Update on Alzheimer's Disease
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Stephen S. Flitman, MD, Medical Director
21st Century Neurology
3100 North Third Ave Suite 100, Phoenix, Arizona
(602) 265-6500
www.neurozone.org

Alzheimer's Disease (AD), first described by Dr. Alois Alzheimer in 1907, is a disorder that 10 million Americans are thought to have, but less than 40% are diagnosed or receiving treatment now. It is very common, affecting people ages 40-90 with 2-4% prevalence at ages 65-75 and increasing in subsequent decades. After heart disease, cancer, and stroke it is the fourth leading cause of death in the US. AD is a disorder of the gray matter of the cerebral cortex. It is characterized clinically by gradually progressive dementia and pathologically by extraneuronal plaques and intraneuronal neurofibrillary tangles by light microscopy. AD progresses anatomically via the connections made by affected neurons. It starts in the entorhinal cortex and then spreads to the hippocampus, basal nuclei, and then to the neocortex. It spares primary motor and sensory cortices, preferentially attacking association areas in the frontal, parietal, and temporal lobes. Affected regions have neurochemical deficits of acetylcholine, glutamate, and serotonin. The degree of dementia correlates with the decline in these neurotransmitters in biopsy or autopsy tissue. While short-term memory deficits predominate early in the progressive dementias, the term dementia is reserved for a clinical syndrome of memory disorder plus at least one other cognitive realm: language, motor or procedural memory (praxis), spatial function, and executive function (decision-making, planning, overall control of behavior). As an etiology for dementia, AD accounts for about two-thirds of cases, with metabolic causes and Lewy body disease making up the lion's share of the remaining third. Beginning between the ages of 40-90, AD inexorably induces neuronal loss in the neocortex and adds the other cognitive deficits to the prominent short-term memory loss in a variable but definite fashion. Eventually psychotic symptoms may occur, such as paranoia, specific delusional states, and hallucinations. Urinary incontinence and some mild gait disorder may occur near the time of presentation, with fecal incontinence and reluctance to ambulate occurring later. The onset of significant incontinence tends to presage transfer to a nursing home, and

subsequent inanition contributes to death from associated illness such as pneumonia or decubiti. It is felt that the illness itself can be fatal, although it is seldom that the cause of death is ascribed directly to AD.

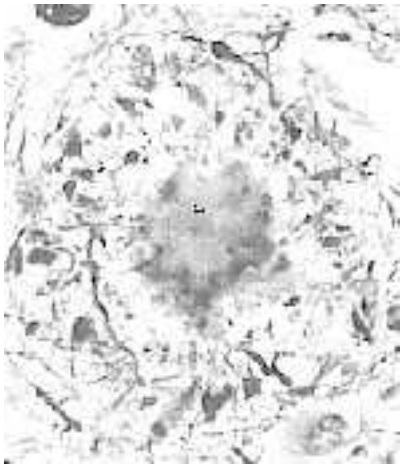
The NINCDS-ADRDA Criteria for AD define two categories of diagnosis, Probable and Definite AD. ***Definite*** requires a clinical diagnosis of ***Probable*** plus the histopathologic demonstration of plaques and tangles, either on brain biopsy or at autopsy. For *Probable*, there must be:

- Dementia with onset between ages 40 and 90
- Cognitive deficits in two or more areas
- Progressive memory and cognitive deterioration
- No other illness that could account for such deficits
- No disturbance of consciousness

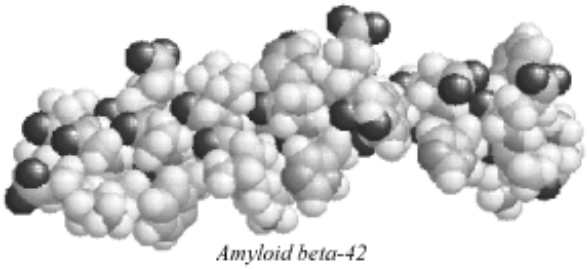
Overall Prevalence of Alzheimer's using NINCDS-ADRDA criteria:

- Age 65-74: 3.0%
- Age 75-84: 18.7%
- Age 85+: 47.2%
- Overall over age 65: 10.3%

While brain biopsy can be performed, it is impractical and not necessary for appropriate clinical diagnosis of patients with dementia. The need for a diagnosis with high confidence without resorting to brain biopsy has prompted the search for useful biomarkers. To be useful, such markers should be strongly correlated with the presence of disease and should be more practical to obtain. Thanks to advances in neurogenetics and CSF protein quantitation truly useful biomarkers have emerged for AD which have now been accepted by the internationally recognized Working Group on Molecular and Biochemical Markers of Alzheimer's Disease, which was funded by the Ronald and Nancy Reagan Research Institute.



