Bangladesh Journal of Neuroscience 2012; Vol. 28 (1) : 52-58

REVIEW ARTICLE

Alzheimer's Disease - An Update

AMINUR RAHMAN[1] ,FARHANA SALAM[2], MD AMINUL ISLAM[3], AKM ANWARULLAH, [4]
MD RAFIQUL ISLAM[4], MD NURUL AMIN MIAH[5] UTTAM KUMAR SAHA[6], ZAHED ALI[6]

Introduction:

Alzheimer's (AD) disease is a progressive and fatal neurodegenerative disorder manifested by cognitive and memory deterioration, progressive impairment of activities of daily living and a variety of neuropsychiatric symptoms and behavioral disturbances[1].

This incurable, degenerative, and terminal disease was first described by German psychiatrist and neuropathologist Alois Alzheimer in 1906 and was named after him[2]. Alzheimer's disease is the most common cause of dementia occurring mostly in patients over 45 years[3]. Generally, it is diagnosed in people over 65 years of age[4], although the less-prevalent early-onset Alzheimer's can occur much earlier. It is one of the most frequent mental illnesses, making up some 20 percent of all patients in psychiatric hospitals and a far larger proportion in nursing homes [4].

The incidence rate of clinically diagnosed Alzheimer disease is similar throughout the world, and it increases with age, approximating 3 new cases yearly per 100,000 persons younger than age 60 years and a staggering 125 new cases per 100,000 of those older than age 60 years. In India incidence rate is 324/100000/year above 65 yrs and 174/ 100000/year above 55 yrs .There is no exact epidemiological data of AD in Bangladesh.

The prevalence of the disease per 100,000 populations is near 300 in the group aged 60 to 69 years; it is 3,200 in the 70- to 79-year-old group and 10,800 in those older than age 80. In the year 2008, there were estimated to be more than 2 million persons with Alzheimer disease in the United States. Prevalence rates, which depend also on overall mortality, are 3 times higher in women, although it does appear that the incidence of new cases is only slightly disproportionate in women[5].

Life expectancy of the population with the disease is reduced[6]. The mean life expectancy following diagnosis is approximately seven years.[7] Fewer than 3% of patients live more than fourteen years[8].

Without advances in therapy, the number of symptomatic cases in the United States is predicted to rise to 13.2 million by 2050[1]. Alzheimer's disease is predicted to affect 1 in 85 people globally by 2050[5]. The association between the pathological features of Alzheimer's disease and dementia is stronger in younger than in older[9]. About 15% of cases are familial and this cases fall into two main groups, an early onset dominant pattern and a later onset group whose inheritance is not so clear[10]. Approximately 10% of all person over the age of 70 years have significant memory loss and in more than half the case is AD[11].

Pathology:

Pathology of AD includes neurofibrillary tangles, senile plaques at the microscopic level. Neurofibrillary tangles and senile plaques were described by Alois Alzheimer's in his original report on the disorder in 1907. They are now universally accepted as a hallmark of the disease. These lesions accumulate in small numbers during normal aging of the brain but occur in excess in AD[12].

Neuropathlogical lesions of Alzheimer's disease like amyloid and diffuse neuritic plaques & neurofibrillary tangles in the entorhinal,

1. Registrar, Department of Neurology, Sir Salimullah Medical College Mitford Hospital, Dhaka.
2. Indoor Medical Officer, Department of Surgery, Dhaka Medical College Hospital, Dhaka.
3. Emergency Medical Officer, Department of Blood Transfusion , National Institute of Neurosciences & Hospital, Dhaka.
4. Professor,Department of Neurology, Bangabandhu Sheikh Mujib Medical University, Dhaka.
5. Assistant Professor, Department of Medicine, Sir Salimullah Medical College, Dhaka.
6 Assistant Professor, Department of Neurology, Sir Salimullah Medical College, Dhaka.

hippocampal, frontal, temporal, parietal and occipital cortexes.(Figure1). Cortical atrophy was assessed macroscopically in each brain area without knowledge of microscopical findings[10].

