Abstract

Alzheimer’s Disease [AD] is one of the most challenging threats to the healthcare system in society. It is believed that this ultimately leads to dysfunction and death of cholinergic neurons, and compensation for this loss had been the primary focus of first generation therapeutic agents. The amyloid and tau hypotheses have lead to a focus on amyloid and tau as therapeutic targets. The current therapeutic goals are to reduce amyloid levels, prevention of amyloid aggregation/toxicity and tau phosphorylation/aggregation. There is also a significant advancement in understanding the function of cholinesterase [ChE] in the brain and the use of ChE inhibitors in AD. The mechanism of a new generation of acetyl- and butyryl ChE inhibitors is being studied and tested in human clinical trials for AD. Other strategies, such as vaccination, anti-inflammatory agents, cholesterol-lowering agents, antioxidants and hormone therapy, are also being studied for treating or slowing the progression of AD. Although several anti-amyloid β compounds have been examined in clinical trials as potentially useful drugs, all of them have failed to show significant benefits so far. In contrast, tau-targeted drugs have been developed and have entered clinical trials. We expect strongly a therapeutic drug for dementia to be released in the near future. Developments of early diagnostic tools based on quantitative biochemical markers will be useful to better follow the course of the disease and to evaluate different therapeutic strategies.

Keywords: Alzheimer Disease; Anti-Amyloid Managements; Cholinesterase Inhibitors; Disease Modifying Agents; Memantine

Management of Alzheimer’s Disease

The first step in AD management is accurate recognition and diagnosis of the disorder, and then disclosing that diagnosis in a sensitive and timely way to the patient and others as appropriate. Disclosure of diagnosis is not harmful, and actually decreases depression and anxiety in patients and their care-givers [1]. The vast majority of patients with mild dementia wish to be fully informed and 75% of caregivers wish their relative to be informed...
Differences among ethnic, cultural, and religious groups may influence how and what disclosure occurs. It offers the patient opportunity to pursue desired activities and maximizes individual autonomy and choice by providing information necessary for decision making and advance planning, including the decision to give informed consent to research projects and autopsy. At time of diagnosis several issues need to be addressed, including the provision of high quality understandable information about the illness and its course to patient and caregiver, a careful assessment for any co-morbidities and consideration given to other services that may be required including social services, mental stimulation, occupational therapy, physiotherapy, speech and language therapy. Occupational therapy can benefit patients daily functioning and reduce the need for informal care. Medicolegal issues need to be addressed, with driving often needing prompt attention and action taken according to the legal framework operating in that particular country. Care-giver support should consist of education about AD, and attending peer support groups may be helpful. Care-giver stress and depression are common and, if present, more intensive care-giver support and counselling and/or specific treatment for depression may be needed. The provision of a standard education and support package to caregivers has been shown in Randomized Controlled Trials (RCT) to decrease psychiatric symptoms in caregivers and lead to delays in institutionalisation for patient. Management should include clear arrangements for follow-up, as regular monitoring of medication response and adverse effects as well as changes in the severity of dementia (using scales like the Mini-Mental State Examination [MMSE]) should be undertaken. Reassessment for development of co-morbidity [including carer stress] should be an integral part of management.

Primary Prevention of AD

This refers to the prevention of subsequent dementia in cognitively normal subjects and is the ultimate goal for AD management. Several risk factors have been well established for AD, though some [such as age, sex and genotype] are not modifiable. Potentially modifiable risk factors which have been established through several epidemiological studies include vascular risk factors [hypertension, smoking, diabetes, atrial fibrillation and obesity] and head injury while protective factors described include use of antihypertensives, non-steroidal anti-inflammatories, statins and hormone replacement therapy, high education, diet, physical activity and engagement in social and intellectual activities. However, whether modifying these factors will reduce risk of dementia is not yet known. A meta-analysis concluded that there is no good evidence to recommend statins for reducing the risk of AD while results of the large, prospective, placebo-controlled Women’s Health Initiative Memory Study showed that the use of estrogen plus progestin in post-menopausal women was actually associated with a significantly increased risk of dementia. Treatment of hypertension for prevention of dementia, including AD, has been the best studied risk factor to date. However, most RCTs have been stopped early because cardiovascular endpoints were reached, meaning they were underpowered to detect differences in rates of dementia. A study of treating hypertension in the very old reached similar conclusions, and contained a meta-analysis of all studies supporting a significant risk reduction. However, the period over which treatment needs to be given is not known, nor has it been established whether treating vascular risk factors, including hypertension, in those with established AD affects disease progression. Currently, no clear recommendations about dementia prevention can be made.

