

# Novel Treatments for Alzheimer's Disease

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## ABSTRACT

Alzheimer's disease (AD) is a multifarious neurodegenerative disorder that leads to cognitive impairment and dementia in late adult life. Pathology hallmarks of Alzheimer's disease were observed intracellular neurofibrillary tangles and extracellular amyloid protein. According to pathology of this disease, abundant studies were performed with focused on pharmacological therapeutics over the last two decades. Current treatments for AD are acetylcholinesterase inhibitors (rivastigmine, galantamine, donepezil) and N-methyl D-aspartate receptor antagonist (memantine) that can decrease the progression of the disease. In this review, authors will discuss the various aspects of pathophysiological mechanisms and therapeutic strategies of Alzheimer's disease.

**Keywords:** Alzheimer's disease; amyloid precursor protein; amyloid-beta; neurofibrillary tangles; acetylcholinesterase inhibitor

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## INTRODUCTION

Alzheimer's disease (AD) is a multifarious neurodegenerative disorder that the German psychiatrist and neuropathologist Dr. Alois Alzheimer reported first time in 1907<sup>1</sup>. It causes progressive decline of mental, learning and behavioral functions. The prevalence of AD is observed on individuals older than 60 years of age. However, there are people younger than 65 years suffering AD. Dr. Alois Alzheimer and neuropathologists have observed extracellular amyloid  $\beta$ -peptide ( $A\beta$ ) deposition and neurofibrillary loss by intracellular tangles produced of phosphorylation of Tau protein in the autopsied brains of individuals with AD, suggesting that these structural abnormalities lead to AD<sup>2,3</sup>. There are two sporadic and familial forms in AD. Sporadic forms of AD are caused via genetic polymorphisms such as genes encoding for apolipoprotein E (APOE)<sup>4</sup>, ubiquilin-1 (UBQLN1)<sup>5</sup> and insulin degrading enzyme (IDE)<sup>6</sup> that those may affect in modulation of gamma-secretase activity, intracellular amyloid precursor protein (APP) trafficking and degradation of amyloid-beta, respectively. Familial

forms are transferred and inherited through mutant genes for example genes encoding for the amyloid precursor protein (APP)<sup>7</sup>, presenilin-1 and presenilin-2 (PSEN1 and PSEN2)<sup>8</sup>, and included about 5% of people. AD is related to basal forebrain cholinergic neurons loss suggesting acetylcholine neurotransmitter level is declined in this disease. Five drugs approved by US Food and Drug Administration (FDA) for cognitive treatment of patients with Alzheimer. Acetylcholinesterase inhibitors are donepezil (*Aricept*), tacrine (*Cognex*), rivastigmine (*Exelon*), and galantamine (*Razadyne*, Reminyl). These drugs are activated via acetylcholinesterase enzyme inhibition and those lead to improvement of cognitive function patients with mild to moderate Alzheimer's disease<sup>9</sup>. Memantine (Namenda) is NMDA receptor antagonist that is currently administrated for moderate to severe Alzheimer's disease. Mechanism of action of memantine is reduction of the NMDA receptor-mediated neurotoxicity<sup>10</sup>. Nowadays, numerous researches are being performed for founding suitable treatment of AD. The present review discusses about the new progressions

in the field of AD pathogenesis such as gamma and beta secretase inhibitors, anti-inflammatory drugs, amyloid-beta vaccination, hormone therapy, cell therapy and gene therapy.