Pathogenesis & Pathophysiology:

There is increasing evidence to suggest that soluble amyloid fibrils called oligomers lead to the dysfunction of the cell and may be the first biochemical injury in Alzheimer's disease. Misfolded Aβ42 molecules may be the most toxic form of the protein. Accumulation of oligomers eventually leads to formation of neuritic plaques. The neuritic plaques contain a central core that includes Aβ amyloid, proteoglycans, Apo E4, α1 antichymotrypsin and other proteins. Aβ amyloid is a protein of 39-42 amino acids that is derived proteolytical from a larger transmembrane protein named amyloid precursor protein when amyloid precursor protein is cleaved by β & γ secretases. The plaque core is surrounded by the debris of degenerating neurons, microglia and macrophages. The accumulation of Aβ amyloid in cerebral arterioles is termed amyloid angiopathy[12] (Figure 2) . Vascular endothelial cells have a central role in the progressive destruction of cortical neurons in Alzheimer's disease. In Alzheimer's disease the brain endothelium secretes the precursor substrate for the b-amyloid plaque and a neurotoxin peptide that selectively kills cortical neurons. Large population of endothelial cells are activated by angiogenesis due to brain hypoxia and inflammation[13] . Cell loss occurs particularly from the deeper layers of the cortex and preferentially involves large neurons. Synapse loss or neuron loss provides the highest correlation with global cognitive impairment[11].

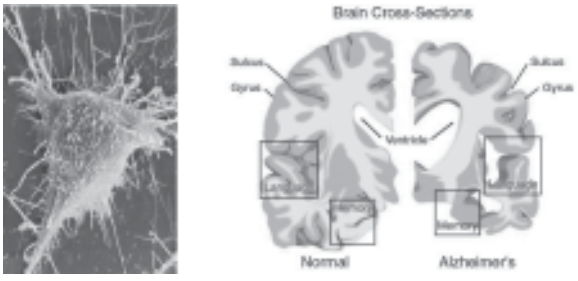
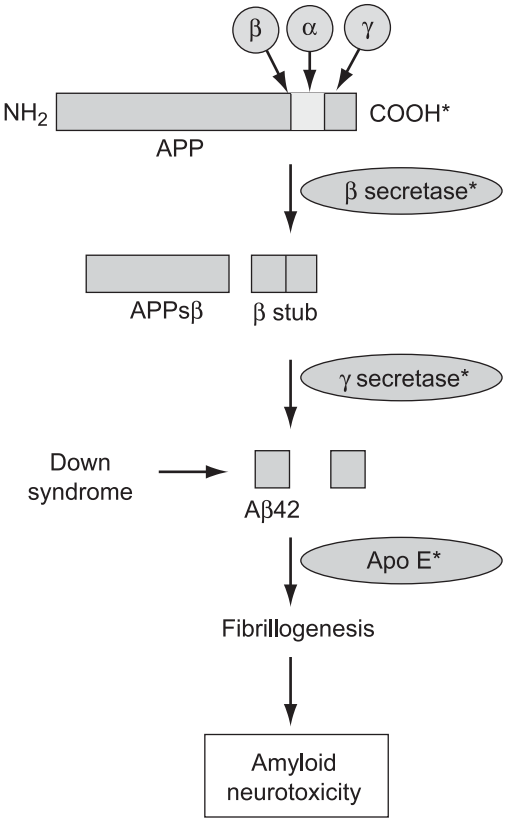


Fig.-1: *Pathological changes in Alzheimer's disease (AD).*



Source: Ropper AH, Samuels MA: Adams & Victor's Principles of Neurology 9th Edition: http://www.accessmedicine.com

Fig.-2: *Pathogenesis: amyloid neurotoxicity*

Neurofibrillary tangles are silver-staining, twisted neurofilaments in neuronal cytoplasm that represent abnormally phosphorylated tau protein. Tau is a microtubule associated protein that may function to assemble and stabilize the microtubules that convey cell organelles, glycoproteins and other important materials throughout the neuron. The ability of tau protein to bind to microtubule segments is determined partly by the number of phosphate groups attached to it. Increased phosphorylation of tau protein distorts this normal process[12].

