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Treatment of Alzheimer's Disease: Current Management and Experimental Therapeutics

Lawrence S. Honig, MD, PhD, FAAN[*] and **Clara D. Boyd, MD, MA**[#]

Lawrence S. Honig: lh456@cumc.columbia.edu; Clara D. Boyd: cdb2014@cumc.columbia.edu

[*]Taub Institute for Research in Alzheimer's Disease and the Aging Brain, Department of Neurology, Columbia University Medical Center, Phone Number: 212-305-9194, Fax Number: 212-305-2526, Address: G. H. Sergievsky Center (P&S Unit 16), 630 West 168 St., New York, NY 10032

[#]Taub Institute for Research in Alzheimer's Disease and the Aging Brain, Department of Neurology, Columbia University Medical Center, Phone Number: 917-547-8952, Fax Number: 212-305-2526, Address: G. H. Sergievsky Center (P&S Unit 16), 630 West 168 St., New York, NY 10032

Abstract

Alzheimer's disease (AD) is a major cause of morbidity in the elderly. AD affects aver 5 million persons in the United States, but because it increases in incidence in the elderly, and the "graying" population, AD is projected to increase in prevalence by many-fold over the coming decades. AD causes progressive mental impairment, resulting in the inability of persons to care for themselves. As a consequence, AD results in enormous costs to society due to both lost productivity, and required care. Thus, improved management and treatment is essential. In this review we will briefly review current understanding of the disease, including roles of beta-amyloid and tau proteins. We will then discuss current therapies in use, including the evidence for treatments with supplements, established drugs, and investigational therapeutic strategies, recently completed and ongoing.

Keywords

Alzheimer's disease; Dementia; Elderly; Amyloid; Beta-amyloid; Tau; Phosphotau; Secretase; Beta-secretase; Gamma-secretase; Monoclonal antibody; Anti-amyloid; Cholinesterase; Treatment; Experimental therapeutics

Introduction

Alzheimer's disease (AD) is the most common cause of dementia, currently afflicting about 5 million persons in the US. AD incidence increases markedly with age, and the US and world population has increasing proportions of elderly individuals, in part due to improved medical care. Thus the prevalence of this disease is increasing in the US [1] as well as worldwide. There are currently no treatments proven to reverse, stabilize, or even slow the course of this progressive dementing disorder. However, there are five medications

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This article does not contain any studies with human or animal subjects performed by any of the authors.

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approved by the US Food and Drug Administration (FDA) for treatment of Alzheimer's disease, which provide modest benefits in cognition, behavior, and function [2], and a pharmacopeia of neuropsychiatric medications can be used to markedly ameliorate symptoms experienced by persons suffering from AD, although some of these latter are "off-label" when used for patients with AD, since their usage is not approved by the FDA for this condition.

The development of medications for AD has followed from the biological understanding of the disease. The medications approved by the FDA include neurotransmitter-based agents that interfere with deficits found in AD, including four drugs that inhibit acetylcholinesterase. The fifth approved drug is also neurotransmitter-based; it is an N-methyl-D-aspartate (NMDA)-receptor antagonist. The behavioral symptoms of AD can be usefully treated with expert use of a variety of neuropsychiatric medications including antidepressant medications, such as the selective serotonin reuptake inhibitors (SSRI), anxiolytic medications, and neuroleptic drugs (the typical and atypical antipsychotic agents). Despite popular interest in use of vitamins and supplements for AD, a large number of well-designed randomized placebo-controlled trials have not shown any benefit for each of these submitted to careful experimental testing. Actively investigated during the past 10 years have been a series of medications, of different types, which all have the aim of not simply ameliorating the symptoms of disease, but actually modifying disease progression, causing slowed degeneration. While none of these have yet shown clear efficacy, these drugs have generally been developed "intelligently," having been designed to interfere with the molecular pathological basis of the disease.

Pathophysiologic basis of AD

Alzheimer's disease is characterized by progressive neuronal dysfunction and degeneration. The pathological hallmarks are neuritic plaques and neurofibrillary tangles [3]. These findings were described by the German physician Alois Alzheimer in 1906. However, the protein constituents of plaques and tangles were not identified until the mid-1980s. Other findings include neuritic threads, which are of the same typology as tangles, granulovacuolar degeneration, neurotransmitter (neurochemical) changes, demonstrable loss of cerebral cortical synapses and, with the progression of disease, neuronal cellular degeneration and death. These latter features of synaptic loss and neuronal loss presumably most directly relate (rather than the pathologically distinctive plaques and tangles) to the cognitive and neuropsychiatric impairment in AD. It is commonly, but not universally believed, that the Aβ present in the plaques, and/or the tangles are "upstream", or causative to the synaptic and neuronal degeneration, which seem to be "downstream" events.

Plaques consist of extracellular deposits of aggregated fibrillary β-amyloid peptides. These β-amyloid (Aβ) peptides, principally the 40-amino acid (Aβ40) and 42-amino acid (Aβ42) peptides, are derived from a larger normal membrane-spanning cellular protein, the β-amyloid precursor protein (βAPP), which itself is of unclear function. Aβ is increased in the brains of persons with AD, partly in the severely aggregated form found in plaques, but also in monomers and oligomers. Increased Aβ may relate to increased production, changes in protein sorting and trafficking mechanisms, seeding and aggregation phenomena, and/or decreased clearance [4,5]. Considerable evidence suggests that Aβ42 is a more prominent constituent of the "senile neuritic plaques" of AD. While Aβ deposits are quite specific for AD (they do not appear in other neurological disease in the non-elderly), they can be found in the brains of persons who are not known to be cognitively symptomatic. The reason why some persons have greater Aβ, and a propensity to develop Aβ deposits, or manifest them at an earlier age is unclear. A few rare individuals (less than 1 % of Alzheimer's patients) develop Aβ deposits and AD as a consequence of autosomal dominantly inherited mutations