### Pathophysiology of Alzheimer's disease

Individuals with AD will be disrupted brain structure and function at the cellular level such as pyramidal cells of brain cortex that are effective in cognitive functions. Also, studies have reported synaptic dysfunction causes communication disruption within neural pathways association to memory, learning and cognitive functions in the early stages of AD. Up to 95% of the cholinergic innervation in the various brain regions such as entorhinal cortex and hippocampus in the medial temporal lobe were degenerated in AD. Degeneration can spread to parietal areas, frontal cortex and neocortex with AD progression<sup>11,12</sup>. There is a hypothesis that neural disruption in AD is associated to aggregation of proteins both within and outside of neurons. Hallmarks of the Alzheimer disease are observed amyloid plaques and hyperphosphorylated NFTs in the autopsied brains of individuals with AD in 1907. Then, AD introduced a multifactorial disorder according to observation of different factors for example cholinergic, amyloid-beta, tau and inflammation hypothesizes<sup>13,14</sup>. Amyloid-beta is the most commonly factor of Alzheimer pathophysiology. There are two pathways of amyloid precursor protein (APP) processing including nonamyloidogenic and amyloidogenic. Alpha-secretase enzyme is active in the nonamyloidogenic pathway.  $\beta$ -secretases and  $\gamma$ -secretases enzymes cleave abnormally APP to amyloid beta 1-40 and amyloid beta 1-42. Extracellular accumulation of insoluble amyloid-beta protein (Ab) induces neuronal death through stress oxidative in the mitochondria, hyperphosphorylation tau and cerebrovascular impairment<sup>15</sup>. Then, astrocytes and microglia product an inflammatory response for clearance of the amyloid aggregates and this reaction causes injury of neurons<sup>16</sup>. Protein tau is an intracellular microtubule stabilizing protein. This protein plays transportation role of synaptic vesicles with neurotransmitters, neurotrophic factors, and mitochondria for neuronal survival. Protein tau abnormally hyper-phosphorylated and form intracellular neurofibrillary tangles' (NFT) in AD<sup>17</sup>.

### Diagnosis

AD diagnosed according to neuropsychological evaluation, medical history and physical and neurological examinations in clinical settings. Laboratory and

neuroimaging studies are performed order to research purposes in AD. American Academy of Neurology have been approved tests of serum B12, thyroid stimulating hormone (TSH), and free thyroxine (T4) levels for evaluating dementia in people with AD<sup>18,19</sup>.

### Various drugs in the treatment of Alzheimer's disease (AD)

#### Proteinopathy-based therapies in established Alzheimer's disease

##### Therapeutic strategies focusing on amyloid-beta protein

Researchers suggested several strategies for reducing formation of amyloid-beta plaques including  $\beta$ -secretase and  $\gamma$ -secretase inhibitors and modulation of  $\alpha$ -secretase activators<sup>20</sup>. Beta-secretase inhibition performed with anti- $\beta$ -site antibodies (BBS1). Antibody seems to cover the  $\beta$ -secretase cleavage site on APP and limit APP processing by  $\beta$ -secretase. Results indicated that cognition performance improved through production reduction of amyloid beta 1-42 in animal models of AD (20). NSAIDs are used as targeting the  $\gamma$ -secretase cleavage site of APP and reduced amyloid  $\beta$  production and aggregation.  $\alpha$ -secretase has neuroprotective on neurons and. it is able to block A $\beta$  formation<sup>21</sup>. Agonists of muscarinic, glutamate, and serotonin receptors, statins, oestrogens, testosterone and protein kinase C activators may stimulate  $\alpha$ - secretase in clinical trials<sup>22</sup>.

##### Therapeutic strategies focusing on tau protein

Tau protein synthesized by neuronal cells for stabilizing the microtubules in order to suitable function of the neurons including axonal morphology, growth, and polarity<sup>23-24</sup>. Tau phosphorylation was performed by enzyme of glycogen synthase kinase 3 (GSK3) that tau hyperphosphorylation inhibited using lithium and valproate in the animal models of AD<sup>25</sup>. Recently, tideglusib as an irreversible inhibitor of GSK3b was examined in phase IIb trials for AD<sup>26</sup>.

### Modulation of neurotransmitter levels involved in AD

#### Acetylcholine

Acetylcholine storage is declined in AD because cholinergic neurons degeneration of cortex different regions and activity decrease of choline acetyltransferase, synthesis enzyme of acetylcholine. Various approaches were recommended according to this condition such as administration of acetylcholine precursors, muscarinic agonists and cholinesterase inhibitors (AChEIs)<sup>27</sup>. Four

AChEIs were approved by the U.S. FDA for the treatment of AD including donepezil, tacrine, rivastigmine and galantamine. AChEIs can increase acetylcholine level through reversible inhibition of acetylcholinesterase enzyme. Also, cholinesterase inhibitors seem to decrease amyloid  $\beta$  production and A $\beta$ -induced toxicity. Clinical studies have used M1 agonists, AF102B, acetylcholine precursors including lecithin and choline for producing acetylcholine for improvement in cognitive function of patients suffering Alzheimer's. These drugs are effective in APP processing and tau phosphorylation<sup>28,29</sup>.