Neuritic plaques consist of a core of β-amyloid formed by beta protein fibrils from the aggregated 42 amino acid A/β peptide, surrounded by swollen, dystrophic neurites. Neurofibrillary tangles fill the interior of degenerating neurons. The presence of plaques and tangles at autopsy is used to confirm a diagnosis of AD.



Amyloid beta-42

The peptide is resistant to proteolysis and forms insoluble aggregates which are directly toxic to neurons, probably via binding to a specific calcium receptor and/or GM_1-ganglioside. It is produced from the amyloid precursor protein by the newly identified β and γ secretases. Normally this precursor (the function of which is unknown) is processed to form an 40 amino acid N-terminal fragment, which is soluble, nontoxic, and non-accumulating. When a combination of genetic and environmental factors permit, the β and γ secretases activates inappropriately and produces a greater amount of 42 amino acid β-peptide (Aβ42), which leads to accumulation of toxic fibrils and the pathogenesis of Alzheimer's disease. Degenerating cells contain neurofibrillary tangles, which are composed of paired helical filaments. These filaments are in turn composed of an abnormally phosphorylated form of the tau protein, a stabilizer of microtubules and hence necessary for maintaining intracellular transport systems. Once abnormally phosphorylated, the tau protein can also aggregate, forming the paired helical filaments and filling the interior of the cell.

There are three spinal fluid biomarkers, two of which have earned support from the Working Group and the Alzheimer's Association. These are Aβ42 and the tau protein which collectively have >95% specificity in the diagnosis of AD by lumbar puncture. The Aβ42 level decreases and the tau level increases; if the opposite should be seen the examination excludes AD, while if both are up or both are down the test is non-diagnostic. The increase in tau protein has been shown to correlate with severity of dementia. A third spinal fluid biomarker AD7C, a measure of the amount of neural thread proteins (NTP) in the spinal fluid, was available but is no longer being offered. Instead, urine NTP testing has been available and data in press suggests both sensitivity and specificity for AD.

Genetic markers have been increasingly useful in AD, both early-onset familial (EOFAD) and the much more common late-onset sporadic type (LOSAD). In EOFAD, three autosomal dominant mutations have been found which are present in small numbers of affected families, in which affected individuals develop dementia in their 30s and 40s, instead of the more typical 70s and 80s of LOSAD. The three genes are the amyloid precursor protein (APP) on chromosome 21, presenilin 1 on chromosome 14, and presenilin 2 on chromosome 1. The fact that patients with Down syndrome develop an Alzheimer's-type dementia in their 30s and 40s, complete with identical plaques and tangles, suggested that the 21st chromosome might harbor an Alzheimer's

gene, which led to the discovery of APP and its relation to amyloid. Rare non-Down patients with EOFAD have been found to have APP mutations. From linkage analysis of other EOFAD families the two presenilins were found; these are rare, drawn from about 120 families worldwide. Interestingly, these mutations are associated with constitutive activation of secretase activity and enhanced secretion of Aβ42, either because mutant APP is predisposed to abnormal cleavage or because of the interaction of the presenilin gene products with the cellular processing machinery. Thus, Aβ42 is found to be elevated in plasma, which may serve as a biomarker of EOFAD. This is not the case in LOSAD. Meanwhile, it is now clear that the presenilins are in fact γ-secretases, directly catalyzing the production of Aβ42.