in one of three genes: βAPP, presenilin-1, and presenilin2. In these families, the mutations are causative of disease, and indeed the existence of these strictly familial forms of the disease have provided support for the primacy of Aβ in the development of AD, since βAPP is the protein precursor of Aβ peptides, and both presenilins are involved in the proteolytic excision of the Aβ peptides from βAPP. Even in the vast majority of AD cases, which are "sporadic" or non-familial, other genetic risk factors have been identified, now over 10 in number. The first-identified of these, the gene apolipoprotein E, carries the most risk, with individuals carrying one or two copies of the ε4 allele having several-fold higher risk of AD. However, apolipoprotein E and the other genetic risk factors each explain only portions of the risk [6]. Extensive experimental manipulations in cell culture, organotypic slices, and experimental animals, as well as the development of transgenic animal models, have all suggested that Aβ has nervous system toxicity [7]. This observation, in combination with the genetic findings, have led to a number of investigational treatments for AD based on decreasing Aβ in the brain [8,9].

The neurofibrillary tangles consist of intracellular deposits of aggregated fibrillary hyperphosphorylated tau protein. Tau is a microtubule-associated protein, normally present in cells in monomeric form, in which form it interacts with tubulin and adds stability to cellular microtubules. There are six isoforms of tau, which can be grouped as "3-repeat" or "4-repeat" isoforms, based on the number of microtubule-binding domains in the protein. These tau molecules, when abnormally aggregated and phosphorylated are a hallmark of AD, in which there is generally a mixture of 3-repeat and 4-repeat isoforms. But neurofibrillary tangles are not nonspecific for AD [10], also being found in a variety of other neurodegenerative diseases, although in some cases with different dominance of 3-repeat or 4-repeat isoforms. These diseases include certain frontotemporal dementias, progressive supranuclear palsy, corticobasal degeneration, Guamanian ALS-parkinsonism dementia complex, and chronic traumatic encephalopathy. There is growing evidence that abnormal intracellular tau may be toxic [11], and transferred between neurons [11,12]. Such trans-synaptic spread might be responsible for some of the neurodegeneration in AD [13]. It is not entirely clear whether the abnormal tau in AD is an essential and/or primary actor in the "cascade" of nervous system degeneration, or a downstream "marker" of neurodegeneration in AD. Regardless, neurofibrillary tangles do present a potential drug target for treating AD [14].

The pattern of neurodegeneration in AD varies between individuals, but typically, certain areas are affected early, including the entorhinal cortex and other temporal lobe structures important for memory. Similarly, some of the deep grey nuclei, including the nucleus basalis of Meynert [15], and locus ceruleus are prominently affected. The involvement of the cholinergic nucleus basalis was the basis for the development of the first successful AD drugs, the cholinesterase inhibitors. Their action is to inhibit normal acetylcholinesterase function in the brain, thereby increasing brain acetylcholine, in essence compensating for the cholinergic deficiency from the degenerative disease process.

The progressive neurodegenerative aspect of AD has also spawned a variety of ideas that certain supplements, vitamins, anti-oxidants, hormones, food items, neurotrophic substances, or other substances, might provide either specific or "general" benefits in the dementia of AD. We will discuss below the results of clinical trials of some of such agents.

Non-disease specific therapies to manage AD symptoms

AD is a disorder marked by memory and cognitive change, but there are commonly changes in behavior, which can be more disturbing to patients and families than the cognitive changes. These include depressive symptoms, such as apathy, disinterest, and loss of

appetite. There are also sleep disturbances, with primary insomnia and/or early morning awakening. Depressive symptoms may relate to both “primary depression” due to neurochemical changes of AD, and “secondary depression” due to the effects of memory and cognitive change on the affected patient’s psyche [16]. More troubling are psychotic symptoms. These symptoms include agitation, aggression, hallucinations, and delusions of various types, mostly paranoid, and/or person or place misidentification. Presence of these symptoms often prompts activation of emergency response systems, emergency room visits, hospitalizations, and ultimately is often responsible for inability of patients to remain in their home environment. These symptoms are often ameliorated by neuropsychiatric medications.

Anti-depressants are commonly used for depressive symptoms, and may improve irritability, depressed mood, apathy, appetite change, and sleep patterns. Most frequently used are antidepressant medications of the SSRI class, such as sertraline, fluoxetine, paroxetine, citalopram, or escitalopram. Antidepressants of other classes including serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine), and other drugs such as trazodone, bupropion, and mirtazapine may also be used. Tricyclic antidepressants are typically avoided because of their anticholinergic side-effects. Antidepressants often improve patients’ sense of well-being, sleep cycles, anxiety, and irritability, [17,18] and may sometimes improve concentration, but do not improve cognition. Psychotic symptoms generally respond best to antipsychotic medications, the neuroleptics. Some reports suggest either limited, or no improvement of psychotic symptoms with acetylcholinesterase inhibitor therapy [19,20], memantine [21], or antidepressant therapy [18]. However, in general, dopaminergic antagonists are required to significantly treat these symptoms, and most frequently the atypical neuroleptics are used. These drugs, which include quetiapine, risperidone, olanzapine, and clozapine, but also iloperidone, aripiprazole, and ziprazidone, are all not approved by the FDA for this use. In fact, the drugs carry warning labels on their US package inserts specifying that use of these drugs in the elderly with dementia may be associated with a small increase in mortality. However, the best controlled studies of such drugs have not demonstrated increased mortality [22]. These drugs, properly used, should be started at low doses, gradually escalated, and carefully monitored, avoiding use of higher doses than necessary to control the psychotic symptoms. Each of these drugs has risks, including sedation, weight gain, and diabetes. With the exception of quetiapine and clozapine, drug-induced parkinsonism is a common side-effect with higher doses. However, despite these risks, and even the possibility of slight increased risk of death with proper use of these drugs, the psychotic symptoms of AD are so threatening to the well-being of patients and their families, that generally physicians and patients’ families are willing to accept risks for the marked benefits these drugs may provide, when used carefully and with expertise. That said, a thorough discussion of the risks, including the FDA “black box warning” is always warranted.