### Glutamate ionotropic receptor

Glutamatergic neurons are important in synaptic plasticity, cognition, learning, memory, neuronal growth and differentiation. Degeneration of glutamatergic neurons occur via excitotoxic in the late stages of disease. Memantine introduced as an uncompetitive NMDA antagonist which block NMDA receptor. Studies have reported that memantine can improve spatial memory and learning, decrease amyloid-beta and free radicals induced toxicity and protect neurons from degeneration<sup>30</sup>.

### Gamma-Aminobutyric acid (GABA)

GABAergic neurons of hippocampus were degenerated in AD. Chronic decrease of growth factors seems to change GABA transmission from inhibitory to excitatory stimulus. So, GABAergic neurons are excitatory in AD and different drugs were design for inhibiting excitation<sup>31</sup>. SGS742 antagonized GABAB receptor that observed positive results in phase I and II trial clinical. Etazolate is a neuroprotective and modulator of GABAA receptor. It seems to act  $\alpha$ -secretase and inhibit phosphodiesterase (PDE)-4<sup>32</sup>.

### Serotonin receptors

There is high density of 5-HT1A, 5-HT4, 5-HT6 and 5-HT7 receptors in the regions of the brain relation to learning and memory<sup>33</sup>. A large number of agonist and antagonist drugs of serotonin receptors were used as monotherapy or along with AChEI for enhancing cognitive in patient with AD<sup>34</sup>. Lecoztan is 5-HT1A receptor antagonist and is testing in phase II trials<sup>35</sup>. 5-HT4 receptor agonists including PRX-03140, Velusetrag, TD-8954, RQ-0000009, SUVN-D1003019 and SUVN-1004028 have cognitive improvement in preclinical studies through effect on amyloid processing. SB-742457, 5-HT6 receptor agonist indicated promising results with treatment of monotherapy or combination with donepezil in phase II trial clinical<sup>36</sup>. However,

5-HT6 receptor antagonists such as Ro-4368554, SB-258585 and SB-399885 increase cognition function in preclinical studies<sup>37</sup>.

### Role of mitochondria and oxidative stress in AD

Mitochondria are intracellular organelles which are abundant synapses of neuron in brain. Mitochondria play important roles including energy production, calcium homeostasis, free radicals production, and apoptosis. Amyloid-beta accumulation destructs normal function of mitochondria such as inhibition of import channels, decrease of complex IV and increase of ROS production<sup>38</sup>. Oxidative stress was caused harmful effects on enzymes, membrane lipids and DNA and hence induces neuronal apoptosis in hippocampus and cortex of brain<sup>39</sup>. Various studies have reported promising results for using antioxidants and free radical scavengers such as vitamins A, C, E, beta-carotene and lycopene to delay the symptoms of Alzheimer's disease<sup>40</sup>. MitoQ, probucol, curcumin, Ferulic acid as antioxidant agents was suggested for using in clinical trials order to prevent from progression of AD symptoms<sup>41</sup>. Also, CoQ10 administration has neuroprotective effects for suppressing of ROS production<sup>42</sup>. Recently, combination therapy such as Lipoic acid in combination with vitamin E and C or omega-3-fattyacids is in phase I/II trials<sup>43,44</sup>.

### Inflammatory modulation through anti-inflammatory therapy

Complement proteins and cytokines were activated against amyloid plaques and lead to neuronal damage in AD. Studies indicated that anti-inflammatory drugs can delay the symptoms of Alzheimer's disease. Anti-inflammatory drugs including indomethacin, diclofenac, celecoxib, prednisone and hydroxychloroquine are suitable for improvement of AD symptoms. NSAIDs exert useful effects through different mechanisms such as maintaining Ca<sup>2+</sup> homeostasis, targeting gamma-secretase, Rho-GTPases, and PPAR<sup>45</sup>. NSAIDs through Rho-GTPases pathway are effective in axon growth, tau phosphorylation, and astrocyte motility<sup>46</sup>. NSAIDs seem to target the  $\gamma$ -secretase cleavage site of APP and reduce production of amyloid beta in cellular models<sup>47</sup>.