Strong support exists for genetic susceptibility loci as well. The best characterized locus is apolipoprotein E (APOE) on chromosome 19. Three alleles are commonly found in the general population: E2, E3, and E4 (sometimes also given as ε2, ε3, or ε4). The most common is E3, present in about 85%, with E4 at 10-15% and the much less common E2 and unusual (and not detected) alleles rounding out the remainder. ApoE4 is associated with LOSAD but not EOFAD. The test assists in increasing the confidence of the clinical diagnosis of AD by the above criteria, with a positive predictive value of 94% (Mayeux, et al, 1998). While ethnicity appears to play a role in variance in the APOE allele distribution, the general consensus remains that the presence of E4 increases risk for developing AD, and the presence of two E4 alleles (homozygosity) virtually guarantees that an individual will develop AD at some point if he or she should survive to their age of onset. Age of onset appears to be shifted downwards by the dose of E4 allele, but the severity or speed of progression of disease is not clearly affected. Interestingly, the E2 allele appears to have a protective effect. In a large autopsy series published by Roses et al, only one subject confirmed to have AD had an E2/E3 genotype, and no-one was found to have E2/E2. But there is no data to suggest that possession of an E2 is absolutely proof against developing AD. It may be that E2 shifts the age of onset curve upwards, beyond observed longevity and therefore illness is not observed before death.

APOE impacts the phosphorylation of the tau protein, with the E4 allele promoting increased phosphorylation and paired helical filament formation, and the E2 allele promoting a decrease in overall phosphorylation, perhaps explaining the observed protective effect of this allele. The standard E3 allele does not appear to impair or assist tau protein. One hypothesis as to the pathogenesis of AD is that tangle formation due to tau aggregation induces an intracellular cascade which culminates in Aβ42-secretion and eventual degeneration and death of the cell. Since it is known that the degeneration of AD follows anatomic pathways, this suggests that some diffusible factor (Aβ42 or tau) is carried down axons to cause havoc in remote locations.

A new locus on chromosome 12 has been described by several investigators. While still controversial, this locus may be one of two genes, the LDL-receptor-related protein gene (LRP) or alpha-2-macroglobulin (A2M). These genes are involved in the metabolism of lipoproteins and may also interact with APOE. There is evidence that alpha-2-macroglobulin, which binds to LRP, can bind to Aβ42 and render it nontoxic. Could the pathogenesis of AD depend on deficiency of this protein (or a problem with binding LRP or Aβ42)? More studies are needed but current data is quite suggestive that A2M and LRP will prove to be important susceptibility loci for AD as well. The current hope is that we will be able to identify individuals with a high likelihood of developing AD long before the disease is clinically manifest. Such individuals would be able to participate in long-term drug trials designed to assess the efficacy of prophylactic measures, some of which are currently contemplated or are yet to be discovered. Yet another locus has been identified at CYP46, but clinical testing is not yet available.

Current treatment is strictly symptomatic, and is used to alleviate the cognitive, functional, and behavioral impairments caused by the disease. Other treatment goals include slowing the disease progression and attempting to reverse any neurological damage. Drug therapy focuses on neurochemical replacement. The first Alzheimer's drug that was available in the United States was a reversible central cholinesterase inhibitors known as tacrine (Cognex™). Tacrine was found to be effective in treating mild to moderate cases of AD. The drug improves cognition, decreases behavioral disturbances, and delays the need for nursing home placement. Tacrine unfortunately is hepatotoxic, causing serum alanine aminotransferase levels to increase greater than three-fold. Use of tacrine can also lead to adverse cholinergic effects.

Donepezil (Aricept™) is a second generation cholinesterase inhibitor that is used in the treatment of AD. Donepezil is metabolized by the liver enzyme cytochrome P-450 and, unlike tacrine, is not hepatotoxic. This drug follows the rule of thirds: one third of patients show modest cognitive improvement, one third have a decrease in cognitive decline, and the last third show no response to treatment. Donepezil is favored over tacrine because of its reduced side effect profile and the fact that it can be administered once a day. Recent data in moderately severe to severe patients show that it continues to have good behavioral effect late in disease. It has also been shown to be effective in patients with vascular dementia. It is given at 5 mg qhs for four weeks, followed by 10 mg qhs for greater effect if necessary. Dosing greater than 10 mg per day tends to bring out peripheral spillover and typical cholinergic side effects.

A third cholinesterase inhibitor, rivastigmine (Exelon™) was approved in 2000. Rivastigmine is given twice per day and may have continuing benefit with disease progression because of a novel dual central cholinesterase inhibitory effect. In addition to the central

acetylcholinesterase, rivastigmine inhibits butyrylcholinesterase, which is typically not present centrally but which increases in amyloid plaque with progression of disease. Rivastigmine can be titrated to good effect and shows measurable benefit in the moderately severe patient. It is generally well tolerated but should be given with food as it can have significant GI side effects. It is initiated at 1.5 mg bid and increased 1.5 mg per two weeks to a maximum of 6 mg bid.

