

Future approaches in drug treatment of alzheimer's disease



Alzheimer's Disease (AD) is a neuropathological condition entailing progressive cognitive neurodegeneration resulting in a loss of memory and speech and disruption of daily functioning. Currently, some AD drug treatments fall under either the cholinergic hypothesis or the glutamate hypothesis of AD causation, dealing respectively with acetylcholinesterase (AChE) inhibitor and N-Methyl-D-Aspartate receptor (NMDAR) antagonist drugs. Future treatments are looking on the A β hypothesis to target amyloid- β (A β) monomers, oligomers, and insoluble fibrils and tau proteins; these are targeted by anti-A β monoclonal antibodies (mAbs) and tau neurodefibrillary drugs, respectively. This essay will review the currently approved and future approaches in drug treatment of Alzheimer's Disease, with a focus on the cholinergic, glutamate, and A β hypotheses.

The cholinergic hypothesis states that AD is caused by a decrease in functioning of the choline acetyltransferase enzyme responsible for acetylcholine (ACh) synthesis (Francis et al., 1999). This in turn results in a reduction in choline uptake and ACh release (Francis et al., 1999). A reduction in ACh leads to a decrease of cortical choline neurotransmission, degenerating the basal forebrain cholinergic neurons and resulting in an impairment of learning, memory, and cognition (Francis et al., 1999). AD drugs centred around the cholinergic hypothesis target AChE and include galantamine, rivastigmine, and donepezil monotherapies for mild to moderate AD (NICE Guidance, 2018). Galantamine is a competitive nicotinic ACh active site inhibitor that functions reversibly to block AChE action (Olin and Schneider, 2002). Used for patients with mild to moderate AD, galantamine successfully passed the Activities of Daily Living functional scale

Instrumental (ADLs), and trials up to 6 months all showed statistically significant efficacy with similar profile as other ACh inhibitors with regards to gastrointestinal side effects (Olin and Schneider, 2002).

Rivastigmine, also used for treatment of mild to moderate AD, shows similar gastrointestinal side effects including nausea, tremors, and vomiting (Emre et al., 2004). However, it also passed ADLs and obtained a difference of 2.1 points in Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-Cog) compared to the placebo (Emre et al., 2004). Furthermore, rivastigmine is also available as a transdermal patch which has shown lower side effects than the oral drug with the same rate of efficacy (Machado, 2009). While donepezil is only AChE-selective, rivastigmine inhibits both the latter and also butylcholinesterase, thus decelerating neurodegeneration through both substances (Bryan, 2010).

Finally, donepezil is another reversible ACh inhibitor used to treat mild to moderate AD that performed successfully in ADLs and cognition tests and, despite showing similar cholinergic gastrointestinal side effects, is widely used in conjunction with other AD drugs in combination therapy (Winblad et al., 2006). In the Mini-Mental State Examination (MMSE), donepezil scored a mean change of +1.73 compared to the placebo, with standard error +/- 0.10 and had an apparent effect in improving patients' social interactions in addition to cognitive abilities (Boada-Rovira et al., 2004). Thus, donepezil, rivastigmine, and galantamine all work by protecting cholinergic neurotransmitters from further degeneration, but this mode of action covers only one of several hypotheses for treating AD.

Another hypothesis states that while excitatory neurotransmission of glutamate through NMDAR is essential for neuronal plasticity and survival, extrasynaptic NMDAR promotes cell death through excitotoxicity, thus contributing to the neurodegeneration and loss of brain mass that is characteristic of AD (Wang and Reddy, 2017). Memantine, an NMDAR antagonist, follows this glutamate hypothesis and treats AD symptoms by selectively blocking these extrasynaptic receptors in order to prevent cell death (Wang and Reddy, 2017). Memantine monotherapy is typically prescribed to patients with severe AD or patients with moderate AD who are AChE-intolerant (NICE Guidance, 2018). Although studies showed that memantine by itself displayed significant but small effects on ADLs and cognition, in mild to moderate AD cases it showed significantly positive results when working synergistically with donepezil (van Marum, 2009). Moreover, unlike ACh drug treatments, memantine showed placebo-comparable side effects, but its cost-effectiveness is debated (van Marum, 2009).

Though studies have demonstrated ACh and NMDAR treatments show considerable success when compared to a placebo, they are symptomatic and thus can only work by mitigating the effects of AD rather than tending to the causes (NICE Guidance, 2018). Because of this, they have been approved as a safe symptomatic AD treatment; however, future therapies will seek to continue research into the causation of the symptoms to create disease-modifying drugs. One example of these disease-modifying drugs are anti-A β mAbs. A β comes in three different polymorphisms which require different targeting drugs due to their peptide length and polarity: monomers, soluble

oligomers, and insoluble fibrils (Liu et al., 2016). According to the A β hypothesis, each of these polymorphs can achieve neurotoxicity through accumulation as A β plaques that impede neurotransmission, leading to loss of cognitive function. Anti-A β mAbs can impede this A β accumulation by several inhibitory mechanisms depending on the three possible regions of epitope specificity: N-terminus, central, and C-terminus (Liu et al., 2016).