Secondary Prevention of AD

This refers to the prevention of development of AD in non-demented subjects with some evidences of cognitive impairment. The groups most often studied in this regard are those with Mild Cognitive Impairment (MCI) and several RCTs of ChEIs have been undertaken in MCI, most using conversion to dementia as the primary outcome. A meta-analysis included eight studies involving all three ChEIs, with duration of treatment ranging from 16 weeks to
3 years [9]. There were no differences in rate of conversion to AD between active and placebo groups, and most secondary outcomes were also negative. There have also been negative studies of aspirin in primary prevention of cognitive decline and of anti-inflammatories and vitamin E in MCI. A large study showed no effect of Gingko on preventing AD [10]. Therefore, no treatments have demonstrated efficacy for preventing or delaying development of AD in MCI subjects until now, while evidence exists that ChEIs, Vitamin E, Gingko Biloba and anti-inflammatories are not substantively helpful.

Treatment of Established AD

There are currently no means of reversing the pathologic processes of AD. Currently available medications do not halt the underlying degenerative process but can slow disease progression and therefore delay symptomatic decline [11]. The specific goals of therapy are to preserve cognitive and functional ability, minimize behavioral disturbances, and slow disease progression with maintenance of patients and caregivers [12]. Nevertheless, realistic expectations of treatment outcomes are needed because the impact for most patients is likely to be modest and temporary, with not every patient responding to treatment. The main benefit of pharmacotherapy is an attenuation of decline over time rather than an improvement in cognitive or behavioral symptoms. It is important to discuss this point with patients and their families, who may expect improvement rather than relative stability [13]. Failure to do so often will result in patient and family dissatisfaction with prescribed therapies and the risk of discontinuation. Beneficial response to a ChEI (ie, delayed deterioration of cognitive or behavioral problems) can be determined from the physician’s global assessment of the patient, the primary caregiver’s report, a neuropsychologic assessment or mental status questionnaire, or evidence of behavioral or functional changes [14].

Four drugs are commonly used for treating AD: Three ChEIs approved for mild to moderate disease, one of which also is approved for severe AD, and a glutamate N-methyl D-aspartate [NMDA] antagonist approved for moderate to severe disease.

Cholinesterase Inhibitors

Cholinesterase inhibitors increase cholinergic transmission at the synaptic cleft, potentially benefiting patients with cholinergic deficits as in AD. Three such drugs are currently available in the US: donepezil, rivastigmine, and galantamine. There has been several well conducted placebo-controlled, large scale RCTs with this three ChEIs, which have shown efficacy on cognitive function, global outcome and Activities of Daily Living (ADL) in patients with mild to moderate AD, usually defined as MMSE between 16 and 26. Mean global improvement over placebo is 3–4 points on the ADAS-Cog, a level of improvement roughly equivalent to the naturalistic decline expected over a 6 month period. Most studies have been over relatively short duration [6 months], though 1 and 3 year studies have been reported with donepezil which suggest the benefits of ChEIs continue in the longer long. Retrospective analysis and some long term open studies suggest a possible effect of ChEI on disease modification, but more data are needed before this can be confirmed. RCTs of ChEIs in more severe AD [MMSE < 10] have also shown positive results and a Cochrane review concluded that trials supported evidence of benefit in mild, moderate and severe AD [15-17]. In light of current evidence, limiting prescribing of ChEIs to only some AD subjects according to certain cut-offs on a measure such as the MMSE, as operated in many countries, does not seem justified. Although a point will be reached in severe AD when ChEI are unlikely to continue to have benefit, it is currently unclear at what point in the disease process ChEI should be withdrawn.

