Society of Medical Education & Research

2024, Volume 4, Issue 1, Page No: 15-21
ISSN: 3108-4826

Journal of Medical Sciences and Interdisciplinary Research

Pharmacogenomic Strategies in Alzheimer's Disease: An In-Depth Review

Yalan Zhou[1], Siqi Peng[1], Huizhen Wang[1], Xinyin Cai[2*], Qingzhong Wang[1]

[1]Institute of Chinese Materia Medica, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China.
[2]Shanghai R&D Centre for Standardization of Chinese Medicines, Shanghai 202103, China.

***E-mail** ✉ caixinyin117@163.com

Abstract

Alzheimer's disease (AD) is a complex neurodegenerative disorder that affects millions worldwide. This review aims to investigate the role of pharmacogenomics in the treatment of AD. Pharmacogenomic strategies aim to improve the efficacy and safety of treatments by identifying genetic factors that influence drug metabolism. These approaches include genetic testing to identify individuals at higher risk for AD and discovering new drug targets based on the genetic causes of the disease. For example, genetic variations in the CYP2D6 gene can significantly affect the metabolism of donepezil, a commonly used cholinesterase inhibitor in AD treatment. Recognizing these genetic differences could lead to personalized drug dosing or the selection of alternative medications. In addition, genetic testing of the APOE gene can identify individuals at higher risk of developing AD, allowing for earlier interventions that may delay or prevent disease onset. Furthermore, research into the genetic basis of AD is driving the development of drugs targeting beta-amyloid, a protein that accumulates in the brains of AD patients. In sum, pharmacogenomic approaches have the potential to revolutionize AD treatment by tailoring treatments to the unique genetic profiles of patients.

Keywords: Personalized medicine, Alzheimer's disease, Genetic variations, Pharmacogenomics, Apolipoprotein E

Introduction

Alzheimer's disease (AD) has become a critical global health challenge due to its rising prevalence and the limitations of current therapeutic options [1, 2]. The genetic complexity of AD has long been recognized as a key factor in its development [3, 4]. Recent advancements in pharmacogenomics have opened new doors to understanding how individuals with AD uniquely respond to treatments within the context of this complex disorder [5, 6]. This section provides an in-depth overview, highlighting the multifaceted nature of AD, its genetic foundation, and the compelling case for integrating pharmacogenomic strategies into its management.

AD, a progressive neurodegenerative disorder, leads to the gradual decline of cognitive functions, memory loss, and behavioral changes, predominantly affecting the elderly [7]. Despite significant research efforts, the development of treatments targeting the underlying causes of AD remains a challenging goal, with current therapies providing only temporary relief from symptoms [1]. Investigations into the genetic factors contributing to AD have highlighted the role of the Apolipoprotein E (APOE) 4 allele in the onset of late-onset AD. This key finding has reshaped our understanding of the disease, prompting further exploration of other susceptibility genes, such as triggering receptor expressed on myeloid cells 2 (TREM2), ATP-binding cassette subfamily A member 7 (ABCA7), and clusterin (CLU), which have further illuminated the complex genetic framework of AD. Alongside this, pharmacogenomics has gained prominence, offering new insights into how genetic

Access this article online https://smerpub.com/

Received: 18 December 2023; **Accepted:** 04 March 2024

How to cite this article: Zhou Y, Peng S, Wang H, Cai X, Wang Q. Pharmacogenomic Strategies in Alzheimer's Disease: An In-Depth Review. J Med Sci Interdiscip Res. 2024;4(1):15-21. https://doi.org/10.51847/q8JX01Pn0m

variations influence drug responses in AD patients. The integration of genetic data with pharmacological research holds great promise for developing personalized treatment approaches, potentially addressing the challenges posed by diverse drug responses and ultimately improving patient outcomes. Understanding the effects of genetic variations on drug metabolism, effectiveness, and adverse reactions is crucial for creating individualized therapies, marking a step forward toward precision medicine in AD treatment [8-12].