### Hormonal deficiencies in AD

Sex steroid hormones are female hormones estrogen and progesterone, and male hormone testosterone. These hormones seem to protect from neurons via decrease of amyloid- $\beta$  accumulation and modulation of tau hyperphosphorylation for improvement of patients with

AD<sup>48</sup>. Sex steroid hormones can modulate signaling pathway of kinases and phosphatases especially glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ )<sup>49</sup>. Studies have reported that age increase is related to androgen loss in men and hence, low testosterone is a risk factor of AD in these individuals<sup>50</sup>.

Insulin is other hormone that is effective in cognitive function of these patients. There are insulin receptors in the olfactory bulb, hippocampus and hypothalamus<sup>51</sup>. Insulin plays role in memory formation in the hippocampus. Insulin receptors (IR) activation through c-Jun N-terminal kinase (JNK) pathway is decreased in the Alzheimer disease<sup>52</sup>. Insulin seems to act as antiamyloidogenic agent in amyloid precursor protein processing in vitro<sup>53</sup>. Currently, intranasal insulin is introduced as a safe method in humans suffering AD. It can increase memory processes in hippocampus by performing spatial and working memory tasks and also function of verbal working memory in frontal cortex<sup>54</sup>.

#### Other researches for treatment of Alzheimer disease

Novel treatments are performing for AD including stem cell, gene therapies, leuprolide acetate administration and reduction of copper induced toxicity.

#### Stem cell therapy

Stem cells transplantation leads to activation of endogenous stem cell and regeneration of damaged cells. Allopregnanolone (Ap $\alpha$ ), fluoxetine, granulocyte colony stimulating factor (G-CSF), AMD3100, stromal cell-derived factor-1 $\alpha$  (SDF-1 $\alpha$ ) and CXCR4 antagonist seem to apply for triggering endogenic stem cells release<sup>55</sup>. These stimulators can induce cell survival, learning and memory, and hippocampal neurogenesis in AD model mice. Also, stem cells Transplantation including stem cells derived from human umbilical cord, amniotic membrane-derived epithelial cells and mesenchyme may enhance neuronal viability, growth factors secretion, reduction of amyloid beta formation, and improvement of memory function in AD model animals<sup>56,57</sup>.

#### Gene therapy

Gene therapy was used by delivering therapeutic genes to target through viral vectors. Different studies were reported that amyloid  $\beta$  plaques reduced using proteases such as neprilysin insulin-degrading enzyme, plasmin and cathepsin B. in AD animal model. Moreover, ChAT-expressing human neural stem cells (HB1.F3.ChAT) and nerve growth factor (NGF) expressing human NSCs

were examined to AD animal model<sup>58</sup>. Improvement of learning and memory functions and acetylcholine in the cerebrospinal fluid were observed as Successful results. Hence, gene therapy can be introduced for effective treatment of AD<sup>59</sup>.

#### Leuprolide acetate

Leuprolide acetate is a synthetic nonapeptide analog of gonadotropin releasing hormone receptor (GnRHR) that inhibits gonadotropin secretion with continuous administration of therapeutic concentrations. Action mechanism of leuprolide acetate is stimulating the pituitary secretion of LH and FSH and following sex steroids hormones were secreted from sex organs after 3 days from treatment initiation<sup>60</sup>. Leuprolide acetate seems to modulate amyloid  $\beta$  production and tau phosphorylation and improve cognitive function in animal models of AD. Combination therapy of acetylcholinesterase inhibitors and leuprolide acetate was used in the clinical trial for improving cognitive of women with mild-to-moderate AD<sup>61</sup>.

#### Reduction of copper induced toxicity

Copper is an essential micronutrient that plays important roles in central nervous system (CNS). Also, copper act as a cofactor for enzymes in intracellular reactions, neurotransmitter synthesis, iron metabolism, mitochondrial oxidative phosphorylation, free radical detoxification, and pigment formation. Hence, brain level of copper is vital for normal function of neuron<sup>62</sup>. Patients with AD were involved with high levels of free copper because high frequency of *ATP7B* variants. Increase of free copper leads to reaction of amyloid  $\beta$  plaques and produce free radicals<sup>63</sup>. So, there are two strategies in order to decrease of copper induced toxicity including consume of zinc and chelating agents to bind excess copper<sup>64</sup>.

#### CONCLUSION

In this review we explain detail about the pathophysiology and progression of AD. Despite of Current drugs including AChEIs and memantine used for the treatment that those can target symptoms only and not the cause of the disease. So, researchers are trying for finding of new therapies that act at the root of the disease process and can stop the disease progress.

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