Neurotransmitter-based therapies for AD

The initial elucidation of the “cholinergic deficit” of AD [15] resulted in the development of anti-cholinesterase therapies for AD [23]. A variety of acetylcholinesterase inhibitors were given to patients with AD in a succession of clinical trials. While a few were apparently either insufficiently efficacious or had unacceptable side-effects, ultimately there were four such acetylcholinesterase inhibitor (AChEI) drugs approved in the US between 1993 and 2001, followed by another neurotransmitter-based drug, memantine hydrochloride in 2003. (See Table 1)

The first neurotransmitter-based drug, tacrine hydrochloride, had a short effective half-life, requiring dosing four times daily, and had common side-effects of hepatic toxicity, requiring blood monitoring. As a result, it is now very rarely used. Donepezil hydrochloride, was

approved in 1996, with once daily dosing. Subsequently, rivastigmine tartrate and galantamine hydrobromide were each approved, initially with twice daily dosing, and then in formulations allowing once daily dosing (See Table 1). In placebo-controlled randomized controlled trials generally of about 6 months duration, but in some cases longer, these three AChEI drugs each shows benefits in a many trials with respect to cognition, behavior, and function. The effect size is modest. In most trials the benefit of drug versus placebo has been about 3–5 points on the 70-point Alzheimer's Disease Assessment Scale (ADAS-cog) [24–27]. This can also be contextualized by comparing this degree of beneficial change to the common rate of decline, which is about the same number of points over 6–12 months. There is no good evidence that these drugs modify disease course, but there is also not evidence that in mild-moderate disease the effect of the drugs "wears-off" or is reduced over time. A variety of side-effects may be observed, which principally involve the gastrointestinal system, due to systemic pro-cholinergic activity. The induced hypermotility of the gut may cause nausea, vomiting, diarrhea, and presumed secondary loss of appetite and weight loss. Other side-effects are also cholinergic in nature and include nightmares, an effect on the brainstem, leg cramps, an effect on the neuromuscular junction, and bradycardia or even syncope (an effect on the vagal heart innervation). However, despite side-effects, the drugs are generally well tolerated. Studies show that all four approved AChEI drugs are effective in mild-to-moderate Alzheimer's disease [24–27]. Donepezil also has FDA approval for use in severe Alzheimer's disease [28], and rivastigmine has approval for dementia associated with Parkinson's disease [29]. For none of these drugs have studies clearly shown a significant benefit in persons suffering from mild cognitive impairment (MCI) [30–32], even in such patients as incipient Alzheimer's disease is strongly suspected. For this reason, there is no FDA approval for the use of AChEI in persons with MCI. However, since the diagnostic line between MCI and mild Alzheimer's disease is often unclear, there is wide usage of the AChEI in the US in patients with MCI, despite the off-label nature of such prescriptions.

Memantine was approved for moderate-to-severe AD in 2003, and is a neurotransmitter-based therapy, that is not based on acetylcholine. This drug is said to act as an activity dependent NMDA antagonist, dampening excitatory activity when it is excessive. The drug shows modest beneficial activity on tests of cognitive impairment, and also in some trials for behavior, and function, but only in patients with moderate -to-severe disease. There is no proven efficacy in patients with mild AD, nor in persons with MCI. Because of the patient population in which this drug was successfully tested, the degree of efficacy cannot be exactly compared to that of the AChEI, but it is likely that it is not dissimilar. Furthermore, studies using memantine as an "add-on" therapy, to patients who already are on a cholinesterase inhibitor such as donepezil, have shown benefit, indicating that the drug is not likely acting by the same mechanism as the AChEI drugs. Side-effects include constipation, but also sometimes dizziness and sedation. Overall it is well tolerated despite these potential side-effects.

Vitamins and Supplements

Vitamins and supplements are widely used by the US population. This usage is both for perceived general "prophylactic" purposes, and because of varied beliefs that these substances, available over the counter, without prescription, and often perceived as more "natural" than prescription medications, might provide benefits in various diseases and conditions. Specifically, there is much advertising on the radio, television, internet, and books and other media promoting the benefits of these substances, that are not FDA-regulated as drugs, for disease of the brain including dementia and specifically AD. Patients and their caregivers often view the use of vitamins or supplements as harmless. Differing substances have had their popularity wax and wane. Supplements prominently advertised for

AD have recently included *Gingko biloba* extracts [33], B vitamins, fish oil or other omega-3 products [34], medium-chain fatty acids (found in a variety of foods including coconuts), and turmeric (otherwise known as curcurmin, and an ingredient of South Asian curries) [35]. Because of this interest and usage, there have been in recent years a number of studies, some of large size, examining in well-performed randomized controlled trials the efficacy and safety of such treatments. For each of these substances, a careful review of the extant high quality studies reveals that there is not good evidence for efficacy, and that in a few cases, there are some significant adverse effects. Table 2 shows a summary of some of the randomized placebo-controlled studies on these substances.

Investigational agents to Modify Disease Course in AD

The neurotransmitter or non-disease-specific therapies for AD do not modify the course of disease. They only provide a symptomatic benefit. Thus, for the past decade, with advances in molecular pathology, there have been increasing attempts to arrive at agents that might modify disease, by slowing, halting, or even potentially reversing the progression of AD. Since significant evidence points to a primacy of Aβ in the disease pathogenetic cascade, many of these interventions have been directed towards Aβ. The three main categories of Aβ-related intervention are therapies to decrease Aβ production, therapies to increase Aβ clearance from the brain, and treatments designed to decrease Aβ fibril formation or aggregation.