As research into AD and its genetic foundations progresses, pharmacogenomic approaches offer a unique perspective on the complex interactions between genetics, drug targets, and disease progression. This review explores the current landscape of pharmacogenomic research in AD, emphasizing the potential of personalized medicine to transform treatment strategies and bring new hope to patients and their families.

Results and Discussion

Mechanism of Alzheimer's disease pathogenesis

Alzheimer's disease (AD) develops due to an imbalance in amyloid-beta (A-beta) peptide production and clearance, leading to the accumulation of these peptides, which form clusters that disrupt both neurons and glial cells [13, 14]. These amyloid aggregates, especially the oligomeric forms, bind to receptors on neuronal surfaces, hindering normal synaptic function. Additionally, neuroinflammation intensifies as astrocytes release inflammatory mediators in response to this disruption [15, 16].

At the same time, tau proteins, which help stabilize microtubules in neurons, undergo abnormal modifications, resulting in tau oligomers and larger aggregates. These altered tau structures interfere with synaptic communication. Microglial cells, which are part of the brain's immune response, engulf these aberrant tau formations, prompting them to release pro-inflammatory cytokines, further amplifying neuroinflammation [17].

The interaction between amyloid-beta and tau proteins underpins the progression of AD, with the breakdown in synaptic function and the accumulation of neurotoxic variants contributing to the cognitive decline observed in patients.

Genetic variants in Alzheimer's disease

Alzheimer's disease presents in two forms: early-onset AD (EOAD) and late-onset AD (LOAD), based on the age of onset. Genetics significantly influence both forms of AD [18]. EOAD is typically associated with mutations in genes like amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2), which follow Mendelian inheritance patterns. LOAD, however, involves multiple genetic factors revealed through genome-wide association studies (GWAS), and these do not strictly adhere to Mendelian principles. Having a first-degree relative with AD increases the risk of developing LOAD, with monozygotic twins showing a higher concordance rate than dizygotic twins, indicating the genetic influence on the disease [19, 20].

The APOE ε4 allele is a well-known genetic risk factor for both EOAD and LOAD [21]. However, AD's genetic landscape is further shaped by non-genetic factors such as occupational exposures (e.g., pesticides, electromagnetic fields), lifestyle choices (e.g., alcohol use, smoking, cognitive engagement), and environmental elements like metal exposure (e.g., aluminum, zinc, lead) [22].

In LOAD, several genetic factors contribute to the disease's development, including APOE ε4, which affects amyloid-beta processing, and mutations in TREM2, ABCA7, and CLU, which influence microglial function and amyloid processing. Additional genes related to lipid metabolism (B1N1), inflammation (INPP5D), and synaptic function (PICALM) further contribute to the disease risk [23-26]. Although these genetic markers increase the likelihood of developing AD, they do not guarantee it. Given the multifactorial nature of AD, broad genetic testing is not widely recommended due to its limited predictive value.

Pharmacogenomics in Alzheimer's disease drug metabolism and efficacy

Pharmacogenomics plays an increasing role in the treatment of AD, highlighting genetic variations that affect drug metabolism and efficacy. Patient genetics, particularly variations in cytochrome P450 (CYP) enzymes, significantly influence how drugs are processed in the body. These genetic differences classify individuals as extensive (EM), intermediate (IM), or poor metabolizers (PM), affecting the pharmacokinetics of AD medications [27, 28].

In addition to drug metabolism, pharmacogenomics also impacts the effectiveness of standard AD treatments. Cholinesterase inhibitors like donepezil, rivastigmine,

and galantamine, as well as memantine, an NMDA receptor antagonist, are commonly used, but their efficacy varies among patients, and adverse effects may occur. Genetic research has helped identify variants in genes such as butyrylcholinesterase (BCHE) and the NMDA receptor gene (GRIN2B) that influence patients' responses to these drugs [29].