In 2001 the fourth cholinesterase inhibitor galantamine (formerly Reminyl™, now Razadyne™) was approved in the USA. It is given twice per day and has a novel effect on prefrontal nicotinic receptors which may increase the efficiency of acetylcholine binding as well as release other neurotransmitters. It acts as a central acetylcholinesterase and has demonstrated reasonable effect in early, middle, and late disease. Tolerability is good with or without food, and GI side effects are minimal. It has demonstrated good behavioral effects in patients as well, which bolsters claims by Cummings and others that the cholinesterase inhibitors may be a new class of antipsychotic agents. It is started at 4 mg bid and increased 4 mg per two weeks to a recommended maximum of 12 mg bid. I have pushed it to 16 mg bid in selected patients with good effects, but bradycardia and syncope may occur at higher than recommended doses. In 2005, an extended release preparation (Razadyne ER™) became available for once-daily dosing.

In 2004 the first of a new class of agents for Alzheimer's disease was approved for moderate and severe stages only. A specific blocker of the NMDA calcium-channel, memantine (Namenda™), showed benefit for improving activities of daily living even in advanced disease. The drug may increase longevity in patients with AD because it appears to block the toxicity of amyloid, which is known to require the NMDA calcium-channel for its pathological effect. Theoretically, this could limit the spread of amyloid plaque production, a cardinal feature of the amyloid cascade hypothesis. Glutamate may be a source of toxicity in AD, in a chronic form of the excitotoxicity known to enhance infarct size in stroke, and cell death in AD is related to calcium entry which is linked to the NMDA channel for which glutamate is a physiological ligand. The drug is started at 5 mg daily and increased 5 mg per week to a maximum of 10 mg bid. Very recent studies suggest the drug may be beneficial in mild stage and potentially even in pre-Alzheimer's disease (MCI?), but such use is off-label. Higher doses have been studied for diabetic neuropathy and found to be tolerable, but have not been formally looked at in AD. Strong data exists showing synergistic effect when memantine is combined with donepezil; presumably it is likely to be also good in combination with rivastigmine and galantamine, but trials are lacking. I have used it in combination with the latter agents without observing any adverse effects.

Other symptoms that arise in patients with Alzheimer's may be responsive to pharmacological treatment as well. Depression triggered by AD can be alleviated by antidepressants, but these drugs may be sedating or stimulating. Patients who experience insomnia can take benzodiazepines or trazodone. These agents are not without their downsides, however. Benzodiazepines often produce unacceptable and cumulative sedation, and trazodone can trigger suicidal ideation and orthostatic hypotension. Barbiturates should be avoided in this population due to sedation and worsening of cognitive and motor performance, including increased risk for falls.

Often behavioral problems can be treated with non-pharmacological intervention. Impairment such as cognitive problems may be compensated with calendars, notebooks, pillboxes, or posted signs. Depression can be treated with a change of environment or demands on a patient. This change can also help lessen apathy and disinterest, other symptoms of AD. Caregiver education is another essential aspect of coping AD. Through reassurance, the caregiver can redirect the patient and ease hallucinations and delusions. For behavioral symptoms that can not be treated with drugs, such as repetitive questions and wandering, non-pharmacological intervention can be adapted. Repetitive questions can often be redirected with caregiver attention and patience. Finally, an ID bracelet or enrollment in certain programs (e.g., Safe Return; Alzheimer's Association) can help control problems with wandering. A new detector by Health Sensor, Inc. can provide remote monitoring and emergency response to potentially injurious falls. The device may soon incorporate inexpensive GPS technology to permit tracking and recovery of patients who wander.

Almost half of all Alzheimer caregivers say they suffer from depression and more than 80% often experience high levels of stress. Some warning signs of stress are denial, anger, social withdrawal, anxiety, depression, exhaustion, sleeplessness, irritability, lack of concentration and health problems. Too much stress can be harmful to both the caregiver and the patient. Support groups are a necessity for any caregiver. Caregivers often feel frustrated and alone, which creates a need for socialization and support. A support group provides a closeness and connection with other people in the same situation. The significance of support groups was studied by researchers at the Aging and Dementia Research Center at New York University Medical Center. Caregivers placed in control groups which received standard advice on managing home care had an average time of two years and five months before the patients were placed in nursing homes. The treatment group which were assigned to a weekly support group had an average of three years and three months before the patients were placed in nursing homes. The difference between the two groups was a ten month increased stay at home.