Rivastigmine is also approved for dementia in Parkinson’s disease. A large double-blind placebo-controlled trial of rivastigmine showed meaningful improvements in cognition and everyday functioning [18].
While there is expert consensus that cholinesterase inhibitors are more effective in Dementia with Lewy Bodies (DLB) than in AD, for both cognitive and behavioral effects, evidence from large controlled trials is lacking [19].

In vascular dementia, evidence is mixed for the cholinesterase inhibitors. They are often prescribed in vascular dementia because of the frequent co-occurrence of cerebrovascular and neurodegenerative disease [19].

In frontotemporal dementia, there is no convincing evidence of benefits from these drugs, and there are reports that they worsen behavior symptoms [20].

There is inadequate evidence on the use of cholinesterase inhibitors in other neurocognitive disorders. Cholinesterase inhibitors (ChEIs) are generally well tolerated, although common gastrointestinal adverse effects such as nausea, diarrhea, and vomiting may sometimes lead to discontinuation of treatment in some patients.

There have been few direct comparisons between ChEIs, and those which have been undertaken have been small in size and not produce consistent evidence of better efficacy of one drug over another. There is some evidence from open-label studies that patients who do not tolerate or do not seem to benefit from one ChEI may tolerate or draw benefit from the other. One of the ChEIs, rivastigmine, is now available in a transdermal [patch] formulation which appears to have lower incidence of side effects than oral administration but equal efficacy [21].

A disease modifying effect of ChEIs has been proposed, and has some basic scientific support, but no convincing clinical data, either from trials of clinical endpoints or of those using biomarkers, has yet been forthcoming to support these claims.

Effects on non-cognitive Behavioural and Psychological Symptoms Of Dementia (BPSD) have also been shown; though as with cognition effect sizes are modest. There remains uncertainty as to which particular non-cognitive symptoms may respond best, though effects on psychosis and apathy are consistently reported. Effects on agitation are less clear, and a large placebo-controlled RCT in moderate to severe AD failed to show an effect of donepezil on patients with clinically significant agitation [22].

**Memantine**

Memantine, a non-competitive N-methyl-D-aspartate receptor antagonist, also has been subject to several RCTs in AD. It is believed to be neuroprotective against excitotoxicity in the cortex and hippocampus. Studies in moderate to severe AD have been more consistently positive than those in mild to moderate AD, previous reviews of the literature have concluded that while there is a significant effect in cognition at all severities, but effects on global outcome, ADL and behaviour were only apparent in the moderate to severe studies [23]. Once daily dosing has been shown to be as effective as the original recommendation of administration twice daily [24]. Modest effects on behaviour were also found in a pooled analysis of six studies which included all those with MMSE < 20, with delusions, agitation/aggression and irritability being the most responsive symptoms, though studies of subjects primarily selected for the presence of these behavioural features have not yet been reported [25].

A systematic review showed that memantine had a small beneficial effect on cognition at six months in moderate to severe AD, marginal effect on mild to moderate AD, and a small but clinically undetectable effect in mild to moderate vascular dementia [26].

In frontotemporal dementia, memantine has shown mixed results. There is preliminary evidence of benefits in DLB and Dementia in Parkinson’s disease; however, there have been reports of worsening delusions and hallucinations in DLB.
Combination therapy of a ChEI and memantine is rational from a pharmacologic perspective because the agents have different mechanisms of action. In a randomized controlled trial, patients with moderate to severe AD who were already receiving donepezil derived significant benefit from the addition of memantine in terms of cognition, ADLs, global outcome, and behavior [27]. There are also economic benefits associated with the addition of memantine to donepezil treatment for patients with advanced AD. A recent study demonstrated improvement in clinical outcomes plus cost savings associated with the use of memantine [28]. In a study by Tariot et al., the incidence of nausea was substantially lower in patients receiving memantine add-on therapy compared with those receiving donepezil monotherapy [27]. The safety and tolerability of combining rivastigmine capsule and memantine also has been studied in a 26-week, prospective, open-label study of patients with moderate AD [29]. The combination was found to be both tolerable and safe, with a reduced incidence of gastrointestinal-related AEs compared with those documented in the US prescribing information for rivastigmine, suggesting that this beneficial effect of memantine may be applicable across ChEIs [29].