Pharmacogenomic insights enable healthcare providers to tailor AD treatments based on a patient's genetic profile, improving therapeutic outcomes while minimizing side effects. This precision medicine approach offers the potential to revolutionize AD management [30, 31].

Pharmacogenomic products in Alzheimer's disease treatment

The treatment landscape for Alzheimer's disease (AD) includes five drugs approved by the FDA: donepezil, galantamine, rivastigmine, memantine, and aducanumab. Among these, aducanumab has sparked debate due to concerns surrounding its efficacy and safety, with its mechanism targeting amyloid-beta plaques [32]. A key advancement in AD treatment is personalizing therapies based on genetic insights. Crucial genes like APOE4, CYP2D6, and BChEK are integral to this process. Variants in APOE4 elevate the likelihood of AD and influence the response to treatment, while changes in CYP2D6 affect how drugs are processed in the body, and alterations in BChEK can impact acetylcholine levels, which are central to symptom severity [33, 34]. This genetic knowledge is paving the way for gene-focused treatments such as gantenerumab, as well as companion diagnostics like those used for aducanumab, and other promising therapies like BAN2401 and ALZ-801, all of which aim to provide more personalized and effective care for AD patients [35].

Tools for genetic testing, including assessments for APOE4 and CYP2D6, empower healthcare providers to better assess the risk of AD and make informed decisions about treatment options. By incorporating pharmacogenomics, the management of AD can be greatly refined, offering not just more precise drug selection but also fewer side effects [36]. The field of pharmacogenomics is rapidly evolving, and it is anticipated that even more tests will emerge in the future. These innovations hold the potential to help clinicians choose the most appropriate medications, ultimately leading to improved quality of life and slower disease progression in AD patients [37].

Alongside pharmacogenomic evaluations, research is underway to develop new drugs that target specific genetic mutations associated with AD. Additionally, novel drug delivery methods are being explored to maximize the effectiveness of existing treatments. The concept of personalized medicine is becoming increasingly relevant in the context of AD, as it allows for treatment plans to be tailored to a patient's genetic profile, improving the likelihood of treatment success while minimizing negative side effects [38, 39]. These approaches aim to enhance patients' quality of life and slow the course of the disease [40].

Personalized treatment approaches in Alzheimer's disease

The treatment approach for Alzheimer's disease is progressively shifting toward personalization, reflecting a deeper understanding of the disease's complexity and individual variability among patients [41]. This neurodegenerative disorder, characterized by gradual cognitive decline and memory impairments, is now being approached through a variety of personalized strategies [42]. Early detection and diagnosis play a pivotal role in this approach, as recognizing the disease in its nascent stages allows for targeted interventions. These interventions may involve the use of biomarkers, genetic tests, and advanced imaging techniques to facilitate precise and timely treatment [43, 44].

Genetic profiling has become a cornerstone in assessing individual risks, identifying variants such as APOE ε4, which help in forecasting the disease's onset and guiding treatment decisions [45]. Personalized treatment plans take into account the patient's genetic profile, disease progression, and medical history. Medications, such as cholinesterase inhibitors and memantine, are tailored to meet the specific needs of the patient to better manage cognitive symptoms [46]. Precision nutrition, for example, adopting diets like the Mediterranean model, is another facet of personalized care that may influence brain health and disease progression [47]. Furthermore, personalized lifestyle modifications are being developed to improve physical activity, cognitive engagement, social interaction, and stress management, all of which contribute to maintaining cognitive function and overall well-being [48].

Tailored cognitive stimulation programs are designed to challenge and enhance cognitive abilities, potentially slowing the progression of memory loss [49]. In addition to these treatment approaches, caregivers also benefit

from personalized support, education, and guidance to manage the demands of caring for someone with AD. Participation in clinical trials offers access to innovative treatments and therapies that align with a patient's unique characteristics. Modifications to the home environment are also being made to enhance safety and independence, while cutting-edge technologies, such as wearable devices and mobile applications, are being used for continuous monitoring of the patient's condition. Finally, providing individualized psychological support helps address the emotional challenges faced by both patients and their families, creating a holistic care environment [50].