Decreased production of Aβ might arguably be the most potent way of intervening in Alzheimer's disease. Aβ production can potentially be decreased through enhancement of alpha-secretase, an enzymatic activity that cuts the βAPP molecule in such a way that Aβ cannot be generated, but such a strategy has not yet resulted in significant human clinical drug studies. Reduction of Aβ production through inhibition of gamma-secretase, has been attempted with several drugs. Flurbiprofen, is a selective inhibitor of Aβ42 production in vitro, and in animal models, but failed in a large trial to beneficially affect AD clinical course [36]. It has been argued that one reason this drug may have failed is inadequate penetration into the human central nervous system. If a drug does not "engage the target", it cannot be expected to be efficacious. Semagacestat and avagacestat are non-selective inhibitors of gamma-secretase. Semagacestat showed pre-clinical and clinical evidence in phase 1 and 2 studies for reduction of production of Aβ. Despite relatively unchanged subject CSF Aβ levels, the drug clearly lowered plasma Aβ, and there was some evidence of decreased production of Aβ in the central nervous system [37–39]. These gamma-secretase inhibitor drugs also showed evidence of significant potential toxicity, particularly in the gastrointestinal system, skin, and eyes. Semagacestat failed to beneficially affect AD, and surprisingly, there was evidence that the drug actually had adverse cognitive effects [40]. Avagacestat, a drug with somewhat more specificity for βAPP than semagacestat, also failed to show evidence of cognitive or functional benefit [41]. Since, there is some evidence that these gamma-secretase inhibitors did affect Aβ production in the human central nervous system, their lack of efficacy is still unexplained, although it is possible that due to pharmacokinetics and rebound effects, there was not an overall chronic decrease in Aβ in the brain. It has not been elucidated whether the adverse effects on cognition were also related to effects on Aβ or were more related to "off-target" effects of inhibition of gamma-secretase. This enzymatic activity has a roster of important target molecules other than βAPP. Beta-secretase inhibitors are now being investigated, as an alternative method of effectively decreasing Aβ production [42].

Increased clearance of Aβ from the brain can also be viewed as a potentially beneficial route to decreasing progression of AD. In 1999, active immunization with Aβ was shown to decrease Aβ in mice brains [43]. Subsequently, human studies with the agent AN-1792 were

halted when this agent caused meningoencephalitis in about 5 % of treated subjects [44]. There was no clear evidence of efficacy in the halted trial [45], although a variety of later reports suggested that Aβ might indeed have been cleared [46], and that perhaps there was suggestive evidence that "responders" to the immunization did better [47]. While AN-1792 development was stopped, other drugs based on active immunization, such as vanutide cridificar (ACC-001) are under investigation. Passive immunization, in which antibody to Aβ is delivered intravenously or subcutaneously, continues to be an important therapeutic avenue of investigation. The drug bapineuzumab failed to show efficacy in recent reports, but the drug solanezumab showed some evidence of possible efficacy in large phase 3 trials, particularly in persons with only mild disease. Other monoclonal antibodies, such as crenezumab, and gantenerumab are likewise under investigation. Some of these antibodies are more active at clearing soluble Aβ, possibly oligomeric Aβ, and others more at providing for clearance of deposited Aβ in plaques. There is reasonable evidence for at least bapineuzumab, that the drug does increase clearance of Aβ, as judged by amyloid-specific positron emission tomography [48]; however at least this drug was unable to be delivered at large doses, due to dose-dependent side-effects of brain vasogenic edema (VE, now termed, ARIA or "amyloid related imaging abnormality") [49]. The failure of bapineuzumab, and lack of clear efficacy of solanezumab to date, have raised the question of whether the failure of these drugs indicates that increased Aβ clearance is not a useful strategy, or whether simply there increased clearance is insufficient in degree, or may be too late in the process. It is possible that by the time significant amyloid is present in the brain, that certain injurious processes are set in place that will proceed regardless of therapy. A number of trials, some sponsored in part by NIH, are proceeding using solanezumab, crenezumab, and gantenerumab, in persons with earlier stages of AD, including persons genetically at risk of AD.

Various other investigational strategies have either been completed, or are underway, in attempts to slow AD progression. In addition to specific anti-amyloid antibody immunization treatment strategies, there has been a large trial of infusion of pooled human intravenous gamma-globulin (IVIG). Recent conclusion of this study revealed no evidence of efficacy of this "immune" treatment in AD. Drug treatments designed to decrease Aβ fibrillization or aggregation, including homotaurine [50] and scyllo-inositol [51] have not proven effective. Various studies of growth factors are in very early stage development. Likewise, drugs which might decrease tau aggregation or deter neurofibrillary tangle formation are only in early stages of development.

Conclusions

The past 20 years have seen the development of five FDA-approved drugs for AD. These drugs, along with the existing armamentarium of neuropsychiatric medications for behavioral symptoms of AD, have some clinical utility. Patients have benefited from having treatments available for this previously untreatable disorder. However, none of these treatments are in disease-modifying. The drugs provide symptomatic benefits without ultimately affecting disease course, which owes to progressive neurodegeneration, ultimately involving synaptic and neuronal cell losses. The rapidly increasing body of knowledge regarding the molecular processes underlying neurodegeneration in AD, including the roles of beta-amyloid, tau, protein aggregation, sorting and traffic, have given rise to a number of conceptual frameworks for intervening in AD. However, drug trials to date (during the past 10 years) designed to decrease Aβ fibrillization or aggregation, lessen production of Aβ, or decrease brain burden of Aβ through increasing Aβ clearance, have not yet resulted in a demonstrably effective therapy. While some investigators have become disheartened by the failed studies, it is most likely that further aggressive research at basic

science, translational, and clinical investigations will indeed result in drug therapies that will improve management of AD by affecting disease course.