In 2009, this theory was updated, suggesting that a close relative of the beta-amyloid protein, and not necessarily the beta-amyloid itself, may be a major culprit in the disease. The theory holds that an amyloid-related mechanism that prunes neuronal

connections in the brain in the fast-growth phase of early life may be triggered by aging-related processes in later life to cause the neuronal withering of Alzheimer's disease[14]. N-APP, a fragment of APP from the peptide's N-terminus, is adjacent to beta-amyloid and is cleaved from APP by one of the same enzymes. N-APP triggers the self-destruct pathway by binding to a neuronal receptor called death receptor 6 (DR6, also known as TNFRSF21)[15]. DR6 is highly expressed in the human brain regions most affected by Alzheimer's, so it is possible that the N-P/DR6 pathway might be hijacked in the aging brain to cause damage. In this model, Beta-amyloid plays a complementary role, by depressing synaptic function.

Biochemically, AD is associated with a decrease in the cerebral cortical levels of several proteins and neurotransmitters especially acetylcholine, its synthetic enzyme choline acetyltransferase and nicotinic cholinergic receptors. There is also reduction in norepinephrine levels in brain stem nucleus[12].

There are no biologic markers for Alzheimer's disease or most other dementias but with careful evaluation and the application of well defined, reliable clinical criteria, diagnosis can be made with component of the workup in careful

Diagnosis:

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA, now known as the Alzheimer's Association) established the most commonly used NINCDS-ADRDA Alzheimer's Criteria for diagnosis in 1984[17], extensively updated in 2007[18]. These criteria require that the presence of cognitive impairment, and a suspected dementia syndrome, be confirmed by neuropsychological testing for a clinical diagnosis of possible or probable AD.

Table-I

*Criteria For The Diagnosis Of Alzheimer's disease**

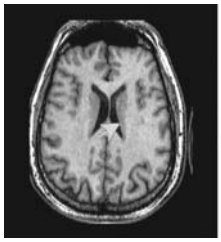
Diagnosis	Criteria	
Probable	Alzheimer's disease	All of the following must be present: Dementia established by examination and documented by objective testing Impairment in memory and at least one other cognitive function (e.g., language or perception). Progressive worsening of memory and at least one other cognitive function. No disturbance in consciousness
		Onset between 40 and 90 years of age. Absence of another brain disorder or systemic disease that might cause dementia. In addition, the diagnosis may be supported by one or more of the following: Loss of motor skills.
		Diminished independence in activities of daily living and altered patterns of behavior. Family history of similar disorder. Laboratory results consistent with the diagnosis (e.g., cerebral atrophy on computed tomography).
Possible	Alzheimer's disease	Fulfillment of the above criteria with variation in the onset of symptoms or manifestations or in clinical course; or a single, but gradually progressive, cognitive impairment without an identifiable cause.
		Another brain disorder or systemic disease that is sufficient to produce dementia, but that is not considered to be the underlying cause of the dementia in the patient.
Definite	Alzheimer's disease	Fulfillment of the above clinical criteria and histologic evidence of Alzheimer's disease based on examination of brain tissue obtained at biopsy or autopsy.

*Criteria were adapted from Mc Khann et al.

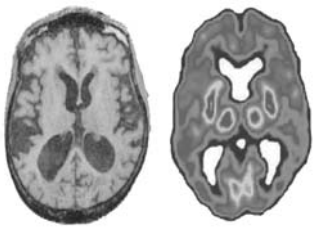
Advanced medical imaging with computed tomography (CT) or magnetic resonance imaging (MRI), and with single photon emission computed tomography (SPECT) or positron emission tomography (PET) can be used to help exclude other cerebral pathology or subtypes of dementia[19].

A new technique known as PiB PET has been developed for directly and clearly imaging beta-amyloid deposits in vivo using a tracer that binds selectively to the A-beta deposits [20]. Recent studies suggest that PiB-PET is 86% accurate in predicting which people with mild cognitive impairment will develop Alzheimer's disease within two years, and 92% accurate in ruling out the likelihood of developing Alzheimer's disease[21].

Assessment of intellectual functioning including memory testing can further characterise the state of the disease[22]. Screening for depression, vitamin B 12 deficiency, and hypothyroidism should be performed. Screening for syphilis is not justified unless there is a clinical suspicion of neurosyphilis. The diagnosis can be confirmed with very high accuracy, post-mortem when brain material is available and can be examined histologically[23].