These personalized strategies represent the evolving landscape of AD treatment, aiming for more precise, effective, and tailored care for each individual.

Challenges and limitations of pharmacogenomics in Alzheimer's disease treatment

While pharmacogenomics holds promising potential in customizing AD treatments, it is accompanied by a range of complex challenges and considerations. A significant barrier is the limited empirical evidence supporting its widespread application [51]. Although pharmacogenomic studies in AD are growing, many of these are small in scale, and their findings may not be universally applicable, thus preventing the development of strong, conclusive data that could guide clinical decisions confidently [52-54].

Moreover, AD's intricate nature, shaped by both genetic and environmental factors, adds another layer of complexity to pharmacogenomics. Although pharmacogenomics offers insights into how individuals may respond to certain treatments, it doesn't account for the full spectrum of factors that influence treatment outcomes. Additionally, there are practical and ethical concerns to address [55]. These include issues related to the cost and accessibility of pharmacogenomic testing, as well as potential challenges in insurance coverage and disparities in availability across different healthcare systems and regions. Furthermore, the current scope of pharmacogenomics is limited to existing medications, providing little guidance for new drugs that are still in development. Ethical issues, such as privacy concerns, the potential for bias, and the risk of genetic data leading to stigmatization, also warrant significant attention [56].

Overcoming these diverse challenges requires a balanced and comprehensive approach to incorporating pharmacogenomic testing in AD treatments. Continued research is needed to develop evidence-based guidelines for practical application, alongside a broader societal and ethical dialogue on the implications of these advanced testing strategies. A key focus will be ensuring that patients fully understand both the benefits and limitations of pharmacogenomic testing as part of a more personalized healthcare approach [57].

Future directions and potential impact of pharmacogenomics in Alzheimer's disease treatment

Despite the obstacles associated with pharmacogenomics in AD, the field holds significant potential for future advancements. One of the most promising aspects is the ability to identify genetic variations that influence drug responses, paving the way for precision therapies that are more effective and cause fewer side effects. By integrating pharmacogenomic data into clinical decision-making, it will be possible to design AD treatment plans that are specifically tailored to each patient's genetic profile, offering more targeted interventions [38, 58].

Pharmacogenomics also promises to revolutionize drug development by providing deeper insights into the genetic components that drive AD. This could lead to the identification of novel drug targets and the development of treatments that surpass current therapies in both efficacy and safety [59]. In terms of healthcare economics, pharmacogenomics has the potential to optimize the allocation of resources by enabling the creation of individualized treatment regimens that reduce unnecessary treatments and healthcare costs. Most importantly, this approach could lead to significant improvements in patient outcomes. By fine-tuning drug therapies according to a patient's unique genetic makeup, the potential to enhance patient well-being and overall quality of life is substantial.

Realizing these potential benefits will require focused efforts in two main areas: first, advancing research to deepen our understanding of the genetic foundations of drug responses, and second, creating and integrating evidence-based guidelines that incorporate pharmacogenomic insights into routine clinical practices [36, 40]. With these steps, pharmacogenomics can transform AD treatment, ushering in an era of more effective, individualized care that improves the overall patient experience.

Conclusion

Pharmacogenomics holds promise for tailoring Alzheimer's disease treatment by leveraging genetic data to optimize drug responses. Although its integration into routine care faces hurdles such as insufficient clinical validation, genetic complexity, high costs, limited pharmacological alternatives, and ethical considerations, the potential advantages—including improved therapeutic precision and enhanced patient outcomes—are considerable. Advancing this field requires concerted efforts in educating healthcare providers, establishing standardized clinical protocols, and ensuring equitable access to genetic testing. Ongoing research remains essential to fully harness the capabilities of pharmacogenomics in Alzheimer's management.

Acknowledgments: I express my gratitude to the staff and management of Srinivas College of Pharmacy for their continuous 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, ed. 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, ed. 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.