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References

1. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the united states (2010–2050) estimated using the 2010 census. Neurology. 2013
2. Schneider LS. Alzheimer disease pharmacologic treatment and treatment research. Continuum (Minneap Minn). 2013; 19(2 Dementia):339–357. [PubMed: 23558481]
3. Nelson PT, Braak H, Markesbery WR. Neuropathology and cognitive impairment in alzheimer disease: A complex but coherent relationship. J Neuropathol Exp Neurol. 2009; 68(1):1–14. [PubMed: 19104448]
4. Bateman RJ, Munsell LY, Morris JC, Swarm R, Yarasheski KE, Holtzman DM. Human amyloid-beta synthesis and clearance rates as measured in cerebrospinal fluid in vivo. Nature medicine. 2006; 12(7):856–861.
5. Small SA, Gandy S. Sorting through the cell biology of alzheimer's disease: Intracellular pathways to pathogenesis. Neuron. 2006; 52(1):15–31. [PubMed: 17015224]
6. Tsuang D, Leverenz JB, Lopez OL, Hamilton RL, Bennett DA, Schneider JA, Buchman AS, Larson EB, Crane PK, Kaye JA, Kramer P, et al. Apoe epsilon4 increases risk for dementia in pure synucleinopathies. JAMA Neurol. 2013; 70(2):223–228. [PubMed: 23407718]
7. Hardy J, Selkoe DJ. The amyloid hypothesis of alzheimer's disease: Progress and problems on the road to therapeutics. Science. 2002; 297(5580):353–356. [PubMed: 12130773]
8. Selkoe DJ, Schenk D. Alzheimer's disease: Molecular understanding predicts amyloid-based therapeutics. Annu Rev Pharmacol Toxicol. 2003; 43:545–584. [PubMed: 12415125]
9. Schenk D, Basi GS, Pangalos MN. Treatment strategies targeting amyloid beta-protein. Cold Spring Harb Perspect Med. 2012; 2(9):a006387. [PubMed: 22951439]
10. Pasquier F, Delacourte A. Non-alzheimer degenerative dementias. Curr Opin Neurol. 1998; 11(5): 417–427. [PubMed: 9847989]
11. de Calignon A, Polydoro M, Suarez-Calvet M, William C, Adamowicz DH, Kopeikina KJ, Pitstick R, Sahara N, Ashe KH, Carlson GA, Spires-Jones TL, et al. Propagation of tau pathology in a model of early alzheimer's disease. Neuron. 2012; 73(4):685–697. [PubMed: 22365544]
12. Liu L, Drouet V, Wu JW, Witter MP, Small SA, Clelland C, Duff K. Trans-synaptic spread of tau pathology in vivo. PLoS One. 2012; 7(2):e31302. [PubMed: 22312444]
13. Walker LC, Diamond MI, Duff KE, Hyman BT. Mechanisms of protein seeding in neurodegenerative diseases. Arch Neurol. 2012:1–7. [PubMed: 23228982]
14. Yoshiyama Y, Lee VM, Trojanowski JQ. Therapeutic strategies for tau mediated neurodegeneration. J Neurol Neurosurg Psychiatry. 2013; 84(7):784–795. [PubMed: 23085937]
15. Whitehouse PJ, Price DL, Struble RG, Clark AW, Coyle JT, Delon MR. Alzheimer's disease and senile dementia: Loss of neurons in the basal forebrain. Science. 1982; 215(4537):1237–1239. [PubMed: 7058341]
16. Even C, Weintraub D. Case for and against specificity of depression in alzheimer's disease. Psychiatry Clin Neurosci. 2010; 64(4):358–366. [PubMed: 20573052]
17. Cummings JL, McRae T, Zhang R. Effects of donepezil on neuropsychiatric symptoms in patients with dementia and severe behavioral disorders. Am J Geriatr Psychiatry. 2006; 14(7):605–612. [PubMed: 16816014]
18. Siddique H, Hynan LS, Weiner MF. Effect of a serotonin reuptake inhibitor on irritability, apathy, and psychotic symptoms in patients with alzheimer's disease. J Clin Psychiatry. 2009; 70(6):915–918. [PubMed: 19422762]
19. Rodda J, Morgan S, Walker Z. Are cholinesterase inhibitors effective in the management of the behavioral and psychological symptoms of dementia in alzheimer's disease? A systematic review

of randomized, placebo-controlled trials of donepezil, rivastigmine and galantamine. International psychogeriatrics/IPA. 2009; 21(5):813–824. [PubMed: 19538824]

