond memory defects. Front Neurosci. 2018;12:37.

[59] van Bokhoven P, de Wilde A, Vermunt L, Leferink PS, Heetveld S, Cummings J, et al. The Alzheimer's disease drug development landscape. Alzheimer's Res Ther. 2021;13(1):186.

ISSN (Online) 2249-6084 (Print) 2250-1029