**Molecular Medicine Communications**
DOI: 10.12345/mmc.001.01.0019

**Review Article**

**Alzheimer’s disease therapy and effects of genetic polymorphisms on its efficacy and safety**

Halima Usman¹, Amama Ghaffar²,³

¹Shifa College of Pharmaceutical Sciences, Shifa Tameer-e-Millat University Islamabad.
²Centre of Excellence in Molecular Biology, University of the Punjab, Lahore.
³University of Maryland, School of Medicine, Baltimore.

*Correspondence: halima.scps@stmu.edu.pk

© The Author(s) 2021. This article is licensed under a Creative Commons Attribution 4.0 International License. To view a copy of this license, visit [http://creativecommons.org/licenses/by/4.0/](http://creativecommons.org/licenses/by/4.0/).

**Abstract**

Alzheimer’s disease (AD) continues to be a significant health burden worldwide as the global population is getting older and health care costs are escalating. AD is a heterogeneous condition having diverse phenotypes and genotypes, which is a major challenge in understanding disease etiopathogenesis. The difficulty in understanding the intricacies of the disease has led to recurrent failure of therapeutic agents in clinical trials resulting in an extremely slow and low success in the new drug discovery process for the AD. Currently approved agents for AD therapy are acetyl cholinesterase inhibitors (AchEIs) (donepezil, galantamine and rivastigmine) and n-methyl d-aspartate (NMDA) antagonist (memantine) that provide symptomatic relief only. However, extensive inter-individual variability in drug responsiveness is observed. ‘Pharmacogenomics’ which refers to how the genome of a patient might affect the treatment response to a drug, appears to play an important role in this inter-individual variability. By bringing pharmacogenomics profile of patients on AD therapy into consideration, it might be possible to gain maximum benefits from available treatments in terms of safety, therapeutic optimization and minimizing adverse effects. The purpose of this review is to provide better understanding of AD pathogenesis, challenges of current AD therapy and insight into the role of genetic polymorphism in drug response with focus on available therapeutic options in AD.

**Keywords:** Alzheimer’s disease; gene polymorphism; pharmacogenetics, pharmacogenomics

**Introduction**

Dementia is one of the leading causes of disability in elderly population and represents an emerging health crisis worldwide. AD is the most prevailing disease among all dementias (60-85% of all cases) affecting almost 47 million people globally as per World Health Organization. Presence of extracellular senile plaques composed of amyloid beta (Aβ) aggregates and neurofibrillary tangles (NFTs) of hyper phosphorylated tau protein (Nebel et al. 2018) followed by dystrophic neurites, oxidative stress, reactive microgliosis and neuronal as well as synaptic loss (Reitz, Brayne, and Mayeux 2011) are the salient features of AD. However, the fundamental mechanisms of these pathologies are still ambiguous. Atrophy of specific brain regions is observed through imaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET), especially in hippocampus (Desikan et al. 2009). The likelihood of disease occurrence is high among people over the age of 65 years and this risk roughly doubles approximately every 5 years after that (Hossain et al. 2019). Early pathogenesis of AD remain unnoticeable in affected persons for a decade or more until the characteristic symptoms of cognitive impairment becomes conspicuous (2020). Initially AD manifests as short-term memory deficits that subsequently progresses to spatial and declarative memory disabilities. As the disease
AD may manifest itself as either familial or sporadic form of dementia; the latter is more prevalent. Sporadic AD (SAD) (DeMattos et al.) or late onset AD, develops in large number of population after 65 years or more, (2020) is a multifaceted disorder having genetic and environmental elements involved in the pathogenesis and progression of the disease (Barber 2012, Chakrabarti et al. 2015). Conversely, the early onset or familial AD (FAD) manifests at comparatively younger age and accompanied by mutations in certain genes such as presenilin 1 (PSEN1), presenilin 2 (PSEN2) and amyloid precursor protein (APP) (Orlowski et al.) (Chakrabarti et al. 2015). However, there are no major differences in clinical symptoms associated with FAD and SAD (Zhang et al. 2014).

According to WHO, around 35.6 million people globally were suffering from dementia in 2010. As the developed and developing nations are rapidly aging, this statistic is anticipated to double after 20 years, expected to reach 65.7 million by 2030 and approximately 115.4 million by 2050 (Maia and Sousa 2019). The worldwide cost of AD burden is predicted to be increased from 1 trillion in 2018 to 2 trillion in 2030 (Cummings, Lee, et al. 2021). Complete knowledge and comprehension of complex mechanisms involved in AD pathophysiology are still elusive, although the disease was discovered more than a century ago (Reitz, Brayne, and Mayeux 2011). Current AD research is focused to identify key factors involved in AD pathogenesis and to discover the potential treatments. To date, the available therapeutic options for AD attempt to slow disease progression and delay the development of clinical symptoms. However, their efficacy can be unpredictable and they show variable improvement in cognitive decline (Yiannopoulou and Papageorgiou 2020b). New therapies scrutinized in preclinical studies failed to show predictive success in humans in terms of efficacy and are associated with undesirable side effects profile (Winslow et al. 2011). Moreover, extensive variation in efficacy of these drugs is observed among different individuals, leading to failure of therapy and increased financial burden of adverse effects management. The variations found in the outcomes of these therapies may be attributed to genetic polymorphisms among the individuals (Sumirtanurdin et al. 2019, Reitz 2016). This review aims to compile and discuss the possible correlation between current available treatment options for AD and their response based on genetic variations.

Pathogenesis of AD

Due to extreme complexity of human brain and lack of effective experimental models, we have an incomplete understanding of AD pathogenesis and, therefore, a therapy that could prevent and/or treat it still seems far away. Several hypotheses have been developed to explain the possible mechanisms involved in AD pathogenesis. Here we review some of the most well established ones (Figure 1) which have garnered significant attention of scientific community (Liu, Xie, et al. 2019).

Cholinergic hypothesis

Peter Davies and A.J.F Maloney first postulated the cholinergic hypothesis in 1976 (Davies and Maloney 1976). They investigated and analyzed the activities of essential enzymes involved in the synthesis of neurotransmitters such as acetyl choline (ACh), dopamine, γ-aminobutyric acid, 5-hydroxytryptamine, and norepinephrine in almost 20 different regions of AD brains and controls. A decline in activity of choline acetyltransferase (ChAT) (Chakrabarti et al.) was observed in AD brain mainly in cortex, hippocampus and amygdala where the concentration of ACh was reduced at synapses (Francis et al. 1999, Liu, Xie, et al. 2019). ChAT is the most critical enzyme involved in the ACh synthesis while choline, acetyl Co-A and adenosine triphosphate (Feigin et al.) are the key substrates required for its catalytic activity. In their study, they identified cholinergic system failure as a cause of AD (Davies and Maloney 1976). Cholinergic neurons present in nucleus basalis and the septal diagonal band are the main source of cholinergic innervation to cerebral cortex and hippocampus respectively, and play a major role in cognitive and attentional function (Mufson et al. 2008). Due to critical implication of ACh in cognitive function, impairment in the cholinergic transmission plays a pivotal role in many forms of dementia including AD. Any interruption in cholinergic input to the cortex can adversely affect the attention and decision-making behavior (Rogers and Kesner 2004). Additionally psychiatric symptoms such as depression and apathy, found frequently in AD patients, are thought to be associated with a loss of cholinergic neurons accompanied by further
impairment of dopaminergic transmission (Ferreira-Vieira et al. 2016).

**Amyloid cascade Hypothesis**

In 1991, John Hardy and David Allsop presented the amyloid hypothesis (Selkoe 1991). A mutation in the APP gene on chromosome 21 was detected which indicated that impaired metabolism and deposition of insoluble Aβ plaques were predominantly involved in AD pathogenesis. They proposed that a plethora of mechanisms involved in AD initiation and progression include mainly Aβ accumulation, tau hyper phosphorylation, NFTs formation and neurodegeneration. Aβ aggregates found in APP mutant (APP751) transgenic model further strengthened the Aβ hypothesis (Hardy and Selkoe 2002, Lazarov et al.). However, almost 30% of clinically normal older people may possess Aβ deposits in brain as shown by data collected from PET (Lazarov et al.) imaging studies (Bennett et al. 2006, Fagan et al. 2007).