20. Howard RJ, Juszczak E, Ballard CG, Bentham P, Brown RG, Bullock R, Burns AS, Holmes C, Jacoby R, Johnson T, Knapp M, et al. Donepezil for the treatment of agitation in alzheimer's disease. N Engl J Med. 2007; 357(14):1382–1392. [PubMed: 17914039]
21. Fox C, Crugel M, Maidment I, Auestad BH, Coulton S, Treloar A, Ballard C, Boustani M, Katona C, Livingston G. Efficacy of memantine for agitation in alzheimer's dementia: A randomised double-blind placebo controlled trial. PLoS One. 2012; 7(5):e35185. [PubMed: 22567095]
22. Schneider LS, Tariot PN, Dagerman KS, Davis SM, Hsiao JK, Ismail MS, Lebowitz BD, Lyketsos CG, Ryan JM, Stroup TS, Sultzer DL, et al. Effectiveness of atypical antipsychotic drugs in patients with alzheimer's disease. N Engl J Med. 2006; 355(15):1525–1538. [PubMed: 17035647]
23. Farlow MR, Cummings JL. Effective pharmacologic management of alzheimer's disease. Am J Med. 2007; 120(5):388–397. [PubMed: 17466645]
24. Birks JS, Harvey R. Donepezil for dementia due to alzheimer's disease. Cochrane database of systematic reviews. 2003; (3):CD001190. [PubMed: 12917900]
25. Onor ML, Trevisiol M, Aguglia E. Rivastigmine in the treatment of alzheimer's disease: An update. Clinical interventions in aging. 2007; 2(1):17–32. [PubMed: 18044073]
26. Cummings J, Winblad B. A rivastigmine patch for the treatment of alzheimer's disease and parkinson's disease dementia. Expert review of neurotherapeutics. 2007; 7(11):1457–1463. [PubMed: 17997695]
27. Olin J, Schneider L. Galantamine for alzheimer's disease. Cochrane database of systematic reviews. 2002; (3):CD001747. [PubMed: 12137632]
28. Winblad B. Donepezil in severe alzheimer's disease. American journal of Alzheimer's disease and other dementias. 2009; 24(3):185–192.
29. Siddiqui MA, Wagstaff AJ. Rivastigmine in parkinson's disease dementia: Profile report. Drugs & aging. 2007; 24(3):255–259. [PubMed: 17362052]
30. Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, Galasko D, Jin S, Kaye J, Levey A, Pfeiffer E, et al. Vitamin e and donepezil for the treatment of mild cognitive impairment. N Engl J Med. 2005; 352(23):2379–2388. [PubMed: 15829527]
31. Winblad B, Wimo A, Engedal K, Soininen H, Verhey F, Waldemar G, Wetterholm AL, Haglund A, Zhang R, Schindler R. 3-year study of donepezil therapy in alzheimer's disease: Effects of early and continuous therapy. Dement Geriatr Cogn Disord. 2006; 21(5–6):353–363. [PubMed: 16508298]
32. Feldman HH, Ferris S, Winblad B, Sfikas N, Mancione L, He Y, Tekin S, Burns A, Cummings J, del Ser T, Inzitari D, et al. Effect of rivastigmine on delay to diagnosis of alzheimer's disease from mild cognitive impairment: The inddex study. Lancet Neurol. 2007; 6(6):501–512. [PubMed: 17509485]
33. McCarney R, Fisher P, Iliffe S, van Haselen R, Griffin M, van der Meulen J, Warner J. Ginkgo biloba for mild to moderate dementia in a community setting: A pragmatic, randomised, parallel-group, double-blind, placebo-controlled trial. Int J Geriatr Psychiatry. 2008; 23(12):1222–1230. [PubMed: 18537221]
34. Jicha GA, Markesbery WR. Omega-3 fatty acids: Potential role in the management of early alzheimer's disease. Clinical interventions in aging. 2010; 5:45–61. [PubMed: 20396634]
35. Ringman JM, Frautschy SA, Teng E, Begum AN, Bardens J, Beigi M, Gylys KH, Badmaev V, Heath DD, Apostolova LG, Porter V, et al. Oral curcumin for alzheimer's disease: Tolerability and efficacy in a 24-week randomized, double blind, placebo-controlled study. Alzheimers Res Ther. 2012; 4(5):43. [PubMed: 23107780]
36. Green RC, Schneider LS, Amato DA, Beelen AP, Wilcock G, Swabb EA, Zavitz KH. Effect of tarenflurbil on cognitive decline and activities of daily living in patients with mild alzheimer disease: A randomized controlled trial. JAMA. 2009; 302(23):2557–2564. [PubMed: 20009055]
37. Siemers ER, Friedrich S, Dean RA, Gonzales CR, Farlow MR, Paul SM, Demattos RB. Safety and changes in plasma and cerebrospinal fluid amyloid beta after a single administration of an amyloid beta monoclonal antibody in subjects with alzheimer disease. Clin Neuropharmacol. 2010; 33(2): 67–73. [PubMed: 20375655]