New treatment approaches include antioxidants, anti-inflammatories, neuromodulators, and therapies directed at the molecular neuropathology, such as amyloid disruptors, amyloid-specific calcium receptor blockers, and β/γ-secretase inhibitors. The nonsteroidal anti-inflammatory COX2 inhibitors celecoxib and rofecoxib have been tested but have not shown benefit. Estrogen therapy in postmenopausal women has been thought to lower the epidemiological incidence of AD because it increases both cerebral blood flow and acetylcholine activity, but prospective studies have been negative. The pros and cons of such a therapy should be considered, however, as replacement estrogen can produce certain health risks, including an increased risk of endometrial cancer. Vitamin E was once thought to offset negative symptoms of moderate AD, but data is lacking; it may have modest preventive effect. Gene therapy may help to prevent disease in afflicted families or in sporadic cases, but this will require massive screening programs to identify potential recipients.

Immunization against Aβ42 might prevent Alzheimer's disease, or even halt progression in patients already bearing plaque. The work of Schenk et al is notable in that it has been replicated in transgenic mice, rabbit, and primate models of knock-in APP mutations, which replicate plaque pathology but not tangles. Early human trials suggested this is safe, but efficacy in humans has not yet been demonstrated. The most recent trial of an amyloid vaccine by Elan Pharmaceuticals has reported a transient but troubling postvaccinal meningo-encephalitis in 15 out of 400 subjects. However, three autopsies in participants of this and a previous trial who died later showed lack of plaques, suggesting that the therapy has efficacy. Currently underway is a trial of therapeutic anti-amyloid antibodies, a passive approach which may be safer and equally beneficial.

Other anti-amyloid strategies are currently in late development. Myriad Pharmaceuticals has a phase III trial underway of their unique compound Flurizan. According to the company, Flurizan changes the point at which brain cell enzymes cleave an amyloid precursor protein. This makes a range of smaller proteins than the typical Aβ42 protein which makes up the core of plaques in AD. Smaller proteins may disrupt accumulation of toxic plaque and enhance transport of plaque proteins into the bloodstream for disposal. Meanwhile, Neurochem has an alternative approach. Their current phase III trial of Alzhemed hopes to determine if amyloid can be reduced by making the protein more soluble, enhancing clearance. The company states the drug has so far demonstrated an excellent safety profile. Large phase III trials of both agents are underway.

Treatment Strategies for Alzheimer's Disease*

Rating			
💣	Not Beneficial	⊗	Investigational, Unlikely Beneficial
∅	Investigational, Hopeful	⊕	Investigational, Worthwhile
☑	Approved, Worthwhile	☒	Approved, Not Worthwhile

Symptomatic
- Antidepressants
  - ☑ Sertraline
  - ☑ Fluoxetine
  - ☑ Paroxetine
  - ☑ Citalopram
  - ☑ Escitalopram
  - ☑ Venlafaxine
  - ☑ Duloxetine
  - ☒ Nefazodone
  - ☒ Mirtazipine
  - ☒ Clomipramine
  - ☒ Tricyclics (eg, amitriptyline)
- Antipsychotics
  - ☑ Aripiprazole
  - ☑ Quetiapine
  - ☑ Ziprasidone
  - ☑ Risperidone (low dose)
  - ☒ Olanzapine, Haloperidol
  - ☒ Older (eg, chlorpromazine)
- Anxiolytics
  - ☒ Barbiturates
  - ☑ Benzodiazepines (low dose)
  - ☑ Buspirone
  - ☑ Chloral hydrate

Circulatory (increase cerebral oxygenation)
- ☒ *Gingko biloba*
- ☒ Vasodilators
- 💣 Hyperbaric oxygen
- 💣 Hydergine, Nicergoline