APP is a single-pass transmembrane cell surface receptor, expressed abundantly in central nervous system and consists of 695 amino acid residues (Liu, Xie, et al. 2019). After synthesis and post translational modification, it is metabolized by enzymes α secretase and later on by γ secretase through a complex process. In non-amyloidogenic pathway APP is responsible for regulation of cell growth, survival and motility along with neuritic outgrowth and functioning, ascribed to release of soluble ectodomains followed by normal cleavage of APP (Tiwari et al. 2019). Pathogenic cascade is followed by the cleavage of APP with β secretase and subsequently γ secretase to form insoluble Aβ fibrils (Tiwari et al. 2019) (Figure 2). The two main types of Aβ fibrils that are directly involved in the formation of insoluble senile plaque deposits and induce neurotoxicity are Aβ40 and Aβ42. The former being less toxic and abundant while later is more neurotoxic, highly insoluble and more prone to aggregation due to its hydrophobic nature, contributing to toxic Aβ build up. Decreased clearance of Aβ42 makes it vulnerable to be deposited as insoluble senile plaque outside the neurons. This deposition elicits gliosis, activation of astrocytes and neuritic dystrophy resulting in the loss of neuronal connection and ultimately leading to neurodegeneration. Aβ depositions begin sequentially in basal, temporal and orbitofrontal neocortex area of brain and later on extend to whole neocortex, hippocampus, amygdala, diencephalon and basal ganglia. Aβ may spread throughout mesencephalon, lower brain stem and cerebellar cortex in most severe cases. Increased concentration of Aβ activates formation of t-tangle mainly present in locus coerules and entorhinal and transentorhinal regions of the brain (Goedert 2015). Mutation in APP in the c-terminus of Aβ domain leads to Aβ42 production in FAD. Probing linkages of FAD or early onset AD unravel three genes most prone to mutations and responsible for pathogenic Aβ42 namely amyloid-beta A4 precursor protein (Orlowski et al.), PSEN1, and PSEN2 (Liu, Xie, et al. 2019) that alter the cleavage site specificity promoting cleavage at position 42 relative to position 40 thus increasing Aβ 42/40 ratio (Selkoe and Wolfe 2007). The other characteristic features of AD pathology are tau aggregation and neurodegeneration which are probably downstream effects (Hong et al. 2014). The gene apolipoprotein E (APOE) linked with late onset AD is present on chromosome 19q13.2. APOE4 is responsible to intensify neurotoxicity, supports formation of filaments and determines the onset and extent of amyloid aggregation in human brain (Liu, Xie, et al. 2019).

**Calcium homeostasis hypothesis**

In 1992, Mattson et al proposed the calcium homeostasis hypothesis (Mattson et al. 1992). The perturbation in calcium homeostasis has been studied vastly to elaborate the mechanisms involved in membrane excitability, release of neurotransmitter, activity dependent changes in genes expression and regulate neuronal growth, differentiation and apoptosis (Bezprozvanny and Mattson 2008). Ca²⁺ signaling is a complex process interconnecting Ca²⁺ influx across the plasma membrane via voltage gated Ca²⁺ channels, NMDA receptor and transient receptor potential (TRP) channels and release of Ca²⁺ from intracellular stores through inositol triphosphate receptor (IP₃R) and ryanodine receptor (RyR) channel in endoplasmic reticulum (ER) (Bezprozvanny and Mattson 2008). APP processing through β secretase pathway may affect the Ca²⁺ homeostasis of neurons via decreased formation of soluble APP (sAPPα) that stimulate K⁺ channels and through formation of APP intracellular domain that perturb Ca²⁺ release from ER by affecting the expression of genes contributing to Ca²⁺ homeostasis. Moreover, in response to the interaction between Aβ and plasma membrane, intracellular Ca²⁺ levels raise,
increasing neuronal susceptibility to excitotoxicity mediated by NMDA receptors particularly (Mattson et al. 1992).

Synaptic terminals are more prone to degeneration due to excessive Ca\(^{2+}\) influx and have high energy demand to maintain ionic hemostasis and signaling process. Evidences suggest that prime location for Aβ generation and aggregation is synaptic region (Lazarov et al. 2002). Aβ induced oxidative stress leads to disruption of Ca\(^{2+}\) homeostasis in synaptic terminal (Spires-Jones et al. 2007). Aβ also suppress the expression of Ca\(^{2+}\) activated phosphatase calcineurin that is integral for synaptic plasticity.

**Figure 1** Alzheimer's disease pathogenesis, biomarkers, and treatment targets.

**Tau propagation hypothesis**
According to tau propagation hypothesis, the tau protein hyper-aggregation appears as a secondary pathogenic event after Aβ deposition that leads to neurodegeneration (Sanabria-Castro, Alvarado-Echeverria, and Monge-Bonilla 2017). Presence of NFTs, another substantial hallmark of AD, is composed of tau (O’Brien and Wong 2011, Tiwari et al. 2019). Tau is a protein consisting of microtubule binding domain and co-connect with tubulin to form structurally stable microtubules (Claeyssen et al. 2012). Excessive accumulation of Aβ releases glycogen synthase kinase 3(GSK3) involved in regulation of Aβ and tau. Increased activity of GSK3 consequently causes hyper-phosphorylation of tau protein (Gibb et al. 2000, Brecht et al. 2004), although other kinases also phosphorylate tau. Hyper phosphorylation of tau protein depolymerizes microtubules resulting in fragmentation and formations of NFTs. NFTs are marked by paired helical filaments found in brain cells. Insoluble NFTs impair the communication and signaling between neurons contributing to neuronal loss through apoptosis (O’Brien and Wong 2011, Tiwari et al. 2019).

**Oxidative stress hypothesis**
The interplay between oxidative stress and neuronal apoptosis has long been accepted as a common feature in neurodegenerative disorders (Lin and Beal...
2006). Presumably, oxidative stress is an important element involved in pathogenesis of AD, the exact mechanism behind redox imbalance and free radical generation is still elusive. It has been proposed that aberrant accumulation of Aβ amplifies ROS generation via mechanisms implicating NMDA receptors activation (Makhaeva et al. 2015). This increase in Aβ generation and deposition facilitate tau phosphorylation and polymerization eventually initiating a self-amplifying cascade of free radical formation and leading to intensification and progression of AD (Zhao and Zhao 2013).

In AD models, neuronal mitochondria exhibit metabolic abnormalities. Mitochondria are extremely vulnerable to oxidative stress, which can directly disrupt their functions, consequently further increasing level of reactive oxygen species (ROS) and, ultimately promoting cell death via caspase activation and apoptosis (Sanabria-Castro, Alvarado-Echeverría, and Monge-Bonilla 2017).

![Diagram of Alternative splicing of APP in normal and Alzheimer's disease state.](image)

**Figure 2 Alternative splicing of APP in normal and Alzheimer’s disease state.**

**FDA approved drugs for pharmacological management of AD**

**Acetyl cholinesterase inhibitors**

Decrease in ACh levels and cholinergic tone is known to be responsible for memory decline in AD and forms the basis for the approval of three currently used AChEIs: donepezil, galantamine, and rivastigmine. Donepezil is a reversible, highly selective and potent antagonist of cholinesterase, preventing hydrolysis of ACh, initially approved for mild cases of AD (1996). Later on in 2006 its indications were revised to include severe AD (Herrmann et al. 2011). Rivastigmine is a long acting, highly selective inhibitor of ChAT as well as butyrylcholinesterase (BChE) (Polinsky 1998). Its duration of action extends to more than 24 hours, showing a dose dependent improvement in functional, cognitive and global domains (Herrmann et al. 2011). Galantamine is a competitive, reversible acetyl cholinesterase inhibitor (AChEI) that improves nicotinic transmission through allosteric modulation of nicotinic ACh receptor (Shimohama 2009). All these agents decelerate the loss of cognitive function, however, they lack the ability to retard the disease progression (Hung and Fu 2017). FDA approved indications for donepezil and rivastigmine are in mild, moderate and severe cases of AD while galantamine is used in mild and moderate AD.

**NMDA receptor antagonists**
Memantine is another option that gained approval to treat moderate to severe AD. It is selective, voltage dependent, non-competitive and low affinity NMDA receptor antagonist (Witt, Macdonald, and Kirkpatrick 2004) having fast blocking and unblocking kinetics. It ameliorates cognitive and synaptic function and reduces memory impairment associated with AD (Wenk, Parsons, and Danysz 2006). On binding selectively with open NMDA receptor-operated calcium channels, memantine inhibits NMDA mediated calcium ion influx and thus reduces the deleterious effects associated with pathologically raised glutamate levels leading to dysfunctional neurons (Yiannopoulou and Papageorgiou 2020a).

**Disease modifying treatment**

Aducanumab is the first FDA approved agent that aims to target the fundamental pathophysiology of AD rather than just providing symptomatic relief. The ability of drug to reduce levels of Aβ plaques in brain, that is widely supposed to initiate a cascade of pathological events resulting in cognitive impairment, formed basis for approval of this drug from FDA (Mullard 2021). It is a monoclonal antibody that reduces Aβ levels and exerts its effect by penetrating blood brain barrier and selectively targeting and binding to accumulated insoluble fibrils and soluble oligomers conformations of Aβ deposits in brain (Padda and Parmar 2021). Aducanumab indication is restricted to patients with mild cognitive decline and memory impairment (Cummings, Aisen, et al. 2021).