38. Bateman RJ, Siemers ER, Mawuenyega KG, Wen G, Browning KR, Sigurdson WC, Yarasheski KE, Friedrich SW, Demattos RB, May PC, Paul SM, et al. A gamma-secretase inhibitor decreases amyloid-beta production in the central nervous system. Annals of neurology. 2009; 66(1):48–54. [PubMed: 19360898]
39. Siemers ER, Quinn JF, Kaye J, Farlow MR, Porsteinsson A, Tariot P, Zoulnouni P, Galvin JE, Holtzman DM, Knopman DS, Satterwhite J, et al. Effects of a gamma-secretase inhibitor in a randomized study of patients with alzheimer disease. Neurology. 2006; 66(4):602–604. [PubMed: 16505324]
40. Carlson C, Estergard W, Oh J, Suhy J, Jack CR Jr, Siemers E, Barakos J. Prevalence of asymptomatic vasogenic edema in pretreatment alzheimer's disease study cohorts from phase 3 trials of semagacestat and solanezumab. Alzheimers Dement. 2011; 7(4):396–401. [PubMed: 21784350]
41. Coric V, van Dyck CH, Salloway S, Andreasen N, Brody M, Richter RW, Soininen H, Thein S, Shiovitz T, Pilcher G, Colby S, et al. Safety and tolerability of the gamma-secretase inhibitor avagacestat in a phase 2 study of mild to moderate alzheimer disease. Arch Neurol. 2012; 69(11): 1430–1440. [PubMed: 22892585]
42. Ghosh AK, Brindisi M, Tang J. Developing beta-secretase inhibitors for treatment of alzheimer's disease. J Neurochem. 2012; 120(Suppl 1):71–83. [PubMed: 22122681]
43. Schenk D, Barbour R, Dunn W, Gordon G, Grajeda H, Guido T, Hu K, Huang J, Johnson-Wood K, Khan K, Kholodenko D, et al. Immunization with amyloid-beta attenuates alzheimer-disease-like pathology in the pdapp mouse. Nature. 1999; 400(6740):173–177. [PubMed: 10408445]
44. Orgogozo JM, Gilman S, Dartigues JF, Laurent B, Puel M, Kirby LC, Jouanny P, Dubois B, Eisner L, Flitman S, Michel BF, et al. Subacute meningoencephalitis in a subset of patients with ad after abeta42 immunization. Neurology. 2003; 61(1):46–54. [PubMed: 12847155]
45. Gilman S, Koller M, Black RS, Jenkins L, Griffith SG, Fox NC, Eisner L, Kirby L, Rovira MB, Forette F, Orgogozo JM. Clinical effects of abeta immunization (an1792) in patients with ad in an interrupted trial. Neurology. 2005; 64(9):1553–1562. [PubMed: 15883316]
46. Holmes C, Boche D, Wilkinson D, Yadegarfar G, Hopkins V, Bayer A, Jones RW, Bullock R, Love S, Neal JW, Zotova E, et al. Long-term effects of abeta42 immunisation in alzheimer's disease: Follow-up of a randomised, placebo-controlled phase i trial. Lancet. 2008; 372(9634): 216–223. [PubMed: 18640458]
47. Vellas B, Black R, Thal LJ, Fox NC, Daniels M, McLennan G, Tompkins C, Leibman C, Pomfret M, Grundman M. Long-term follow-up of patients immunized with an1792: Reduced functional decline in antibody responders. Curr Alzheimer Res. 2009; 6(2):144–151. [PubMed: 19355849]
48. Rinne JO, Brooks DJ, Rossor MN, Fox NC, Bullock R, Klunk WE, Mathis CA, Blennow K, Barakos J, Okello AA, Rodriguez Martinez de Liano S, et al. 11c-pib pet assessment of change in fibrillar amyloid-beta load in patients with alzheimer's disease treated with bapineuzumab: A phase 2, double-blind, placebo-controlled, ascending-dose study. Lancet Neurol. 2010; 9(4):363–372. [PubMed: 20189881]
49. Sperling RA, Jack CR Jr, Black SE, Frosch MP, Greenberg SM, Hyman BT, Scheltens P, Carrillo MC, Thies W, Bednar MM, Black RS, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: Recommendations from the alzheimer's association research roundtable workgroup. Alzheimers Dement. 2011; 7(4):367–385. [PubMed: 21784348]
50. Aisen PS, Gauthier S, Ferris SH, Saumier D, Haine D, Garceau D, Duong A, Suhy J, Oh J, Lau WC, Sampalis J. Tramiprosate in mild-to-moderate alzheimer's disease - a randomized, double-blind, placebo-controlled, multi-centre study (the alphase study). Arch Med Sci. 2011; 7(1):102–111. [PubMed: 22291741]
51. Salloway S, Sperling R, Keren R, Porsteinsson AP, van Dyck CH, Tariot PN, Gilman S, Arnold D, Abushakra S, Hernandez C, Crans G, et al. A phase 2 randomized trial of elnd005, scyllo-inositol, in mild to moderate alzheimer disease. Neurology. 2011; 77(13):1253–1262. [PubMed: 21917766]
52. Aisen PS, Schneider LS, Sano M, Diaz-Arrastia R, van Dyck CH, Weiner MF, Bottiglieri T, Jin S, Stokes KT, Thomas RG, Thal LJ. High-dose b vitamin supplementation and cognitive decline in alzheimer disease: A randomized controlled trial. JAMA. 2008; 300(15):1774–1783. [PubMed: 18854539]

53. Sun Y, Lu CJ, Chien KL, Chen ST, Chen RC. Efficacy of multivitamin supplementation containing vitamins b6 and b12 and folic acid as adjunctive treatment with a cholinesterase inhibitor in alzheimer's disease: A 26-week, randomized, double-blind, placebo-controlled study in taiwanese patients. Clin Ther. 2007; 29(10):2204–2214. [PubMed: 18042476]
54. Galasko DR, Peskind E, Clark CM, Quinn JF, Ringman JM, Jicha GA, Cotman C, Cottrell B, Montine TJ, Thomas RG, Aisen P. Antioxidants for alzheimer disease: A randomized clinical trial with cerebrospinal fluid biomarker measures. Arch Neurol. 2012; 69(7):836–841. [PubMed: 22431837]
55. Arlt S, Muller-Thomsen T, Beisiegel U, Kontush A. Effect of one-year vitamin c- and e-supplementation on cerebrospinal fluid oxidation parameters and clinical course in alzheimer's disease. Neurochem Res. 2012; 37(12):2706–2714. [PubMed: 22878647]
56. Stein MS, Scherer SC, Ladd KS, Harrison LC. A randomized controlled trial of high-dose vitamin d2 followed by intranasal insulin in alzheimer's disease. J Alzheimers Dis. 2011; 26(3):477–484. [PubMed: 21694461]
57. Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M, Woodbury P, Growdon J, Cotman CW, Pfeiffer E, Schneider LS, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for alzheimer's disease. The alzheimer's disease cooperative study. N Engl J Med. 1997; 336(17):1216–1222. [PubMed: 9110909]
58. Lloret A, Badia MC, Mora NJ, Pallardo FV, Alonso MD, Vina J. Vitamin e paradox in alzheimer's disease: It does not prevent loss of cognition and may even be detrimental. J Alzheimers Dis. 2009; 17(1):143–149. [PubMed: 19494439]
59. Quinn JF, Raman R, Thomas RG, Yurko-Mauro K, Nelson EB, Van Dyck C, Galvin JE, Emond J, Jack CR Jr, Weiner M, Shinto L, et al. Docosahexaenoic acid supplementation and cognitive decline in alzheimer disease: A randomized trial. JAMA. 2010; 304(17):1903–1911. [PubMed: 21045096]
60. Freund-Levi Y, Eriksdotter-Jonhagen M, Cederholm T, Basun H, Faxen-Irving G, Garlind A, Vedin I, Vessby B, Wahlund LO, Palmblad J. Omega-3 fatty acid treatment in 174 patients with mild to moderate alzheimer disease: Omegad study: A randomized double-blind trial. Arch Neurol. 2006; 63(10):1402–1408. [PubMed: 17030655]
61. Rafii MS, Walsh S, Little JT, Behan K, Reynolds B, Ward C, Jin S, Thomas R, Aisen PS. A phase ii trial of huperzine a in mild to moderate alzheimer disease. Neurology. 2011; 76(16):1389–1394. [PubMed: 21502597]
62. Schneider LS, DeKosky ST, Farlow MR, Tariot PN, Hoerr R, Kieser M. A randomized, double-blind, placebo-controlled trial of two doses of ginkgo biloba extract in dementia of the alzheimer's type. Curr Alzheimer Res. 2005; 2(5):541–551. [PubMed: 16375657]
63. Baum L, Lam CW, Cheung SK, Kwok T, Lui V, Tsoh J, Lam L, Leung V, Hui E, Ng C, Woo J, et al. Six-month randomized, placebo-controlled, double-blind, pilot clinical trial of curcumin in patients with alzheimer disease. J Clin Psychopharmacol. 2008; 28(1):110–113. [PubMed: 18204357]
64. Henderson ST, Vogel JL, Barr LJ, Garvin F, Jones JJ, Costantini LC. Study of the ketogenic agent ac-1202 in mild to moderate alzheimer's disease: A randomized, double-blind, placebo-controlled, multicenter trial. Nutr Metab (Lond). 2009; 6(31)