Management of Mild to Moderate Disease

Since the introduction of the first ChEI in 1997, most clinicians would consider these agents to be first-line pharmacotherapy for mild to moderate AD [30]. Four ChEIs are currently available: tacrine, donepezil, rivastigmine, and galantamine. Tacrine is not commonly used because of a poor tolerability profile and low oral bioavailability, and it is, therefore, excluded from this discussion [21]. ChEIs raise acetylcholine levels in the brain by inhibiting acetylcholinesterase [31]. Despite minor variations in their mode of action there is no evidence to suggest any difference in efficacy between the 3 commonly used ChEIs [30]. Likewise, the tolerability profile is similar between the ChEIs for the oral formulations. However, the 10-cm² rivastigmine patch has shown efficacy similar to oral rivastigmine formulations, but with approximately two-thirds fewer reports of nausea and vomiting, with Adverse Event [AE] rates similar to those of placebo [32]. AD often is accompanied and worsened by malnutrition, and weight loss is a frequent complication of AD, occurring in approximately 40% of patients at all stages [33]. Donepezil, rivastigmine, and galantamine cause a broad spectrum of AEs, of which nausea, vomiting, diarrhea, and weight loss are the most common [34, 35].

There continues to be debate regarding the extent of the benefits achieved with ChEIs. Although some assert that the most that can be achieved with ChEIs is symptom modification, others consider these agents to have disease-modifying effects [30,36]. In one study, after discontinuation of therapy, rivastigmine treated patients showed less deterioration in cognitive function compared with placebo treated patients, suggesting an effect on disease progression [37]. In another study, donepezil treatment slowed progression of hippocampal atrophy compared with untreated patients, suggesting a neuroprotective effect of donepezil in AD [38]. However, these early observations require confirmation, and, at present, the ChEIs generally are considered symptomatic medications.

A systematic analysis of double-blind, placebo controlled trials of ChEIs demonstrated treatment effects ranging from a 1.4- to 3.9-point improvement at 6 months and 1 year, in the midrange of the 70-point ADAS-Cog scale [30]. In clinical trials, a change of 4 points is considered clinically significant for patients with mild to moderate dementia [39,40]. As such, the symptomatic improvements observed are modest and of debatable clinical significance, despite being statistically significant [35]. In a meta-analysis of 16 double-blind, placebo-controlled trials of ChEIs composed of almost 8000 patients, the numbers needed to treat for one additional patient to benefit were 7 for stabilization or better, 12 for minimal improvement or better, and 42 for marked improvement [41]. Although the numbers needed to treat seem favorable, uncertainty remains regarding the clinical relevance of these outcomes and the duration of the apparent benefit because the majority of trials reviewed were of less than 26 weeks’ duration.
In addition to their effects on cognition, these agents also have demonstrated beneficial effects on measures of behavior, Activities of Daily Living (ADLs), and global patient function. A recent meta-analysis that analyzed clinical results from 29 randomized, placebo-controlled trials of patients with mild to moderate AD found that ChEI therapy was associated with significant modest benefits in terms of neuropsychiatric and functional outcomes [42]. Current guidelines acknowledge that preventing or delaying further loss of ADL function is an important goal of AD therapy and that the benefits of ChEIs may be diminished when treatment is delayed [11,43]. Significant preservation of ADL function has been observed with donepezil, galantamine, and rivastigmine compared with placebo [12].