Membrane-based
- ∅ Gangliosides
- 💣 Phosphatidylserine

Restitutive
- Cholinergic
  - 💣 Cholinergic precursors (lecithin; phosphatidylcholine)
  - ☑ Cholinesterase inhibitors
    - ☒ Tacrine
    - ☑ Donepezil
    - ☑ Rivastigmine
    - ☑ Galanthamine
    - ☑ Galanthamine ER
    - 💣 Metrifonate
    - ☒ Physostigmine
    - 💣 Phenserine
  - 💣 Cholinergic agonists
    - 💣 Muscarinic agonists
  - 💣 Cholinergic enhancers
    - 💣 MKC-231
- Dopaminergic
  - 💣 Bromocriptine
- Glutamatergic
  - 💣 CX516
  - ∅ CX717
- Serotonergic
  - 💣 Ondansetron
- Triple Reuptake Inhibitor
  - 💣 NS-2330

Nootropics
- ∅ CX-516 (Ampalex)
- 💣 Aniracetam, Piracetam

Neurotrophic and hormonal factors
- Nerve growth factors
  - 💣 NGF, CNTF, BDNF
  - 💣 Neotrofin (AIT-082)
- 💣 Estrogen
- ∅ Testosterone
- ∅ Leuprolide (anti-androgen)

* These treatment strategies and their therapeutic values are believed to be accurate by the author as of the time of this writing; no liability can be assumed for unintended inaccuracies. The author's clinical opinion and viewpoint are solely his and are not necessarily the views of industry sponsors. 'Approved' means for approved by FDA for some indication and therefore available by prescription, not specifically approved for use in patients with dementia.

Anti-inflammatory agents
- 💣 Steroids
- 💣 Vinca alkaloids (eg, vinpocetine)
- NSAIDs
  - ⊗ Ibuprofen
  - ☒ Indomethacin
  - 💣 Naproxen
  - COX-2 Inhibitors
    - 💣 Celecoxib
    - 💣 Rofecoxib
- Statins
  - ∅ Atorvastatin
  - ∅ Simvastatin

Antitoxic agents
- ⊕ Vitamin E, Vitamin C
- 💣 Idebenone
- ☒ Selegiline (deprenyl)
- Calcium-channel blockers
  - 💣 Nimodipine

💣 Excitatory amino acid blocking agents
- NMDA antagonists
  - ☑ Memantine
  - ⊕ Neramexane
- Chelating agents
  - ⊗ Clioquinol

Surgical
- ⊗ Omental transfer
- 💣 Shunt
- ∅ Neural stem cell graft

Anti-amyloid therapy
- 💣 AN1792 Amyloid Vaccine
- 💣 Gamma-secretase inhibitors
- ⊕ Anti-amyloid antibodies
- ⊕ Flurizan: selective amyloid lowering agent
- ⊕ Alzhemed: amyloid disaggregating agent

Miscellaneous
- 💣 Acetyl-l-carnitine
- ∅ Angiotensin-converting enzyme
- 💣 Sabeluzole