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Table 1

FDA-approved medications for Alzheimer's Disease

Drug	Tacrine hydrochloride	Donepezil hydrochloride	Rivastigmine tartrate	Galantamine hydrobromide	Memantine hydrochloride
Type of Inhibition	Reversible	Reversible	Irreversible	Reversible	Reversible
Metabolism & Excretion	Hepatic	Hepatic	Plasma/renal	Hepatic/renal	Hepatic
Plasma Half-Life	Short (~ 3 hr)	Long (~ 70 hr)	Short (~ 1.5 hr)	Medium (~ 6 hr)	Long (~80 hr)
Dose forms	Oral	Oral, oral dissolvable, oral ER	Oral, transdermal	Oral, Oral ER	Oral, Oral ER
Doses daily	4	1	2 (oral)	1 (oral ER)	2 (oral)
			1 (transdermal)		1 (oral ER)

ER extended release

Table 2

Placebo-controlled trials of vitamins & supplements in AD treatment

Vitamin A	No randomized trials of vitamin A alone; combination studies did not use it in significant quantities.
B vitamins and folate	Negative [52] 2008 Multicenter trial with 340 probable AD patients (mild to mod) also taking AChEI +/− Memantine receiving neutriceutical formula (Vitamin B6 + Vitamin B12 + Folic Acid) for 18 months. Treatment group had no benefit on cognitive or functional outcomes.
	Negative [53] 2007 Single center trial of 89 AD patients also taking AChEI received placebo or formula (B12 + B6 + folic acid + small amounts of other vitamins + iron) over 6 mos. Treatment group had no benefit on cognitive or functional outcomes.
Vitamin C	Negative [54] 2012 Multicenter Phase 1 of formula containing 500 mg VitC (below). No randomized trials of vitamin C alone.
	Negative [55] 2010 Single center trial of 23 patients with AD getting either both vitamins C and E or placebo, showed no benefit on cognition.
Vitamin D	Negative [56] 2011 Single-center trial of 95 patients with AD involving both vitamin D and intranasal insulin showed no benefit of high-dose vitamin D.
Vitamin E	Positive [57] 1997 Multicenter Phase 3 in probable AD (moderate) for 2 yrs, showed, after adjustment, some functional, but no cognitive benefit.
	Negative [58] 2009 Single center RCT of 57 probable AD patients also taking AChEI showed no benefit
	Negative [54] 2012 Multicenter RCT of formula containing 800 IU/d α-tocopherol showed some additional cognitive decline on formula.
	Negative [55] 2010 Single center trial of 23 patients with AD getting either both vitamins C and E or placebo, showed no benefit on cognition.
Coenzyme Q	Negative [54] 2012 multicenter trial of probable AD required to be taking AChEI +/− Memantine, with duration 16 weeks. Subjects received neutriceutical formula (Vitamin E + Vitamin C + α-Lipoic acid) or Coenzyme Q. There was no benefit to cognition or function of neutriceutical or Coenzyme Q, but some evidence of worsening cognition on formula.
Fish-Oil/Omega-3/eicosopentonic acid (EPA)	Negative [59] 2010 Multicenter trial of 402 probable AD pts on AchEI +/− memantine showed no benefit over 18 months on cognition, function, or brain atrophy.
	Negative [60] 2006 single center efficacy trial of 204 AD patients taking AChEI showed no benefit of DHA + EPA over 6 months on cognition.
Huperzine A	Negative [61] 2011 multicenter RCT with 210 AD patients showed no effect over 16 weeks on cognition or global function
Gingko biloba	Negative [62] 2005 Multicenter US RCT with no benefit.
	Negative [33] 2008 Multicenter UK RCT with no benefit.
Curcurmin/Turmeric	Negative [63] 2008 Single center RCT with no benefit
	Negative [35] 2008 Single center RCT with 36 AD patients over 48 weeks with no benefit.
AC-1202/medium chain triglycerides	Negative [64] 2009 Multicenter trial did not show benefit in cognition on intent-to-treat analysis at end of trial (90 days).

AChEI acetylcholinesterase inhibitor; *RCT* randomized controlled trial.