**Challenges with current therapies**

Despite great advances in understanding pathophysiology of AD, we are still far from the therapies that could cure AD. Current treatment options such as AChEIs and memantine are symptomatic that can temporarily relieve decline in cognitive loss and improve brain function; however these drugs do not represent a cure that can arrest the progression of AD (Hung and Fu 2017). Moreover, a meta-analysis of the potency of AChEIs and memantine shows that many of these treatments have minimal efficacy clinically (Galimberti and Scarpini 2011). These drugs are associated with most commonly experienced cholinergic side effects such as nausea, vomiting and diarrhea that frequently lead to discontinuation of therapy. With memantine the most commonly reported side effects are headache, dizziness and confusion (Galimberti and Scarpini 2011).

On June 7, 2021 after decades of clinical trials, FDA approved a monoclonal antibody aducanumab that claims to modify the progression of AD. However, this approval has sparked a controversial debate among researcher all over the world. The efficacy of this agent is highly questionable, as the data obtained from one of the two phase 3 trial showed negative results. Also, the results from the other study showed insufficient evidence of improvement and benefits to the patient (Mahase 2021). Moreover, aducanumab produces non-negligible adverse effects, according to the evidence. Almost 40 % participant developed swelling of brain during the treatment. Most people remained asymptomatic. However, they would need regular brain screening to preclude hazardous complications (Mullard 2021).

Despite of all the arduous research efforts, prolong and high budget trials, currently there is no effective approved disease modifying agent available for AD (Hukins, Macleod, and Boland 2019). Although roughly 200 or more research projects have been halted or rejected in last ten years, still the drug pipeline is full of agents aiming to modify or treat AD symptomatically (Yiannopoulou and Papageorgiou 2020b).

**Pharmacogenomics: Impact on therapeutic strategies in AD**

As discussed previously, currently available treatments (AChEI and memantine) are modestly effective (Sumirtanurdin et al. 2019). Almost 15-20% of AD patients show aberrant metabolism of AChEI, out of these 50% are ultra-rapid metabolizer and need more dose than normal to exhibit therapeutic effect while 50 % are slow metabolizer and show adverse effect even on low dose (Cacabelos 2007). Pharmacogenetics and pharmacogenomics factors are probably responsible for 60-90% of variations in disposition and response of drug (Figure 3).

Therefore, appropriate use of pharmacogenomics/pharmacogenetics data of AD patients may enhance therapeutic optimization through development of cost effective drugs, explaining the queries regarding inter individual variable drug response, reducing safety, efficacy and patient compliance and decreasing adverse outcomes and unnecessary cost for community as well as industry (Cacabelos 2005).

In this section we discuss studies that are particularly investigated the association between genetic
polymorphisms and therapeutic outcomes of currently available AD treatments (table 1).

**Donepezil**

Donepezil is indicated as first line treatment for mild to moderate AD symptomatically in more than 75% countries globally (Birks and Harvey 2018, Knowles 2006). However large disparity in clinical response is observed having approximately 20-60% variation in therapeutic outcomes (Yang et al. 2011). Several related studies have identified genetic factors as the main cause of divergence in clinical effect of donepezil therapy (Raskind et al. 2000, Lu et al. 2020). Some of the most important genes implicated in the variation in therapeutic response to donepezil are discussed below.

**ATP-binding cassette A1 transporter (ABCA1)**

ABCA1 gene located on chromosome 9 is known to be involved in the pathogenesis of late onset AD. ABCA1, regulates efflux of cholesterol in cellular lipid removal pathway to form high density lipoprotein by transferring cholesterol and phospholipids to APO from cell membrane. Moreover, ABCA1 expedites removal of Aβ aggregation by transporting it directly into blood (Lupton et al. 2014). In a recent clinical study, patients with the ABCA1 rs2230806 GG genotype exhibited better response to donepezil treatment as compared to those having AA and AG genotypes (p = 0.001). Moreover, non-carrier patients of APOE3 having ABCA1 rs2230806 GG genotype showed better clinical response to donepezil treatment (Lu et al. 2018). In fact, the best response to donepezil therapy is shown in patients having GG genotype (21 of 49 responders) and the lowest incidence of non-responder phenomenon (3 of 39 non-responders) (Lu et al. 2018).

**APOE**

ApoE is the most investigated gene considered to be involved in both familial and sporadic AD (Kim, Basak, and Holtzman 2009). ApoE is a protein carrier for transport of cholesterol in brain having three isoforms: ApoE2, ApoE3 and ApoE4 (Sumirtanurdin et al. 2019) ApoE3 is the normal form that exists most commonly while ApoE2 and ApoE4 differ in a single amino acid substitution at position 112 or 158, respectively (Huang and Mahley 2014). ApoE4 is a predisposing genetic factor for AD while ApoE2 is deemed protective. Several studies have shown the critical involvement of ApoE in AD pathogenesis through influencing Aβ metabolism (Kim, Basak, and Holtzman 2009). There is a strong association between ApoE polymorphism and response to donepezil therapy in AD patients (Lu et al. 2020). However, several of these studies trying to find associations between ApoE gene and donepezil efficacy showed conflicting outcomes (Lu et al. 2020). According to some studies, the best response to donepezil was observed in ApoE4 carriers (Cacabelos and Martinez-Bouza 2011). On the other hand, there are studies which assert ApoE4 non-carriers as best responder of donepezil therapy (Borroni et al. 2002). Besides this, some findings conclude no influence of ApoE4 on the efficacy of donepezil (Yaowaluk et al. 2019, Waring et al. 2015). Furthermore, some studies found ApoE3 non-carriers as better responders to donepezil treatment than ApoE3 carriers (Lu et al. 2016).

The cumulative effect of ApoE and CYP2D6 genotype on efficacy of donepezil is also investigated implicating CYP2D6 related effects on hepatic metabolism of drug (Lu et al. 2016). The therapeutic outcome in AD may alter depending on ApoE-CYP2D6 relationship through variation in lipid metabolism and hepatic function (Cacabelos and Martinez-Bouza 2011).

**Cytochrome P450 2D6 (CYP2D6)**

Almost 95% of donepezil binds to plasma proteins at steady state after oral administration, metabolized by hepatic P450 enzymes and its most active metabolite is 6-0-DNP (Barth et al. 2012). CYP2D6 is the primary metabolic enzyme responsible for the metabolism of donepezil (Lu et al. 2015). Therefore, efficacy of donepezil in AD patients may be governed by CYP2D6 gene polymorphism and changes to this gene may result in variation in therapeutic effectiveness at the recommended dose. This may depend on link between CYP2D6 genetic variation and donepezil plasma concentration as per studies conducted to investigate response of Caucasian and Mongoloid population, against donepezil treatment (Lu et al. 2020). Single nucleotide polymorphisms (SNP) in CYP2D6 (rs1065852, rs1080985, rs35742686, rs3892097, rs5030655, and rs1065852) have been scrutinized to observe their relation with efficacy of donepezil. These studies indicate different outcomes with different genetic variants of CYP2D6 (Lu et al. 2020).
BCHE
BCHE is a serine hydrolase that catalyzes hydrolysis of choline ester such as ACh. Under non-pathological conditions AChE predominantly regulates ACh levels in brain while BCHE involvement remains insignificant. Conversely, BCHE activity consistently increases in AD, although AChE activity reduces or remain unaltered (Greig, Lahiri, and Sambamurti 2002). Studies have identified two important SNPs in BCHE gene - rs1803274 (the K allele) and rs1355534 (Lu et al. 2020). In a study with a 3 years observation in 145 patients with mild cognitive impairment (Caucasian), BCHE rs1803274 carriers exhibited poor drug response to Donepezil therapy suggesting this SNP as a possible genetic marker for donepezil efficacy (Sokolow et al. 2017). On the other hand, an Italian investigation deduced that no association exists between BCHE rs1355534 and rs1803274 gene polymorphisms and efficacy of donepezil in delayed onset AD (Scacchi et al. 2009a). Another study which evaluated the effect of donepezil and Lismin on AD found no statistically significant relationship between donepezil efficacy and presence of K allele (rs1803274) (Blesa et al. 2006).

ChAT
ChAT is an enzyme that catalyzes formation of neurotransmitter ACh utilizing choline and acetyl coenzyme A (Liu, Zhang, et al. 2019). Gene encoding ChAT has a locus on chromosome 10q11.23 (Chakrabarti et al.). Because donepezil exhibits its effect via cholinergic system, ChAT is presumed to be implicated in its efficacy. According to a study aimed to find any link between ChAT rs2177369 genetic variant and effectiveness of donepezil in late onset AD, the G/G genotype was associated with lower drug response. This study consisted of 87 patients (randomly from both genders with age range 56-93 years) to whom 5mg of donepezil was administered daily and 10mg dose of donepezil was administered to another 14 patients. The analysis of ChAT rs2177369 polymorphism concluded that ChAT rs2177369 G/G genotype carriers exhibited suboptimal response to donepezil when compared to G/A+A/A genotypes carriers suggesting it as an important marker of donepezil treatment response (Scacchi et al. 2009a).