Investigational Alzheimer's Drug Therapies*

Generic Name	*Company*	*Drug Type/Mechanism*	*Status*
ABT-418	Abbott	Neuromodulator	**Discontinued**
AC-3933	Aventis/Dainippon	Partial GABA inverse agonist	Phase II
AF-102B (FKS-508)	Forest	Muscarinic agonist	**Discontinued**
Alcar (acetyl-l-carnitine, ST200)	Sigma-Tau	Cofactor	**Discontinued**
Alvameline (LU 25-109)	Forest	Muscarinic agonist	**Discontinued**
Alzene (linolenic/linoleic acid)	Ivax	Fatty acids	**Discontinued**
Alzhemed	Neurochem	Disaggregates amyloid	Phase III
Ampalex (CX516)	Cortex	AMPAKINE	**Discontinued**
CX717	Cortex	AMPAKINE	Phase IIa
APP modulators	Sibia	Modulate production of amyloid precursor protein	Preclinical
Arecoline	(natural compound)	Cholinergic agonist, an alkaloid found in betel nuts	**Discontinued**
Atorvastatin (Lipitor)	Pfizer	Cholesterol inhibitor	Phase III
Besipirdine	Aventis	Cholinergic/adrenergic	**Discontinued**
Betabloc	Elan	Amyloid vaccine	**Suspended**
Beta amyloid protease inhibitors	Scios	Inhibit amyloid production	Preclinical
Celecoxib (Celebra, Celebrex)	Pfizer	Cox-2 inhibitor	**Discontinued**
CEP 1347/KT7515	Cephalon	Neuroprotectant	Phase I
Cerebrolysin	Ebewe	Neurotrophic, neuroprotectant	Phase III
Cevimeline (Evoxac)	Daiichi	Muscarinic agonist	**Discontinued**
CN134	Bristol-Meyers Squibb	Gamma-secretase inhibitor	**Discontinued**
CGP-50068A	Novartis	Unknown mechanism	**Discontinued**
CHF 2060	Chiesi Farmaceutici	Unknown mechanism	Phase I
CI-1017	Pfizer	Muscarinic agonist	**Discontinued**
Citicoline (CDP-choline)	Interneuron/Takeda	Metabolite	**Discontinued**
CL-287663	Wyeth	Unknown mechanism	**Discontinued**
Clioquinol	Prana	Zinc-copper chelator	Phase II
Cognishunt	Eunoe (CSFluids)	Mechanical CSF filtration	Phase III?
Corticotrophin releasing factor	Neurocrine	Hormone	Preclinical
CPI-1189	Centaur	Unknown mechanism	**Abandoned**
CP-118954	Pfizer/Eisai	Cholinesterase inhibitor	Phase II
DHEA	Novartis/Neurocrine	Neurosteroid	**Discontinued**
Donepezil (Aricept)	Pfizer/Eisai	Cholinesterase inhibitor	**Approved**
DP-543	Bristol-Myers Squibb	Unknown mechanism	Phase II
T-588	Toyama	Free radical scavenger	Phase II
Eptastigmine	Mendiolanum	Cholinesterase inhibitor	**Discontinued**
Fenchylamine sulfonamides	Aventis	Gamma-secretase inhibitor	Preclinical
FK960	Astellas	LTP enhancer	**Discontinued**
FK962	Astellas	LTP enhancer	Phase II
Flurizan (R-Flurbiprofen)	Myriad	Selective amyloid lowering agent	Phase III
Galantamine (Razadyne)	Janssen	Cholinesterase inhibitor	**Approved**
Galantamine ER (Razadyne ER)	Janssen	Cholinesterase inhibitor	**Approved**
Ganstigmine (CHF 2819)	Chiesi Farmaceutici	Cholinesterase inhibitor	Phase IIb
Gingko biloba	Schwabe	Antioxidant, anticoagulant	**Not beneficial**
GR253035	GlaxoWellcome	Cox-2 inhibitor	Phase I
GTS-21	Taiko	Alpha-7 nicotinic agonist	Phase II

*Status of these therapies is believed to be accurate by the author as of the time of this writing; no liability can be assumed for unintended inaccuracies. Sources are multiple and include the World Wide Web and personal communications from figures in industry and academia. Please contact the author if you find an error, it will be corrected in the next edition.