Normal aging
http://www.med.harvard.edu/AANLIB/cases/caseNA/pb9.htm



Scans of Patients with Probable Alzheimer's Disease. In Panel A, a magnetic resonance image shows cortical atrophy and ventricular enlargement. In Panel B, a positron-emission tomographic scan shows reduced glucose metabolism in the parietal lobes bilaterally (blue-green) as compared with more normal metabolism in other cortical areas (yellow).

Management:

Guidelines for Management of Dementia are described as follows.

Standards:

Use of cholinesterase inhibitors should be considered in patients with mild-to-moderate Alzheimer's disease, although the benefit is limited.

Antipsychotic agents should be used to treat agitation and psychosis when environmental manipulations fail.

Behavior modification and scheduled toileting are helpful to reduce urinary incontinence.

Guidelines:

Use of vitamin E should be considered in an attempt to slow the progression of Alzheimer's disease.

Use of antidepressant medications should be considered for patients with depression.

Educational programs can be supportive for caregivers and nursing-home staff.

* The guidelines are based on those of the Quality Standards Subcommittee of the American Academy of Neurology.

Cholinesterase inhibitors are approved for the treatment of mild-to-moderate Alzheimer's disease and should be considered as a standard of care for patients with Alzheimer's disease. Four cholinesterase inhibitors are available: tacrine, donepezil, rivastigmine, and galantamine (Table-II)[24].

Side effects reported in clinical trials of cholinesterase inhibitors included nausea, vomiting, and diarrhea, as well as weight loss, insomnia, abnormal dreams, muscle cramps, bradycardia, syncope, and fatigue[25].

Memantine (Table-II), an *N*-methyld-aspartate antagonist recently approved by the Food and Drug Administration (FDA) for the treatment of moderate-to severe Alzheimer's disease may interfere with glutamatergic excitotoxicity or may provide symptomatic improvement through effects on the function of hippocampal neurons[26]. A double-blind, placebo- controlled trial of memantine in patients with moderate-to-severe Alzheimer's disease showed the superiority of memantine over placebo as indicated by both the Activities of Daily Living Inventory and the Severe Impairment Battery (a neuropsychological test for patients with severe dementia),but not on the Global Deterioration Scale[27].

Major depression occurs in 5 to 8 percent of patients with Alzheimer's disease[28]. Up to 25

Table-II

*Clinical Pharmacology of Agents Useful for Reducing the Signs of Dementia.**

Characteristic	Donepezil	Rivastigmine	Galantarmine	Memantine
Time to maximal serum concentration (hr)	3-5	0.5-2	0.5-1	3-7
Absorption affected by food	No	Yes	Yes	No
Serum half-life (hr)	70-80	2h	5-7	60-30
Protein binding (%)	%	40	0-20	45
Metabolism	CYP2D6, CYP3A4	Nonhepatic	CYP2D6, CYP3A4	Nonhepatic
Dose (initial/maximal)	5 mg daily/ 10 mg daily	1.5 mg twice daily/ 6 mg twice daily	4 mg twice daily/ 12 mg twice daily	5 mg daily/ 10 mg twice daily
Mechanism of action	Cholinesterase inhibitor	Cholinesterase inhibitor	Cholinesterase inhibitor	NMDA-receptor antagonist

CYP2D6 denotes cytochrome P-450 enzyme 2136, CYP3A4 cytochrome P-450 enzyme 3A4, and IN MDA N-methyl-D-aspartate.
y Rivastigmine is a pseudo-irreversible acetylcholinesterase inhibitor that has a eight-hour half-life for the inhibition of acetylcholinesterase in the brain.

percent have depressed mood at the time of onset of memory loss. Few studies of the use of antidepressant drugs in patients with Alzheimer's disease have been published, although these drugs are frequently used [29].

The effects of the tricyclic antidepressant imipramine were similar to those of placebo in alleviating depression in 61 patients with Alzheimer's disease [30]. In a crossover study of 26 depressed patients with Alzheimer's disease, in which clomipramine and placebo were each given for six weeks, both treatments resulted in a 40 to 50 percent reduction in the score on the Hamilton Depression Rating Scale [31].