ACh receptor subunit a7 (CHRNA7)
CHRNA7 located on chromosome 15q14, is implicated in both prevention and pathogenesis of AD. There is scanty information available to explain association between CHRNA7 gene polymorphism and its effect on donepezil response in AD patients. A study in the Brazil attempted to unravel association between CHRNA7 gene polymorphism, the T allele
### Table 1 Gene polymorphism and therapy response.

| Genes          | Sample Size | Study Locations | Drug                        | Association/Correlation                                                                 | Reference               |
|----------------|-------------|-----------------|-----------------------------|----------------------------------------------------------------------------------------|-------------------------|
| ABCA1 rs2230806| 88          | China           | Donepezil                   | Improvement with GG in DNP than those with the AA and AG genotypes                      | (Lu et al. 2018)        |
| AChE           | 171         | Italy           | Rivastigmine and donepezil  | AChE AA genotype carriers had the best response                                         | (Scacchi et al. 2009b)  |
| APOE           | 85          | China           | Donepezil                   | ApoE3 non-carriers had better response to DNP treatment                                  | (Lu et al. 2016)        |
| APOE           | 146         | Korea           | Rivastigmine and memantine  | APOE ε4 allele showed better response to memantine plus rivastigmine patch              | (Han et al. 2012)       |
| APOE           | 177         | Brazil          | AChEIs                      | APOE4 allele presence was associated with the worst response to treatment               | (Braga et al. 2015)     |
| BCHE K allele  | 146         | Republic of Korea| Rivastigmine and memantine  | BCHE-K genotype correlated with poor cognitive response, especially in the presence of APOE4 | (Han et al. 2015)       |
| ChAT           | 158         | Korea           | AChEIs                      | Genetic polymorphism of CHAT has an influence on variability in drug response           | (Yoon et al. 2015)      |
| ChAT           | 135         | Korea           | Donepezil                   | Positively influences the treatment outcomes of donepezil                               | (Lee et al. 2015)       |
| CHRNA7 gene rs6494223 | 177         | Brazil          | Donepezil                   | Improved response to ChEI therapy in patients                                            | (Braga et al. 2015)     |
| CHRNA7 rs8024987|Rivastigmine and memantine | rs8024987 carrier women showed better treatment outcome after 6 months | (Weng et al. 2014) |
| CYP2D6*10      | 190         | China           | Galantamine and Donepezil   | CYP2D6*10 carriers showed improvement in ADAS-Cog                                       | (Ma et al. 2019)        |
| CYP2D6 rs1080985| 115         | Italy           | Donepezil                   | Exhibited poor response to DNP treatment                                                | (Pilotto et al. 2009)   |
| CYP2D6 rs1080985| 415         | Italy           | Donepezil                   | evidence of association between rs1080985 and response to donepezil was observed after 6 months of therapy | (Albani et al. 2012)    |
| CYP2D6         | 85          | China           | Donepezil                   | CYP2D6*10/*10 carriers exhibited the best therapeutic responses to DNP                   | (Lu et al. 2016)        |
| CYP2D6 rs1080985| 208         | China           | Donepezil                   | No association was identified                                                           | (Liu et al. 2014)       |
| CYP2D6 rs1080985| 88          | Poland          | Donepezil                   | No association was found                                                               | (Klimkowicz-Mrowiec et al. 2013) |
| CYP2D6         | 38          | India           | Donepezil                   | CYP2D6 polymorphism, though not significant, might partially be involved in the plasma concentration of AD drug | (Sonali et al. 2014)    |
| CYP2D6*10      | 96          | China           | Donepezil                   | Presence of mutant allele (*10) in CYP2D6 gene may respond better to donepezil          | (Zhong et al. 2013)     |
| ESR1           | 184         | Italy           | Donepezil or rivastigmine   | ESR1 may be contributing to inter-individual variability in response to treatment with ChEIs | (Scacchi et al. 2014)   |
| PON-1 192 Q/R  | 73          | Italy           | AChEIs                      | Associated with better response to treatment                                           | (Pola et al. 2005)      |
| UGT2B7         | 18          | North India     | Rivastigmine and memantine  | Higher drug levels with a poor response to the drug treatments                         | (Sonali et al. 2013)    |
(rs6494223) and donepezil efficacy and after 6 months of observation found that patients receiving donepezil showed signification association between the T allele of rs6494223 and donepezil effectiveness. However, no such association was found after 24 months of donepezil treatment (Braga et al. 2015).

Rivastigmine
Almost 27% of the patients on rivastigmine (6-12 mg/day) treatment suffer from adverse effects culminating in discontinuation of therapy (Rösler et al. 1999). Several pharmacogenomics studies conducted may explain the underlying reason for variability in response of rivastigmine therapy.

APOE
A survey was conducted comprising 146 Korean participants, aimed to investigate effect of APOE genotype, on response to rivastigmine transdermal patch monotherapy and memantine plus rivastigmine patch in the mild to moderate AD patients. Conclusion drawn from this survey states that APOE4 carriers showed better response to rivastigmine plus memantine patch than APOE4 non carriers (Han et al. 2012).

BCHE
The K variant of BCHE-K rs.1803274 is found to exhibit less ACh hydrolyzing ability than BCHE-K non carriers, consequently producing variability in efficacy of rivastigmine. Han et al., performed a study on 146 AD patients to evaluate the probable effect of BCHE gene variation on response of rivastigmine. AD Assessment Scale-cognitive subscale (ADAS-cog) score at sixteenth week was used to differentiate responders from non-responders. BCHE-K genotype particularly in presence of APOE4 was found to exhibit low response with rivastigmine patch or memantine add on treatment(Han et al. 2015)

Presenilin (Feigin et al.)
Evaluation of drug response as per genotypes of PS revealed that AD patients having +A/-A genotype exhibited best response to rivastigmine treatment showing no cognitive decline when compared with baseline. Conversely patients with PSEN2 +A/+A and APO E3/E4 genotypes exhibited worst therapeutic response showing exacerbation of disease despite treatment with rivastigmine (Zamani et al. 2011)

UGT2B7
UDP glucuronosyltransferase 2B7 is an important conjugate metabolic enzyme encoded by UGT2B7 gene, involved in metabolism of various endogenous compounds and drugs in phase II metabolic reactions (Carrier et al. 2000). Hence, polymorphisms in UGT2B7 may alter glucuronidation reaction and can affect the toxicity and efficacy of some drugs (Innocenti et al. 2008). A study was conducted with 36 AD patients to assess the effect of UGT polymorphism on steady state plasma concentration and efficacy of rivastigmine alone (n=18) as well as in combination with memantine (n=18) (Sonali et al. 2013). UGT2B7 variant (rs7439366) showed poor clinical response to rivastigmine therapy; however larger sample size needs to be studied to reaffirm these results (Sonali et al. 2013).

Galantamine
CYP3A4 and CYP2D6 are significantly involved in metabolism of galantamine (Noetzli, Guidi, Ebbing, Eyer, Zumbach, et al. 2013). About 25% of galantamine is excreted unchanged through kidney. Besides, galantamine is a putative substrate of P-glycoprotein; significantly involved in absorption, distribution and elimination of drugs. Thus, the therapeutic outcome or adverse effects and disposition of galantamine may be influenced by genetic variation in these enzymes and transporters (Noetzli, Guidi, Ebbing, Eyer, Zumbach, et al. 2013).

CYP2D6
A study carried out in China (n=190) to analyze association of CYP2D6 genetic variants with clinical outcomes and side effects of cholinesterase inhibitors (galantamine and donepezil), revealed that CYP2D6*10 rs1065852 carriers in AD patients were better responder of treatment ascertained through ADAS-Cog and MMSE score and reported fewer adverse effects (Ma et al. 2019).

CHRNa7
Dual mode of action is the distinctive feature of galantamine among other ChEIs, exerting effect via cholinesterase inhibition as well as allosteric modulation of CHRNA7 (Albuquerque et al. 2001, Texidó et al. 2005). As per a study in Caucasian population, CHRNA7 rs8024987 (C/G) or rs6494223 (C/T) carrier AD patients exhibited better response to galantamine (Patrizia et al. 2017). In another study
conducted in Taiwan (n=204), six month treatment of AD patients with galantamine, revealed that \textit{CHRNA7} rs8024987 was significantly associated with better clinical outcome of therapy particularly in women (Weng et al. 2014).

**Memantine**

Memantine, the most commonly prescribed anti AD drug is extensively eliminated via kidney (75—90 %) and is a known substrate of the organic cation/carnitine transporters (OCTN 1—3), organic cation transporter (OCT), the multidrug and toxin extrusion proteins (MATE1-2) and P-glycoprotein (P-gp) (Noetzli, Guidi, Ebbing, Eyer, Wilhelm, et al. 2013). Moreover, studies implicate constitutive androstane receptor (CAR), pregnane X receptor (PXR) and peroxisome proliferator-activated receptor (PPAR) in the regulation of cationic transporter (Klaassen and Slitt 2005, Maeda et al. 2007). Significant inter-individual disparity is observed in plasma concentration among the patients on memantine therapy, suggesting that genetic polymorphism may affect the drug response in these individuals (Tampi and van Dyck 2007, Valis et al. 2019). However, genetic variation is addressed explicitly by only a few studies.