Huperzine A	Nutrapharm	Cholinestrase inhibitor in Chinese club moss	Phase II
Idebenone	Takeda	Nootropic agent	**Discontinued**
Ketasyn	Accera	Neuronal energizer	Phase II
KA-672-HCI	Schwabe	Cholinesterase inhibitor	Preclinical
Ladostigil (TV-3326)	Teva	Neuroprotectant, MAO and Cholinesterase inhibitor	Phase I
Lecozatan SR	Wyeth	$5HT_2$ antagonist	Phase II
Leuprolide (Lupron)	Voyager	Gonadotropin inhibitor	Phase II
Linopirdine	DuPont Merck	Cholinergic agonist	**Discontinued**
Marinol	Unimed	Cannabinoid	Phase II
M-100907B	Aventis	$5HT_2$ antagonist	Phase I
MCI-225	Mitsubishi	Monoamine modulator	**Discontinued**
Memantine	Forest	NMDA antagonist	**Approved**
Memantine MR	Forest	NMDA antagonist	Phase II
Memex (NADH)	Telluride	Cofactor	Phase II/III
Metrifonate (Promem)	Bayer	Cholinesterase inhibitor	**Suspended**
Milameline	Aventis	Muscarinic M1 agonist	**Discontinued**
MKC-231	Mitsubishi	Choline reuptake inhibitor	**Discontinued**
NDD-094	Novartis	Unknown mechanism	Phase II
Nefiracetam (DM-9384)	Daiichi	Nicotinic agonist	**Discontinued**
Neotrofin (AIT-082)	NeoTherapeutics	Protein Synthesis Enhancer	**Discontinued**
Neramexane	Forest	NMDA antagonist	Phase II
Neurodex (AVP-923; dextromethorphan)	Avanir	NMDA antagonist plus enzyme inhibitor	Phase III, but may be discontinued; causes uncontrolled laughter
NGD 97-1	Pfizer	GABA receptor inverse agonist	Phase II
NS-2330	Boehringer Ingelheim	Triple reuptake inhibitor	**Discontinued**
NS-105	Nippon Shinyaku	Cholinesterase inhibitor	**Discontinued**
Oxiracetam	SmithKline Beecham	Nootropic	**Discontinued**
Pakio	Hoffman La Roche	Unknown mechanism	Phase III
Parafluoroselegiline	Sanofi	MAO B inhibitor	Preclinical
Phenserine	Axonyx	Cholinesterase inhibitor	Phase III failed
Phenethylnorcymserine (PENC)	Axonyx	Butyrylcholinesterase inhibitor	Preclinical
Physostigmine SR (Synapton)	Forest	Cholinesterase inhibitor	**Discontinued**
Posiphen [(+)-phenserine]	Axonyx	Cholinesterase inhibitor	Phase I
Propentofylline	Aventis	Adenosine reuptake, phosphodiesterase inhibitor	**Discontinued**
Rasagiline (TVP-1012)	Teva	MAO B inhibitor	Phase II
Rivastigmine (Exelon)	Novartis	Cholinesterase inhibitor	**Approved**
Rivastigmine Daily Patch	Novartis	Cholinesterase inhibitor	Phase III
S-12024-2	Servier	Neuromodulator	Preclinical
S-9977-2	Servier	Muscarinic agonist	Preclinical
Sabeluzole	Janssen	Glutamate antagonist	**Discontinued**
Sabcomeline (SB 202026, Memric)	Glaxo	Muscarinic agonist	**Discontinued**
SB-271046	Glaxo	$5HT_6$ agonist	Phase I
SC-110	Scotia	COX-2 inhibitor	**Discontinued**
Selegiline (Eldepryl)	Watson/Somerset	MAO B inhibitor	**Discontinued**
Sermion	Pfizer	Ergot Derivative	Phase III
SIB-1553A	Sibia	Nicotinic Agonist	Phase I
Simvastatin (Zocor)	Merck	Cholesterol inhibitor	Phase III
SL 25.1188	Synthelabo	MAO B inhibitor	Phase II
SL 65.102	Synthelabo	Gamma-secretase inhibitor	Phase II
SR 46559	Sanofi	Muscarinic agonist	**Discontinued**
SR 57446	Sanofi	Neurotrophic agent	Phase II
SRA-333	Wyeth	$5HT_{1A}$ antagonist	Phase II
Suritozole	Sanofi-Aventis	Inverse GABA agonist	**Discontinued**
Talsaclidine	Boehringer Ingelheim	Muscarinic agonist	**Discontinued**

Tazomeline	(unknown)	Muscarinic agonist	**Discontinued**
Thiatolserine	Axonyx	Cholinesterase inhibitor	Preclinical
Tolserine	Axonyx	Cholinesterase inhibitor	Preclinical
Velnacrine	Aventis	Cholinesterase inhibitor	**Discontinued**
Vinconate	OmniChem	Vinca alkaloid	**Discontinued**
Vinpocetine (Intelectol)	Covex	Vinca alkaloid	**Not beneficial**
Viviq	Sanofi-Aventis	Unknown mechanism	Phase III
WAS-2014	Boehringer Ingelheim	Muscarinic agonist	**Discontinued**
Xaliproden	Sanofi-Aventis	Neuroprotectant	Phase III
Xanomeline	Eli Lilly	Muscarinic agonist	Oral **Discontinued** Skin Patch Phase III
YM-796	Yamanouchi	Muscarinic agonist	Phase II
Z-321	Zeria	Endopeptidase inhibitor	Phase I
Zanapezil (TAK-147)	Takeda	Neurotrophic factor/ cholinesterase inhibitor	Phase III
Zifrosilone	Aventis	Muscarinic agonist	**Discontinued**

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