The first region, the N-terminus, includes anti-A β mAbs such as bapineuzumab, GSK-933776, and AAB-003 (Liu et al., 2016). While bapineuzumab initially displayed significant though ambiguous differences in biomarker concentrations for carriers of the APOE ϵ 4 allele, it displayed no significant difference between carriers and non-carriers and thereafter its clinical development was terminated (Salloway et al., 2014; Liu et al., 2016). Similarly, though clinical trials revealed that GSK-933776 successfully decreased A β concentrations in the cerebrospinal fluid (CSF) and was safe for clinical use, its development was discontinued with no plans of future development due to the drug's inability to meet efficacy criteria (Leyhe et al., 2013; Rosenfeld, 2017). On the other hand, AAB-003, a derivative drug of bapineuzumab, displayed promising results with safety up to 8 mg/kg and a decreased risk of developing amyloid-related imaging abnormalities (ARIA) as a side effect compared to bapineuzumab (Delnomdedieu et al., 2016). These results support the current hypothesis that there is a relationship between decreased drug action on Fc-receptors and ARIA as a mAbs side effect (Delnomdedieu et al., 2016).

Anti-A β mAbs for the central epitope region are more unusual, exemplified by solanezumab, a mAbs drug which binds to soluble A β oligomers (Siemers <https://assignbuster.com/future-approaches-in-drug-treatment-of-alzheimers-disease/>

et al., 2016). The drug performed significantly better than the placebo in phase 3 clinical trials and passed the ADAS-Cog, MMSE, and ADLs tests (Siemers et al., 2016). Finally, C-terminus region mAbs include ponezumab and MEDI-1814 (Liu et al., 2016). In phase II clinical trials, ponezumab demonstrated good tolerance and safety; however, it had poor CSF penetration and did not significantly alter A β at clinical levels (Landen et al., 2017). Unlike many mAbs, ponezumab contains two Fc region amino acid substitutions that decrease the risk of developing ARIA and cytotoxicity side effects, and it is administered intravenously (Landen et al., 2017). It is believed that ponezumab does not cross the blood-brain barrier (BBB), but rather functions by binding with A β contained in peripheral blood, thus decreasing the available A β concentrations that can diffuse into the CSF (Landen et al., 2017).

Another target molecule for AD research is tau protein, which is believed to cause AD through a similar process as the one described by the A β hypothesis by build-up of tau neurofibrillary tangles in certain neurons' perikaryal cytoplasm (Perl, 2010). AADvac1, a tau neurodefibrillary vaccine, recently passed phase 1 clinical trials with great efficacy, with over 96% of trial patients successfully developing an IgG immune response (Novak et al., 2017). Additionally, no patients developed vasogenic oedema or meningoencephalitis, and the worst observed side effects were reactions at the injection site, making it a drug with promising clinical prospects (Novak et al., 2017). Another promising tau-targeting drug in phase 3 clinical development is LMTX, a tau-aggregator inhibitor that has shown encouragingly high tolerability and absorption even at high dosages

(Wischik, 2014). Curiously though, only patients who were not taking any other AD drugs displayed significant benefits when given LMTX, a finding that incites further research (Gallagher, 2016).

Nevertheless, although anti-A β mAbs have had considerable success in arresting neurodegeneration, a causal relationship between A β plaques and AD has yet to be established: rather, current research stems solely from *post hoc ergo propter hoc* assumptions (Selkoe and Hardy, 2016). For this reason, further research is required to understand the role of A β and tau protein in AD, much of which comes from post-mortem autopsies. These, while not beneficial to the patient in question, reveal information concerning BM loss that cannot be otherwise observed from an FMRI or PET scan because these reveal brain activity rather than structural information (Love, 2005).

However, future approaches are seeking to implement diagnostic AD testing in population within the primary concern age group (> 65 yrs.), including CSF sampling and proactive amyloid imaging through PET scans (Robinson, Tang, and Taylor, 2015). This will allow for earlier drug intervention and, possibly, with the development of improved disease-modifying drugs, arrest of neurodegenerative symptoms (Robinson, Tang, and Taylor, 2015).

Thus, the fact that approved current AD drug treatments such as those involving the cholinergic and glutamate hypotheses deal primarily with symptomatic relief has encouraged further research into the A β hypothesis for the development of more disease-modifying drugs. This, coupled with the need for more efficacious treatments with fewer side-effects, has prompted proactive diagnostic testing CSF sampling and amyloid imaging PET scans in the hope of developing early drug intervention strategies. By focusing on <https://assignbuster.com/future-approaches-in-drug-treatment-of-alzheimers-disease/>

developing drugs to treat mild AD in its early stages of development rather than continuing to treat the symptoms associated with it, it becomes possible to arrest neurodegeneration for increasingly longer, thus increasing patients' expectancy and quality of life.

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