**NR1I2**

Pregnane X receptors encoded by \textit{NR1I2} gene regulates transporters and enzymes involved in metabolism of drugs (Ma, Idle, and Gonzalez 2008). According to a study designed to quantify the consequence of variations in genes of renal cation transporters and nuclear receptors and other factors affecting memantine plasma concentrations, reported that \textit{NR1I2} rs1523130 CT/TT genotypes carriers presented 16% slower elimination of memantine than CC genotype carriers (Noetzli, Guidi, Ebbing, Eyer, Wilhelm, et al. 2013). This study suggests that \textit{NR1I2} genetic variants may cause perturbations in the plasma drug concentration with consequent variations in the treatment response and adverse effects.

**Future perspective**

Regardless of the substantial progress in the diagnosis, pathophysiology, and treatment of AD, its primary causes remain elusive, precise biomarkers are not well established; the available treatment options provide symptomatic relief only and their effectiveness is limited. Currently, the most successful pharmacological approach considered to treat AD is through improving ACh levels with AChEIs. However, significant variation in response to AD treatment is observed accompanied by undesirable adverse effects, as discussed in this review, explicating that same conventional dose and selection of drug for every single patient may not be appropriate. The obvious heterogeneity in response to existing treatment options for AD challenges us to amend the way we think about therapeutics of AD. A strong correlation exists between therapeutic response to the conventional drugs and genotypes in AD. In fact, pharmacogenomics and pharmacogenetics factors are accountable for 60-80% of variations in pharmacodynamics and pharmacokinetics of drugs. This review provides an insight into the contribution of genetic variants to altered drug response in AD treatment. Identification of gene variants is the preliminary step leading to more refined treatment selection. Therapeutic optimization can be enhanced in AD by incorporating pharmacogenomics principles in research and clinical practice that may help to establish cost efficient treatments and improve their safety and efficacy. Such an approach would promise development of precision medicine in which the doses and combination of drugs are optimized according to individual’s unique genetic makeup, environmental and life style factors. The personalized medicine treats and examines genotype instead of merely relying on apparent symptoms of disease known as phenotype. Systematic addition of pharmacogenomic studies in research and drug development can lead to worthwhile decrease in cost of drug development, reduce number of failures in clinical trials and ensures safe and effective therapy.

**Conflict of interest**

The authors declare that they have no competing interests.

**Funding**

There was no funding available for this project.

**Ethics approval**

Not applicable.

**Consent forms**

Not applicable
Authors contribution
HU conceptualized the study, HU & AG searched the literature, wrote the manuscript and finalized it. All the authors have read and approved the final version of the manuscript.

Acknowledgements
Not applicable.

References
2020. "2020 Alzheimer's disease facts and figures." Alzheimer's & Dementia 16 (3):391-460. doi: https://doi.org/10.1002/alz.12068.
Albani, D., F. Martinelli Boneschi, G. Biella, G. Giacalone, S. Lupoli, F. Clerici, L. Benussi, R. Ghidoni, D. Galimberti, R. Squitti, S. Mariani, A. Confalonieri, G. Bruno, C. Mariani, E. Scarpini, G. Binetti, G. Magnani, M. Franceschi, and G. Forloni. 2012. "Replication study to confirm the role of CYP2D6 polymorphism rs1080985 on donepezil efficacy in Alzheimer's disease patients." J Alzheimers Dis 30 (4):745-9. doi: 10.3233/jad-2012-112123.
Albuquerque, E. X., M. D. Santos, M. Alkondon, E. F. Pereira, and A. Maelicke. 2001. "Modulation of nicotinic receptor activity in the central nervous system: a novel approach to the treatment of Alzheimer disease." Alzheimer Dis Assoc Disord 15 Suppl 1:S19-25. doi: 10.1097/00002093-200108001-00004.
Barber, Robert C. 2012. "The Genetics of Alzheimer’s Disease." Scientifica 2012:246210. doi: 10.6064/2012/246210.
Barth, T., R. Conti, M. T. Pupo, L. T. Okano, and P. S. Bonato. 2012. "Chiral HPLC analysis of donepezil, 5-O-desmethyl donepezil and 6-O-desmethyl donepezil in culture medium: application to fungal biotransformation studies." Anal Bioanal Chem 404 (1):257-66. doi: 10.1007/s00216-012-6107-3.
Bennett, D. A., J. A. Schneider, Z. Arvanitakis, J. F. Kelly, N. T. Aggarwal, R. C. Shah, and R. S. Wilson. 2006. "Neuropathology of older persons without cognitive impairment from two community-based studies." Neurology 66 (12):1837-44. doi: 10.1212/01.wnl.0000219668.47116.e6.
Bezprozvanny, Ilya, and Mark P. Mattson. 2008. "Neuronal calcium mishandling and the pathogenesis of Alzheimer’s disease." Trends in neurosciences 31 (9):454-463. doi: 10.1016/j.tins.2008.06.005.
Birks, J. S., and R. J. Harvey. 2018. "Donepezil for dementia due to Alzheimer’s disease." Cochrane Database Syst Rev 6 (6):Cd001190. doi: 10.1002/14651858.CD001190.pub3.
Blesa, R., R. Bullock, Y. He, H. Bergman, G. Gambina, J. Meyer, G. Rapatz, J. Nagel, and R. Lane. 2006. "Effect of butryrylcholinesterase genotype on the response to rivastigmine or donepezil in younger patients with Alzheimer's disease." Pharmacogenet Genomics 16 (11):771-4. doi: 10.1097/01.fpc.0000220573.05714.a.
Borroni, B., F. Colciaghi, L. Pastorino, S. Archetti, P. Corsini, F. Cattabeni, M. Di Luca, and A. Padovani. 2002. "ApoE genotype influences the biological effect of donepezil on APP metabolism in Alzheimer disease: evidence from a peripheral model." Eur Neuropsychopharmacol 12 (3):195-200. doi: 10.1016/s0924-977x(02)00013-5.
Braga, I. L., P. N. Silva, T. K. Furuya, L. C. Santos, B. C. Pires, D. R. Mazzotti, P. H. Bertolucci, M. S. Cendoroglo, and M. C. Smith. 2015. "Effect of APOE and CHRNA7 genotypes on the cognitive response to cholinesterase inhibitor treatment at different stages of Alzheimer’s disease." Am J Alzheimers Dis Other Demen 30 (2):139-44. doi: 10.1177/1533317514539540.
Brecht, W. J., F. M. Harris, S. Chang, I. Tesseru, G. Q. Yu, Q. Xu, J. Dee Fish, T. Wyss-Coray, M. Buttini, L. Mucke, R. W. Mahley, and Y. Huang. 2004. "Neuron-specific apolipoprotein e4 proteolysis is associated with increased tau phosphorylation in brains of transgenic mice." J Neurosci 24 (10):2527-34. doi: 10.1523/jneurosci.4315-03.2004.
Cacabelos, R., and R. Martinez-Bouza. 2011. "Genomics and pharmacogenomics of dementia." CNS Neurosci Ther 17 (5):566-76. doi: 10.1111/j.1755-5949.2010.00189.x.
Cacabelos, Ramón. 2005. "Pharmacogenomics and therapeutic prospects in Alzheimer’s disease." *Expert Opinion on Pharmacotherapy* 6 (12):1967-1987. doi: 10.1517/14656566.6.12.1967.

Cacabelos, Ramón. 2007. "Donepezil in Alzheimer’s disease: From conventional trials to pharmacogenetics." *Neuropsychiatric disease and treatment* 3 (3):303-333.

Carrier, Jean-Sébastien, David Turgeon, Kim Journault, Dean W. Hum, and Alain Bélanger. 2000. "Isolation and Characterization of the Human UGT2B7 Gene." *Biochemical and Biophysical Research Communications* 272 (2):616-621. doi: https://doi.org/10.1006/bbrc.2000.2795.

Chakrabarti, Sasanka, Vineet Kumar Khemka, Anindita Banerjee, Gargi Chatterjee, Anirban Ganguly, and Atanu Biswas. 2015. "Metabolic Risk Factors of Sporadic Alzheimer’s Disease: Implications in the Pathology, Pathogenesis and Treatment." *Aging and disease* 6 (4):282-299. doi: 10.14366/AD.2014.002.

Claeysen, S., M. Cochet, R. Donneger, A. Dumuis, J. Bockaert, and P. Giannoni. 2012. "Alzheimer culprits: cellular crossroads and interplay." *Cell Signal* 24 (9):1831-40. doi: 10.1016/j.cellsig.2012.05.008.

Cummings, Jeffrey, P. Aisen, L. G. Apostolova, A. Atri, S. Salloway, and M. Weiner. 2021. "Aducanumab: Appropriate Use Recommendations." *The Journal of Prevention of Alzheimer’s Disease*. doi: 10.14283/jpad.2021.41.