ChEIs also have been shown to reduce AD caregiver burden: in patients with moderate to severe AD, donepezil treatment for 24 weeks significantly reduced caregiver time spent assisting patients with basic and instrumental ADLs (<52 minutes/day; P < .005) [44]. A small study has demonstrated that rivastigmine treatment reduces caregiver time spent assisting with ADLs (up to 690 hours over 2 years) [45]. Longer periods of treatment with ChEIs also decrease the risk for nursing home placement [46,47]. A retrospective analysis of a large US medical claims database showed that over a 27 months follow-up period, more patients who were not treated with ChEIs were placed in nursing homes (11.0%) than were those who received either rivastigmine (3.7%) or donepezil (4.4%) [47]. These studies suggest that ChEIs enable patients to live longer in community settings with associated personal, social, and economic benefits [12].

Memantine is sometimes used to treat patients with less severe disease, despite its use in early AD not being supported by the FDA. Although memantine has been reported to improve cognition, global status, and behavior in patients with mild to moderate AD, its mechanism of action would suggest that it does not have a place in early AD [48]. Memantine is not a ChEI; it is a low- to moderate affinity, noncompetitive (channel blocking), NMDA receptor antagonist that seems to block pathologic neural toxicity associated with prolonged glutamate release [49]. Blockade of NMDA receptors by memantine could confere disease-modifying activity in AD by inhibiting the “weak” NMDA receptor–dependent excitotoxicity that contributes to the neuronal loss underlying the progression of dementia [49]. As such, memantine is not effective until weakened neurons become vulnerable to glutamate-induced excitotoxicity, and therefore it cannot substitute for ChEIs because of its inability to enhance cholinergic neurotransmission required for memory and learning [49].

Management of Moderate to Severe Disease

Memantine is approved for the treatment of moderate to severe AD on the basis of a study in which patients with moderate to severe AD who received 20 mg memantine monotherapy showed less decline in cognition and function while maintaining good tolerability after 6 months compared with those who received placebo [50]. The ChEI donepezil also recently has been approved for use in severe AD.

Recently, donepezil 23 mg/day has been approved for the treatment of moderate to severe AD. Results from a 24-week, randomized, double-blind study reported that donepezil 23 mg/day was associated with greater benefits in cognition (as assessed by the Severe Impairment Battery) compared with donepezil 10 mg/day, although the between-treatment difference in the Clinician’s Interview-Based Impression of Change plus Caregiver Input Scale was not significant. The most commonly reported side effects with donepezil 23 mg/day were nausea, vomiting, and diarrhea, which occurred at a higher incidence than with donepezil 10 mg/day [51]. Combination therapy of a ChEI and memantine is rational from a pharmacologic perspective because the agents have different mechanisms of action. In a randomized controlled trial, patients with moderate to severe AD who were already receiving donepezil derived significant benefit from the addition of memantine in terms of cognition, ADLs, global outcome, and behavior [27]. There are also economic benefits associated with the addition of memantine to donepezil treatment for patients with advanced AD. A
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Other Drugs and Interventions

Several other treatments have been suggested as potentially beneficial for AD, including non-steroidal antiinflammatory drugs, oestrogens and statins. A large, placebo-controlled RCT of vitamin E (1000 IU, twice a day over 2 years) in moderate AD, was found to significantly delay the time to a composite outcome of primary outcome measures, but a study in MCI has been negative and the conclusion of a Cochrane review is that there is insufficient evidence for the efficacy of vitamin E in the treatment of AD or MCI [52]. Studies of steroidal, non-steroidal and cyclo-oxygenase-2 inhibitors in AD and MCI have been negative yet have had potentially serious side effects.

Many other compounds, such as piracetam, nicergoline, selegiline, vinpocetine, pentoxyphyllins and Cerebrolysin are prescribed in some countries as treatments for AD. For example, a recent Cochrane review of piracetam, one of the most widely studied drugs to date, found poor study design, possible publication bias and that overall the evidence from trials did not support the use of piracetam in people with dementia or cognitive impairment [53]. A review of 6 Cerebrolysin trials found an effect on global outcome but no consistent effect on other scales. Further evidence is therefore required before its use can be recommended [54]. Similarly, a Cochrane review of selegiline found no evidence for its efficacy in AD [55]. At present, therefore, there is no convincing evidence for efficacy of any of these drugs for AD.