Delusions and psychotic behavior increase with the progression of Alzheimer's disease and, once present, are persistent in 20 percent of patients. Agitation may coexist in up to 20 percent more patients, and it tends to increase with advancing disease [32]. In a study comparing high-dose haloperidol (2 to 3 mg per day), low-dose haloperidol (0.5 to 0.75 mg per day), and placebo in 71 patients with Alzheimer's disease and psychosis or disruptive behavior, the high dose produced a 30 percent greater improvement than either placebo or the low dose.

Alpha-tocopherol and selegiline delay the development of the later stages of Alzheimer's disease, but it is difficult to say whether a delay of 20 to 30 weeks is meaningful in a disease that lasts a decade or more [33].Unlike selegiline, alpha-tocopherol does not interact with other drugs and therefore can be administered to the majority of patients, regardless of other treatments for Alzheimer's disease. The studies of idebenone, propentofylline, and *Ginkgo biloba* provide no clinically meaningful information on the basis of which to make treatment recommendations [34].

As of August 2010 there were more than 812 clinical trials under way to understand and treat Alzheimer's disease. There were 149 of these studies in the last phase before commercialization (phase three trials) [35].

Amyloid beta is a common target, existing many trials which aim to reduce it with different agents such as bapineuzumab, an antibody in phase III for patients in the mild to moderate stage, semagacestat, a ã-secretase inhibitor, MPC-7869, and acc-001, a vaccine to amyloid beta in phase II to be used in the mild stage. However, in a recent study an experimental vaccine was found to have cleared patients of amyloid plaques but did not have any significant effect on their dementia, casting doubt on the utility of such approaches[36]. Other approaches are neuroprotective agents, like AL-

108 (phase II completed); or metal-protein interaction attenuation, as is the case of PBT2 (phase II completed) [37]. Finally, there are also many basic investigations trying to increase the knowledge on the origin and mechanisms of the disease that in the future may help to find new treatments.

Conclusion:

Current treatments for patients with Alzheimer's disease target the biochemical pathway that is associated with the disease and is considered amenable to modification.. Therapeutic approaches should focus on methods to prevent or delay the progression of Alzheimer's disease.The development of such approaches will depend on increasing our knowledge of the pathophysiology of the disease.

References:

1. Wood Ajj, Cummings JL. Drug therapy, Alzheimer's disease. The New England J of Medicine 2004;35:56-7.
2. Alzheimer A. "Über eine eigenartige Erkrankung der Hirnrinde [About a peculiar disease of the cerebral cortex]" (in (German)). Allgemeine Zeitschrift fur Psychiatrie und Psychisch-Gerichtlich Medizin 1907;64 (1–2): 146–8.
3. Allen CMC, Lueck CJ, Dennis M. Alzheimer's disease. In: Boon NA, Colledge NR, walker BR, Hunter JAA eds. Davidson's principles & practice of medicine. 20th ed. Churchill Livingstone; 2006; P.1217.
4. Biller J, Love BB, Schneck MJ. 'Ischemic cerebrovascular disease', In: WG Bradley,RB Darott, GM Fenichel, Jankovic J (eds.) Neurology in Clinical Practice, 5th edn, Butterworth Heinemann. 2008; pp.1165-224.
5. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. "Forecasting the global burden of Alzheimer's disease". Alzheimer's and Dementia 2007; 3 (3): 186–91.
6. Katzman R: Education and the prevalence of dementia and Alzheimer's disease. Neurology 1993; 43:13
7. Li G, Silverman JM, Smith CJ. Age at onset and familial risk in Alzheimer's disease. Am J Psychiatry 1995; 152:4
8. Plassman BL, Langa KM, Fisher GG. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology 2007; 29(1-2): 125-32.
9. Nee LE, Eldridge R, Sunderland T. Dementia of the Alzheimer type: Clinical and family study of 22 twin pairs. Neurology 1987; 37:359
10. Savva GM, Wharton SB, Ince PG, Forster G, Matthews FE, Brayne C. Age, neuro-pathology, and dementia. N Engl J Med 2009; 360(22):2302-9.
11. Alzheimer's Association. Alzheimer's disease facts and figures. Alzheimer's & Dementia Mar 2010;6:158-94
12. Wenk GL. "Neuropathologic changes in Alzheimer's disease". J Clin Psychiatry 2003; 9: 7–10.
13. Hardy J, Allsop D. "Amyloid deposition as the central event in the aetiology of Alzheimer's disease". Trends Pharmacol. 1991; 12 (10): 383–88.
14. Lacor PN, Buniel MC, Furlow PW, Clemente AS, Velasco PT, Wood M et al.. "Aß Oligomer-Induced Aberrations in Synapse Composition, Shape, and Density Provide a Molecular Basis for Loss of Connectivity in Alzheimer's Disease". Journal of Neuroscience 2009; 27 (4): 796–807
15. Games D, Adams D, Alessandrini R. "Alzheimer-type neuropathology in transgenic mice overexpressing V717F beta-amyloid precursor protein". 1995; 373 (6514): 523–27
16. Wenk GL. "Neuropathologic changes in Alzheimer's disease". J Clin Psychiatry 2003; 9: 7–10.
17. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. "Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human