Cummings, Jeffrey, Garam Lee, Kate Zhong, Jorge Fonseca, and Kazem Taghva. 2021. "Alzheimer’s disease drug development pipeline: 2021." *Alzheimer’s & Dementia: Translational Research & Clinical Interventions* 7 (1):e12179. doi: https://doi.org/10.1002/trc2.12179.

Davies, P., and A. J. Maloney. 1976. "Selective loss of central cholinergic neurons in Alzheimer's disease." *Lancet* 2 (8000):1403. doi: 10.1016/s0140-6736(76)91936-x.

DeMattos, Ronald B., John R. Cirrito, Maia Parsadanian, Patrick C. May, Mark A. O'Dell, Jennie W. Taylor, Judith A. K. Harmony, Bruce J. Aronow, Kelly R. Bales, Steven M. Paul, and David M. Holtzman. 2004. "ApoE and clusterin cooperatively suppress Abeta levels and deposition: evidence that ApoE regulates extracellular Abeta metabolism in vivo." *Neuron* 41 (2):193-202. doi: 10.1016/s0896-6273(03)00850-x.

Desikan, R. S., H. J. Cabral, C. P. Hess, W. P. Dillon, C. M. Glastonbury, M. W. Weiner, N. J. Schmansky, D. N. Greve, D. H. Salat, R. L. Buckner, and B. Fischl. 2009. "Automated MRI measures identify individuals with mild cognitive impairment and Alzheimer’s disease." *Brain* 132 (Pt 8):2048-57. doi: 10.1093/brain/awp123.

Fagan, A. M., C. M. Roe, C. Xiong, M. A. Mintun, J. C. Morris, and D. M. Holtzman. 2007. "Cerebrospinal fluid tau/beta-amyloid(42) ratio as a prediction of cognitive decline in nondemented older adults." *Arch Neurol* 64 (3):343-9. doi: 10.1001/archneur.64.3.noc60123.

Feigin, Valery L., Amanuel Alemu Abajobir, Kalkidan Hassen Abate, Foad Abd-Allah, Abdishakur M. Abdulle, Semaw Ferede Abeera, Gebre Yitayih Abyu, Muktar Beshir Ahmed, Amani Nidhal Aichour, Ibtihel Aichour, Miloud Taki Eddine Aichour, Rufus Olusola Akinyemi, Samer Alabeled, Rajaa Al-Raddadi, Nelson Alvis-Guzman, Azmeraw T. Amare, Hossein Ansari, Palwasha Anwari, Johan Arnlöv, Hamid Asayesh, Solomon Weldegebreal Asgedom, Tesfay Mehari Atey, Leticia Avila-Burgos, Euriptime Frinel, G. Arthur Avokpahoh, Mahmoud Reza Azarpazhooh, Aleksandra Barac, Miguel Barboza, Suzanne L. Barker-Collo, Till Bärrnighausen, Neeraj Bedi, Ettore Beghi, Derrick A. Bennett, Isabela M. Bensenor, Adugnaw Berhane, Balem Demtsu Betsu, Soumyadeep Bhaumik, Sait Mentes Birlik, Stan Biryukov, Dube Jara Boneya, Lemma Negesa Bulto Bulto, Hélène Carabin, Daniel Casey, Carlos A. Castañeda-Orjuela, Ferrán Catalá-López, Honglei Chen, Abdulaal A. Chitieer, Rajiv Chowdhury, Hanne Christensen,
Sayed Zaki, Joseph R. Zunt, Christopher J. L. Murray, and Theo Vos. 2017. "Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015." *The Lancet Neurology* 16 (11):877-897. doi: 10.1016/S1474-4422(17)30299-5.

Ferreira-Vieira, T. H., I. M. Guimaraes, F. R. Silva, and F. M. Ribeiro. 2016. "Alzheimer's disease: Targeting the Cholinergic System." *Curr Neuropharmacol* 14 (1):101-15. doi: 10.2174/1570159x13666150716165726.

Francis, P. T., A. M. Palmer, M. Snape, and G. K. Wilcock. 1999. "The cholinergic hypothesis of Alzheimer's disease: a review of progress." *J Neurol Neurosurg Psychiatry* 66 (2):137-47. doi: 10.1136/jnnp.66.2.137.

Galimberti, Daniela, and Elio Scarpini. 2011. "Disease-modifying treatments for Alzheimer's disease." *Therapeutic advances in neurological disorders* 4 (4):203-216. doi: 10.1177/1756285611404470.

Greig, N. H., D. K. Lahiri, and K. Sambamurti. 2002. "Butyrylcholinesterase: an important new target in Alzheimer's disease therapy." *Int Psychogeriatr* 14 Suppl 1:77-91. doi: 10.1017/s1041610203008676.

Huang, Yadong, and Robert W. Mahley. 2014. "Apolipoprotein E: structure and function in lipid metabolism, neurobiology, and Alzheimer's disease." *Mol Med. Comm.* 01 (01) 2021, 33-53.

Han, H. J., J. C. Kwon, J. E. Kim, S. G. Kim, J. M. Park, K. W. Park, K. C. Park, K. H. Park, S. Y. Moon, S. W. Seo, S. H. Choi, and S. J. Cho. 2015. "Effect of Rivastigmine or Memantine Add-on Therapy Is Affected by Butyrylcholinesterase Genotype in Patients with Probable Alzheimer's Disease." *European Neurology* 73 (1-2):23-28. doi: 10.1159/000366198.
diseases." Neurobiology of disease 72 Pt A:3-12. doi: 10.1016/j.nbd.2014.08.025.

Hukins, D., U. Macleod, and J. W. Boland. 2019. "Identifying potentially inappropriate prescribing in older people with dementia: a systematic review." Eur J Clin Pharmacol 75 (4):467-481. doi: 10.1007/s00228-018-02612-x.

Hung, Shih-Ya, and Wen-Mei Fu. 2017. "Drug candidates in clinical trials for Alzheimer's disease." Journal of biomedical science 24 (1):47-47. doi: 10.1186/s12929-017-0355-7.

Innocenti, Federico, Wanqing Liu, Donna Fackenthal, Jacqueline Ramirez, Peixian Chen, Xin Ye, Xiaolin Wu, Wei Zhang, Snezana Mirkov, Soma Das, Edwin Cook, Jr., and Mark J. Ratain. 2008. "Single nucleotide polymorphism discovery and functional assessment of variation in the UDP-glucuronosyltransferase 2B7 gene." Pharmacogenetics and genomics 18 (8):683-697. doi: 10.1097/FPC.0b013e3283037fe4.

Kim, Jungsu, Jacob M. Basak, and David M. Holtzman. 2009. "The role of apolipoprotein E in Alzheimer's disease." Neuron 63 (3):287-303. doi: 10.1016/j.neuron.2009.06.026.

Klaassen, C. D., and A. L. Slitt. 2005. "Regulation of hepatic transporters by xenobiotic receptors." Curr Drug Metab 6 (4):309-28. doi: 10.2174/1389200054633826.

Klimkowicz-Mrowiec, A., P. Wolkow, M. Sado, A. Dziubek, J. Pera, T. Dzedzic, A. Szczudlik, and A. Slowik. 2013. "Influence of rs1080985 single nucleotide polymorphism of the CYP2D6 gene on response to treatment with donepezil in patients with alzheimer's disease." Neuropsychiatr Dis Treat 9:1029-33. doi: 10.2147/ndt.s46689.

Knowles, Joanne. 2006. "Donepezil in Alzheimer's disease: an evidence-based review of its impact on clinical and economic outcomes." Core evidence 1 (3):195-219.

Lazarov, O., M. Lee, D. A. Peterson, and S. S. Sisodia. 2002. "Evidence that synaptically released beta-amyloid accumulates as extracellular deposits in the hippocampus of transgenic mice." J Neurosci 22 (22):9785-93. doi: 10.1523/jneurosci.22-22-09785.2002.

Lee, Kang Uk, Jung Hie Lee, Dong Young Lee, Jong Chul Youn, Jeong Lan Kim, Seok Woo Moon, Bong-Jo Kim, Seung-Ho Ryu, Moon Doo Kim, Chang-Uk Lee, Nam-Jin Lee, Sung Man Chang, Young Hoon Kim, Do Hoon Kim, Hae-Kook Lee, Jong Inn Woo, Ki Woong Kim, and Jin Hyeong Jhoo. 2015. "The Effect of Choline Acetyltransferase Genotype on Donepezil Treatment Response in Patients with Alzheimer's Disease." Clinical psychopharmacology and neuroscience : the official scientific journal of the Korean College of Neuropsychopharmacology 13 (2):168-173. doi: 10.9758/cpn.2015.13.2.168.

Lin, M. T., and M. F. Beal. 2006. "Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases." Nature 443 (7113):787-95. doi: 10.1038/nature05292.