Management of Behavioural and Psychological Symptoms

Management of BPSD begins with careful search for trigger and/or exacerbating factors that including environmental cues, physical problems [infections, constipation], medication and depression or psychosis. As studies of BPSD indicate a high placebo response, safe non-pharmacological management [education, exercise, aromatherapy, sensory stimulation, personalised music] should be tried wherever possible in the first instance as symptoms may naturally resolve within a short time. The beneficial effects of ChEIs and memantine for mild BPSD have been described above, but a recent RCT found donepezil did not help clinically significant agitation in those with moderate to severe AD [22]. Both conventional and atypical antipsychotics reduce BPSD, with particular effects demonstrated for risperidone for agitation/aggression and psychosis [56,57]. However, antipsychotics have important and potentially serious side effects, most especially increased stroke risk, increased mortality, parkinsonism and cognitive impairment [58]. They should be used with caution, at low dose, and for the shortest period needed only for those with moderate to severe symptoms causing distress and after careful assessment of risk and benefit and after discussion with care-giver and, where possible, patient. There is no evidence that conventional agents are any safer in regard to risk of stroke or mortality than atypical agents and they have a less established evidence base and greater side effects [59]. Low doses of antipsychotics should be used with careful monitoring, and drugs prescribed for the minimum period required. When BPSD have settled, antipsychotics can be withdrawn in most cases without re-emergence of BPSD, unless behavioural disturbance is still present [60]. Evidence for other drugs is limited, carbamazepine may help aggression, though most studies of valproate have been negative.
Antidepressants, especially Selective serotonin reuptake inhibitors [SSRIs], may be useful for depression in dementia and do not have the adverse anticholinergic effects of older tricyclics [63].

**Duration of Management**

Placebo-controlled clinical trials with marketed cholinesterase inhibitors generally have lasted 6 months, with a few exceptions lasting up to 12 months or longer. Inferences are made that if the drugs are effective over this period then they will continue to be beneficial far longer, perhaps indefinitely. Over the long term, however, as patients inevitably worsen, it becomes even more difficult to determine whether any given individual is benefiting from the drugs.

In some 3-month-long and 6-month-long trials, after medication has been discontinued patients on average return to the cognitive level of the patients contemporaneously treated with placebo within 6 weeks. Such findings are taken to indicate that the drugs have overall symptomatic effects and that continuous use is required to maintain benefits.

Some observational studies using clinic databases or open-label extensions of clinical trials suggest that patients who continue cholinesterase inhibitors over at least 1 year have a delay in nursing-home placement compared to those who cannot tolerate or do not take them, and that the addition of memantine could further contribute to the delay [64-67]. These observations, however, are not controlled and are subject to the potential bias that patients who experience a less progressive course continue their medications, while patients who are destined to progress more quickly do not continue, resulting in apparent therapeutic effects that are illusory. Moreover, comparisons are made between cohorts from time periods both before and after the ready availability of the cholinesterase inhibitors [68]. These observational studies, however, contrast with the long-term controlled trials in MCI and with observations from the Australian Imaging Biomarkers and Lifestyle datasets, where the use of cholinesterase inhibitors over the long term is associated with faster decline [69,70]. Thus, duration of treatment remains an unresolved issue.

**Withdrawal of Cholinesterase Inhibitors or Memantine**

Discontinuation of cholinesterase inhibitors has been associated with worsening of cognition and confusion in some patients. This effect was evident in a clinical trial in which donepezil was stopped after a fixed period of 12 weeks and patients were then randomized to continuing drug or to placebo as well as when patients were discontinued from some 6-month trials [71]. Yet worsening of behavior and confusion do not appear common when the drugs are stopped in clinical practice, as is frequently done. In clinical practice only 19% to 23% of patients continued to take donepezil or rivastigmine for more than 1 year, and about one-third discontinued the drugs within 2 months [72].