Services Task Force on Alzheimer's Disease". Neurology 1984; 34 (7): 939–44

18. Dubois B, Feldman HH, Jacova C. "Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria". Lancet Neurol 2007; 6 (8): 734–46.
19. Wong DF, Rosenberg PB, Zhou Y, Kumar A, Raymont V, Ravert HT et al. "In vivo imaging of amyloid deposition in Alzheimer disease using the radioligand 18F-AV-45 (flobetapir F 18)". J Nucl Med 2010; 51 (6): 913–20.
20. O'Brien JT. "Role of imaging techniques in the diagnosis of dementia". Br J Radiol 2010; 80 (Spec No 2): S71–7.
21. Abella HA. "Report from SNM: PET imaging of brain chemistry bolsters characterization of dementias". Diagnostic Imaging, 16, 2010.
22. Pasquier F. "Early diagnosis of dementia: neuropsychology". J. Neurol. January 1999; 246 (1): 6–15.
23. Geldmacher DS, Whitehouse PJ. "Differential diagnosis of Alzheimer's disease". Neurology 1997; 48 (5 Suppl 6): S2–9.
24. Patterson C, Feightner JW, Garcia A, Hsiung GY, MacKnight C, Sadovnick AD. "Diagnosis and treatment of dementia: 1. Risk assessment and primary prevention of Alzheimer disease". CMAJ 2002; 178 (5): 548–56.).
25. Wolfe MS. Therapeutic strategies for Alzheimer's disease. Nat Rev Drug Discov 2003; 1:859-66.
26. Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003; 348:1333-41.
27. Tariot PN, Farlow MR, Grossberg GT,Graham SM, McDonald S, Gergel I. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA 2004; 291:317-24.
28. Rovner BW, Broadhead JH, Spencer M, Carson K, Folstein MF. Depression and Alzheimer's disease. Am J Psychiatry 1989; 146:350-3.
29. Devanand DP, Sano M, Tang M-X. Depressed mood and the incidence of Alzheimer's disease in the elderly living in the community. Arch Gen Psychiatry 1996; 53:175-82.
30. Reifler BV, Teri L, Raskind M. Double-blind trial of imipramine in Alzheimer's disease patients with and without depression. Am J Psychiatry 1989; 146:45-9.
31. .Petracca G, Teson A, Chemerinski E, Leiguarda R, Starkstein SE. A double-blind placebo-controlled study of clomipramine in depressed patients with Alzheimer's disease. J Neuropsychiatry Clin Neurosci 1996; 8:270-5.
32. Brodaty H, Ames D, Snowdon J. A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. J Clin Psychiatry 2003; 64:134-43.
33. Sano M, Ernesto C, Thomas RG. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. N Engl J Med 1997; 336:1216-22.
34. Oken BS, Storzbach DM, Kaye JA. The efficacy of Ginkgo biloba on cognitive functions in Alzheimer's disease. Arch Neurol 1998; 55:1409-15.
35. "Clinical Trials. Found 812 studies with search of: alzheimer". U.S National Institutes of Health. http://www.clinicaltrials.gov/ct2 / results? term=alzheimer.
36. "Study Evaluating ACC-001 in Mild to Moderate Alzheimers Disease Subjects". Clinical Trial. US National Institutes of Health. 2008-03-11.
37. "Study Evaluating the Safety, Tolerability and Efficacy of PBT2 in Patients with Early Alzheimer's Disease". Clinical Trial. US National Institutes of Health. 2008-01-13.