Liu, M., Y. Zhang, Y. R. Huo, S. Liu, S. Liu, J. Wang, C. Wang, J. Wang, and Y. Ji. 2014. "Influence of the rs1080985 Single Nucleotide Polymorphism of the CYP2D6 Gene and APOE Polymorphism on the Response to Donepezil Treatment in Patients with Alzheimer's Disease in China." Dementia and Geriatric Cognitive Disorders Extra 4 (3):450-456. doi: 10.1159/000367596.

Liu, Pei-Pei, Yi Xie, Xiao-Yan Meng, and Jian-Sheng Kang. 2019. "History and progress of hypotheses and clinical trials for Alzheimer’s disease." Signal Transduction and Targeted Therapy 4 (1):29. doi: 10.1038/s41392-019-0063-8.

Liu, Zhimei, Li Zhang, Danmin Shen, Changhong Ding, Xinying Yang, Weihua Zhang, Jiwei Li, Jie Deng, Shuai Gong, Jun Liu, Suyun Qian, and Fang Fang. 2019. "Compound Heterozygous CHAT Gene Mutations of a Large Deletion and a Missense Variant in a Chinese Patient With Severe Congenital Myasthenic Syndrome With Episodic Apnea." Frontiers in Pharmacology 10 (259). doi: 10.3389/fphar.2019.00259.

Lu, J., J. Fu, Y. Zhong, P. Chen, Q. Yang, Y. Zhao, L. Wan, and C. Guo. 2016. "The roles of
apolipoprotein E3 and CYP2D6 (rs1065852) gene polymorphisms in the predictability of responses to individualized therapy with donepezil in Han Chinese patients with Alzheimer’s disease.” Neurosci Lett 614:43-8. doi: 10.1016/j.neulet.2015.12.062.

Lu, J., J. Fu, Y. Zhong, Q. Yang, J. Huang, J. Li, Y. Huo, Y. Zhao, L. Wan, and C. Guo. 2018. "Association between ABCA1 gene polymorphisms and the therapeutic response to donepezil therapy in Han Chinese patients with Alzheimer's disease." Brain Res Bull 140:1-4. doi: 10.1016/j.brainresbull.2018.03.014.

Lu, J., L. Wan, Y. Zhong, Q. Yu, Y. Han, P. Chen, B. Wang, W. Li, Y. Miao, and C. Guo. 2015. "Stereoselective metabolism of donepezil and steady-state plasma concentrations of S-donepezil based on CYP2D6 polymorphisms in the therapeutic responses of Han Chinese patients with Alzheimer's disease." J Pharmacol Sci 129 (3):188-95. doi: 10.1016/j.jphs.2015.10.010.

Lu, Jin, Xiuzhe Wang, Lili Wan, Jianliang Fu, Yan Huo, Yuwu Zhao, and Cheng Guo. 2020. "Gene Polymorphisms Affecting the Pharmacokinetics and Pharmacodynamics of Donepezil Efficacy." Frontiers in Pharmacology 11 (934). doi: 10.3389/fphar.2020.00934.

Makhaeva, G. F., S. V. Lushchekina, N. P. Boltneva, V. B. Sokolov, V. V. Grigoriev, O. G. Serebryakova, E. A. Vikhareva, A. Y. Aksenenko, G. E. Barreto, G. Aliev, and S. O. Bachurin. 2015. "Conjugates of γ-Carbolines and Phenothiazine as new selective inhibitors of butyrylcholinesterase and blockers of NMDA receptors for Alzheimer Disease." Sci Rep 5:13164. doi: 10.1038/srep13164.

Mattson, M. P., B. Cheng, D. Davis, K. Bryant, I. Lieberburg, and R. E. Rydel. 1992. "beta-Amyloid peptides destabilize calcium homeostasis and render human cortical neurons vulnerable to excitotoxicity." J Neurosci 12 (2):376-89. doi: 10.1523/jneurosci.12-02-00376.1992.

Mufson, Elliott J., Scott E. Counts, Sylvia E. Perez, and Stephen D. Ginsberg. 2008. "Cholinergic system during the progression of Alzheimer’s disease: therapeutic implications." Expert review of neurotherapeutics 8 (11):1703-1718. doi: 10.1586/14737175.8.11.1703.

Mullard, A. 2021. "Landmark Alzheimer’s drug approval confounds research community." Nature 594 (7863):309-310. doi: 10.1038/d41586-021-01546-2.

Nebel, R. A., N. T. Aggarwal, L. L. Barnes, A. Gallagher, J. M. Goldstein, K. Kantarcı, M. P. Mallampalli, E. C. Mormino, L. Scott, W. H. Yu, P. M. Maki, and M. M. Mielke. 2018. "Understanding the impact
of sex and gender in Alzheimer’s disease: A call to action.” *Alzheimers Dement* 14 (9):1171-1183. doi: 10.1016/j.jalz.2018.04.008.

Noetzli, M., M. Guidi, K. Ebbing, S. Eyer, L. Wilhelm, A. Michon, V. Thomazic, A. M. Alnawaqil, S. Maurer, S. Zumbach, P. Giannakopoulos, A. von Gunten, C. Csajka, and C. B. Eap. 2013. "Population pharmacokinetic study of memantine: effects of clinical and genetic factors.” *Clin Pharmacokinet* 52 (3):211-23. doi: 10.1007/s40262-013-0032-2.

Noetzli, Muriel, Monia Guidi, Karsten Ebbing, Stephan Eyer, Serge Zumbach, Panteleimon Giannakopoulos, Armin von Gunten, Chantal Csajka, and Chin B. Eap. 2013. "Relationship of CYP2D6, CYP3A, POR, and ABCB1 Genotypes With Galantamine Plasma Concentrations.” *Therapeutic Drug Monitoring* 35 (2):270-275. doi: 10.1097/FTD.0b013e318282ff02.

O'Brien, R. J., and P. C. Wong. 2011. "Amyloid precursor protein processing and Alzheimer’s disease.” *Annu Rev Neurosci* 34:185-204. doi: 10.1146/annurev-neuro-061010-113613.

Orlowski, Piotr, Michael Chappell, Chang Sub Park, Vicente Grau, and Stephen Payne. 2011. "Modelling of pH dynamics in brain cells after stroke.” *Interface Focus* 1 (3):408-416. doi: 10.1098/rsfs.2010.0025.

Padda, I. S., and M. Parmar. 2021. "Aducanumab.” In *StatPearls*. Treasure Island (FL): StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC.

Patrizia, Russo, Ksialiou Aliaksei, Moroni Rossana, Prinzi Giulia, and Fini Massimo. 2017. "Effect of Genetic Polymorphisms (SNPs) in CHRNA7 Gene on Response to ACChsterase Inhibitors (AChEI) in Patients with Alzheimer’s Disease.” *Current Drug Targets* 18 (10):1179-1190. doi: http://dx.doi.org/10.2174/138945011666151001111826.

Pilotto, Alberto, M. Franceschi, G. D’Onofrio, A. Bizzarro, F. Mangialasche, L. Cascavilla, F. Paris, M. G. Matera, Andrea Pilotto, A. Daniele, P. Mecocci, C. Masullo, B. Dallapiccola, and D. Seripa. 2009. "Effect of a CYP2D6 polymorphism on the efficacy of donepezil in patients with Alzheimer disease.” *Neurology* 73 (10):761-767. doi: 10.1212/WNL.0b013e3181b6be3.

Pola, Roberto, Andrea Flex, Michele Ciaburri, Emilio Rovella, Angela Valiani, Giada Reali, Maria C. Silveri, and Roberto Bernabei. 2005. "Responsiveness to cholinesterase inhibitors in Alzheimer’s disease: A possible role for the 192 Q/R polymorphism of the PON-1 gene.” *Neuroscience Letters* 382 (3):338-341. doi: https://doi.org/10.1016/j.neulet.2005.03.027.

Polinsky, R. J. 1998. "Clinical pharmacology of rivastigmine: a new-generation ACChsterase inhibitor for the treatment of Alzheimer’s disease.” *Clin Ther* 20 (4):634-47. doi: 10.1016/s0149-2918(98)80127-6.

Raskind, M. A., E. R. Peskind, T. Wessel, and W. Yuan. 2000. "Galantamine in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group.” *Neurology* 54 (12):2261-8. doi: 10.1212/wnl.54.12.2261.

Reitz, Christiane. 2016. "Toward precision medicine in Alzheimer’s disease.” *Annals of translational medicine* 4 (6):107-107. doi: 10.21037/atm.2016.03.05.

Reitz, Christiane, Carol Brayne, and Richard Mayeux. 2011. "Epidemiology of Alzheimer disease.” *Nature Reviews Neurology* 7 (3):137-152. doi: 10.1038/nrneurol.2011.2.

Rogers, J. L., and R. P. Kesner. 2004. "Cholinergic modulation of the hippocampus during encoding and retrieval of tone/shock-induced fear conditioning.” *Learn Mem* 11 (1):102-7. doi: 10.1101/lm.64604.