Tapering and withdrawal of donepezil after maintenance treatment for an average of 2 to 3 years was formally tested in a randomized controlled trial of severely impaired patients with Alzheimer disease; continuing donepezil was compared with discontinuing it, and, simultaneously, starting memantine was compared with not starting it [73]. Over the 1-year follow-up period, continuing donepezil was associated with better cognitive scores and ADLs, and adding memantine when donepezil was discontinued was better than not adding it. Many patients, however, discontinued donepezil without difficulty; notably, only half of the patients who were assigned to continue donepezil actually continued treatment beyond the 1-year follow-up, suggesting that many patients perceived that continuing donepezil, at least under double blinded conditions, was not effective. Thus, the outcomes support decisions either to continue medication or to taper and discontinue it when physicians are uncertain of continuing benefit [74]. This trial also did not support the typical use for memantine as an add-on to donepezil, showing that the add-on was not better than
continuing donepezil alone, a finding that adds to the controversy of whether the drugs taken together are better than either alone. It is generally good practice to taper these medications before discontinuing, even though both donepezil and memantine have long terminal half-lives.

**Future Therapeutic Approaches and Management of AD**

There are three feet on AD course modifying research.

First is to select high-risk population with current evidence and to provide primary prevention. This step aims to manage modifiable risk factors [75]. Second is to diagnose patient at preclinical phase, which took 10-20 years before symptoms occur. Researchers focus on new neuroimaging techniques, new laboratory and CSF investigations and genetic studies [75]. Third is to discover disease-modifying molecules. Studies are mainly focused on: [1] to inhibit extracellular amyloid plaque accumulation and to inhibit intracellular tau based neurofibrillary tangles accumulation [75,76].

**Anti-amyloid agents**

The initial process of AD is not determined yet, but one of the main proposed pathophysiological processes is ‘Amyloid Cascade Hypothesis’. All autosomal dominant AD genetic forms are due to mutations of amyloid metabolism encoding genes. Although ‘Amyloid Cascade Hypothesis’ does not capture all aspects of disease process, there is clinical and experimental data showing toxic effects of accumulated amyloid plaques. Focused amyloid-directed therapies could be divided to three classes including secretase modulators, amyloid anti-aggregants and immunotherapies [77].

**Secretase modulators**

To decrease Aβ production, research aimed to modulate enzymes that breakdown amyloid precursor protein [by stimulating α secretase or inhibiting γ and β secretase activity]. Whereas effective α secretase was infrequently identified, numerous γ and β secretase inhibitors developed. γ secretase have critical role in Aβ generation but this enzyme has multiple cleavage actions including notch receptor signaling and thought to have important side effects. Currently developed β secretase inhibitors also failed to show disease-modifying effects but there are still ongoing researches [78].

**Amyloid anti-aggregants**

Another point is to prevent aggregation of amyloid in non-soluble forms. It’s known that Aβ forms oligomers, fibrils and then deposition of amyloid plaques exists. New studies also report soluble form of Aβ have also toxic effects. Tramiprosate, colotrinin, clioquinol are some of the studied anti-Aβ aggregation agents. Phase II and III studies showed conflicting results, including no effects and minimal effects. There are ongoing studies to research current molecules and to develop new molecules [78,79].

**Amyloid removal [Immunotherapy]**

Although there is no proven exact mechanism how immunotherapy might attenuate Aβ plaques in the brain, some mechanisms have postulated. Therapeutic aim is to induce a humoral immune response to fibrillary-Aβ42 or passive administration of anti Aβ antibodies. First studies of active vaccination were halted due to induction of serious side effects-meningoencephalitis. There are alternative new molecules developed and ongoing Phase I-III trials with active and passive immunization (CAD106, Bapineuzumab, Solanezumab, Intravenous Immunoglobulin) [80, 81].

**Tau-based therapies**

Hyperphosphorylated tau aggregates in neurons and forms neurofibrillary tangles [NFT], lastly causes neuronal death in AD. Tau is a microtubule- associated protein and encoded
by the MAPT gene and has functions like, to assemble microtubules and regulate axonal transport. Hyperphosphorylated tau has been shown to cause, disruption of mitochondrial respiration and axonal transport. It’s important to emphasize that tau hyperphosphorylation is also regarded as pathologic hallmark of other neurodegenerative diseases, including Pick disease, progressive supranuclear palsy, corticobasal degeneration, and frontotemporal dementia with parkinsonism (FTD-P). FTD-P is caused by mutations of tau encoded MAPT gene. Thus support tau dysfunction could drive neurodegeneration without amyloid deposition [82]. Tau based therapies are still at conceptual stages and include passive immunization against tau, preventing tau hyperphosphorylation and anti-aggregants of tau. Methylthioninium chloride and lithium are some of the agents with ongoing studies. There are also some trials ongoing about anti-tau vaccines at AD [83,84].

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<thead>
<tr>
<th>Name</th>
<th>Company</th>
<th>Phase</th>
<th>Antigen</th>
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<tbody>
<tr>
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<td>Affiris/GlaxoSmithKline</td>
<td>II</td>
<td>Aβ1–6</td>
</tr>
<tr>
<td>CAD106</td>
<td>Novartis</td>
<td>II</td>
<td>Aβ1–6</td>
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<td>Vanutide cridificar</td>
<td>Elan/Johnson &amp; Johnson/Pfizer Inc.</td>
<td>II</td>
<td>Aβ1–6</td>
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<tr>
<td>AN1792</td>
<td>Elan</td>
<td>Terminated</td>
<td>Aβ1–42</td>
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Aβ, amyloid-beta.

**Table 1:** Ongoing and terminated active amyloid-beta immunotherapy clinical programs in Alzheimer’s disease [85].

<table>
<thead>
<tr>
<th>Name</th>
<th>Company</th>
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<td>Roche</td>
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<td>Conformational Aβ</td>
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<td>Eisai/ BioArctic Neuroscience/Eisai</td>
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<td>MCI due to AD or mild AD</td>
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<td>Soluble Aβ protofibrils</td>
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<td>Genentech/Roche</td>
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<td>Prodromal and mild/ moderate AD</td>
<td>Aβ 12–23</td>
<td>Soluble oligomeric/ fibrillar Aβ and plaque</td>
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<tr>
<td>Bapineuzumab</td>
<td>Elan/ Pfizer Inc./ Johnson &amp; Johnson</td>
<td>Intravenous and subcutaneous programs terminated</td>
<td>Mild/moderate AD</td>
<td>Aβ1–5</td>
<td>Soluble and aggregated Aβ</td>
</tr>
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<td>BIIB037</td>
<td>Biogen Idec/ Neuroimmune Therapeutics</td>
<td>1</td>
<td>MCI due to AD or mild AD</td>
<td>Conformational Aβ</td>
<td>Fibrillar Aβ</td>
</tr>
<tr>
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<td>Elan/Pfizer Inc./ Janssen</td>
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<td>Mild/moderate AD</td>
<td>Aβ1–6</td>
<td>Soluble and aggregated Aβ</td>
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<td>SAR228810</td>
<td>Sanofi</td>
<td>1</td>
<td>Mild/moderate AD</td>
<td>Not published</td>
<td>Soluble oligomeric/ protofibrillar Aβ</td>
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<td>AD</td>
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<td>Aggregated Aβ</td>
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<td>Pfizer Inc.</td>
<td>1</td>
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<td>Aβ33–40</td>
<td>Soluble and aggregated Aβ</td>
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</table>

Aβ, amyloid-beta; AD, Alzheimer’s disease; MCI, mild cognitive impairment.

**Table 2:** Ongoing and terminated passive immunotherapy clinical programs in Alzheimer’s disease [85].

As for conclusion, Aβ immunotherapy has gained a lot of attention and emerges as one of the most attractive approaches for disease intervention in AD. Aβ neurotoxicity has been shown to be caused by soluble protofibrils rather than insoluble fibrils, and this highlights protofibrils as targets for immunotherapy. Other encouraging efforts in immunotherapy as well as in the small-molecule field offer hope for new innovative therapies for AD in the future.
References