Rösler, M., R. Anand, A. Cicin-Sain, S. Gauthier, Y. Agid, P. Dal-Bianco, H. B. Stähelin, R. Hartman, and M. Gharabawi. 1999. "Efficacy and safety of rivastigmine in patients with Alzheimer’s disease: international randomised controlled trial.” *BMJ (Clinical research ed.)* 318
Sanabria-Castro, Alfredo, Ileana Alvarado-Echeverría, and Cecilia Monge-Bonilla. 2017. "Molecular Pathogenesis of Alzheimer's Disease: An Update." Annals of neurosciences 24 (1):46-54. doi: 10.1159/000464422.

Scacchi, R., G. Gambina, E. Broggio, and R. M. Corbo. 2014. "Sex and ESR1 genotype may influence the response to treatment with donepezil and rivastigmine in patients with Alzheimer's disease." Int J Geriatr Psychiatry 29 (6):610-5. doi: 10.1002/gps.4043.

Scacchi, R., G. Gambina, G. Moretto, and R. M. Corbo. 2009a. "Variability of AChE, BChE, and ChAT genes in the late-onset form of Alzheimer's disease and relationships with response to treatment with Donepezil and Rivastigmine." American Journal of Medical Genetics Part B: Neuropsychiatric Genetics 150B (4):502-507. doi: https://doi.org/10.1002/ajmg.b.30846.

Selkoe, D. J. 1991. "The molecular pathology of Alzheimer's disease." Neuron 6 (4):487-98. doi: 10.1016/0896-6273(91)90052-2.

Selkoe, D. J., and M. S. Wolfe. 2007. "Presenilin: running with scissors in the membrane." Cell 131 (2):215-21. doi: 10.1016/j.cell.2007.10.012.

Shimohama, S. 2009. "Nicotinic receptor-mediated neuroprotection in neurodegenerative disease models." Biol Pharm Bull 32 (3):332-6. doi: 10.1248/bpb.32.332.

Sokolow, Sophie, Xiaohui Li, Lucia Chen, Kent D. Taylor, Jerome I. Rotter, Robert A. Rissman, Paul S. Aisen, and Liana G. Apostolova. 2017. "Deleterious Effect of Butyrylcholinesterase K-Variant in Donepezil Treatment of Mild Cognitive Impairment." Journal of Alzheimer's disease : JAD 56 (1):229-237. doi: 10.3233/JAD-160562.

Sonali, N., M. Tripathi, R. Sagar, T. Velpandian, and V. Subbiah. 2014. "Impact of CYP2D6 and CYP3A4 Genetic Polymorphism on Combined Cholinesterase Inhibitors and Memantine Treatment in Mild to Moderate Alzheimer's Disease." Dementia and Geriatric Cognitive Disorders 37 (1-2):58-70. doi: 10.1159/000350050.

Sonali, Nirmal, Manjari Tripathi, Rajesh Sagar, Thirumurthy Velpandian, and Vivekanandhan Subbiah. 2013. "Clinical effectiveness of rivastigmine monotherapy and combination therapy in Alzheimer's patients." CNS neuroscience & therapeutics 19 (2):91-97. doi: 10.1111/cns.12036.

Spires-Jones, Tara L., Melanie Meyer-Luehmann, Jennifer D. Osetek, Phillip B. Jones, Edward A. Stern, Brian J. Bacskai, and Bradley T. Hyman. 2007. "Impaired spine stability underlies plaque-related spine loss in an Alzheimer's disease mouse model." The American journal of pathology 171 (4):1304-1311. doi: 10.2353/ajpath.2007.070055.

Sumirtanurdin, Riyadi, Amirah Y. Thalib, Kelvin Cantona, and Rizky Abdullah. 2019. "Effect of genetic polymorphisms on Alzheimer's disease treatment outcomes: an update." Clinical interventions in aging 14:631-642. doi: 10.2147/CIA.S200109.

Tampi, Rajesh R., and Christopher H. van Dyck. 2007. "Memantine: efficacy and safety in mild-to-severe Alzheimer's disease." Neuropsychiatric disease and treatment 3 (2):245-258. doi: 10.2147/nedt.2007.3.2.245.

Texidó, L., E. Ros, M. Martín-Satué, S. López, J. Aleu, J. Marsal, and C. Solsona. 2005. "Effect of galantamine on the human alpha7 neuronal nicotinic ACh receptor, the Torpedo nicotinic ACh receptor and spontaneous cholinergic synaptic activity." Br J Pharmacol 145 (5):672-8. doi: 10.1038/sj.bjp.0706221.

Tiwari, Sneham, Venkata Atluri, Ajeet Kaushik, Adriana Yndart, and Madhavan Nair. 2019. "Alzheimer's disease: pathogenesis,
diagnostics, and therapeutics.” *International journal of nanomedicine* 14:5541-5554. doi: 10.2147/IJN.S200490.

Valis, Martin, David Herman, Nela Vanova, Jiri Masopust, Oldrich Vysata, Jakub Hort, Zbysek Pavelek, Blanka Klimova, Kamil Kuca, Jan Misik, and Jana Zdarova Karasova. 2019. "The Concentration of Memantine in the Cerebrospinal Fluid of Alzheimer's Disease Patients and Its Consequence to Oxidative Stress Biomarkers." *Frontiers in pharmacology* 10:943-943. doi: 10.3389/fphar.2019.00943.

Waring, Jeffrey F., Qi Tang, Weining Z. Robieson, David P. King, Ujjwal Das, Jordan Dubow, Sandeep Dutta, Gerard J. Marek, and Laura M. Gault. 2015. "APOE-ɛ4 Carrier Status and Donepezil Response in Patients with Alzheimer's Disease." *Journal of Alzheimer's disease : JAD* 47 (1):137-148. doi: 10.3233/JAD-142589.

Wenk, G. L., C. G. Parsons, and W. Danysz. 2006. "Potential role of N-methyl-D-aspartate receptors as executors of neurodegeneration resulting from diverse insults: focus on memantine." *Behav Pharmacol* 17 (5-6):411-24. doi: 10.1097/00008877-200609000-00007.

Winslow, B. T., M. K. Onysko, C. M. Stob, and K. A. Hazlwood. 2011. "Treatment of Alzheimer disease." *Am Fam Physician* 83 (12):1403-12.

Witt, A., N. Macdonald, and P. Kirkpatrick. 2004. "Memantine hydrochloride." *Nat Rev Drug Discov* 3 (2):109-10. doi: 10.1038/nrd1311.

Yang, Y. H., S. L. Wu, M. C. Chou, C. L. Lai, S. H. Chen, and C. K. Liu. 2011. "Plasma concentration of donepezil to the therapeutic response of Alzheimer's disease in Taiwanese." *J Alzheimers Dis* 23 (3):391-7. doi: 10.3233/jad-2010-100936.

Yaowaluk, T., V. Senanarong, C. Limwongse, R. Boonprasert, and P. Kijsanayotin. 2019. "Influence of CYP2D6, CYP3A5, ABCB1, APOE polymorphisms and nongenetic factors on donepezil treatment in patients with Alzheimer's disease and vascular dementia." *Pharmgenomics Pers Med* 12:209-224. doi: 10.2147/pgpm.s211259.

Yiannopoulou, Konstantina G., and Sokratis G. Papageorgiou. 2020a. "Current and Future Treatments in Alzheimer Disease: An Update." *Journal of central nervous system disease* 12:1179573520907397. doi: 10.1177/1179573520907397.

Yiannopoulou, Konstantina G., and Sokratis G. Papageorgiou. 2020b. "Current and Future Treatments in Alzheimer Disease: An Update." *Journal of Central Nervous System Disease* 12:1179573520907397. doi: 10.1177/1179573520907397.

Yoon, H., W. Myung, S. W. Lim, H. S. Kang, S. Kim, H. H. Won, B. J. Carroll, and D. K. Kim. 2015. "Association of the choline acetyltransferase gene with responsiveness to AChsterase inhibitors in Alzheimer’s disease." *Pharmacopsychiatry* 48 (3):111-7. doi: 10.1055/s-0035-1545300.

Zamani, M., M. Mehri, A. Kollaee, P. Yenki, M. Ghaffarpour, M. H. Harirchian, and M. Shahbazi. 2011. "Pharmacogenetic Study on the Effect of Rivastigmine on PS2 and APOE Genes in Iranian Alzheimer Patients." *Dementia and Geriatric Cognitive Disorders Extra* 1 (1):180-189. doi: 10.1159/000329514.

Zhao, Y., and B. Zhao. 2013. "Oxidative stress and the pathogenesis of Alzheimer's disease." *Oxid Med Cell Longev* 2013:316523. doi: 10.1155/2013/316523.

Zhong, Y., X. Zheng, Y. Miao, L. Wan, H. Yan, and B. Wang. 2013. "Effect of CYP2D6*10
and APOE polymorphisms on the efficacy of donepezil in patients with Alzheimer's disease.” *Am J Med Sci* 345 (3):222-6. doi: 10.1097/MAJ.0b013e318255a8f9.