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Advances in Alzheimer's Disease Therapy: A Comprehensive Update

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Alzheimer's disease is a devastating neurodegenerative disorder manifested by deterioration in memory and cognition, impairment in performing activities of daily living, and many behavioral and neuropsychiatric illnesses. The pathological hallmark of Alzheimer's disease is widespread neuritic plaques which are accumulations of amyloid beta protein and neurofibrillary tangles. Studies report that deficit in cholinergic system is responsible for cognitive decline and memory loss in patients with Alzheimer's disease. Various pharmacologic approaches are developed for the treatment of Alzheimer's disease. The leading edge therapies of Alzheimer's disease are approved drugs; Acetylcholinesterase inhibitors and NMDA receptor antagonist. The experimental therapies are mostly disease modifying and have neuroprotective approaches. Gamma secretase inhibitors aim to reduce amyloid beta formation. Antioxidants, antiinflammatory agents and statins help by preventing oxidation and inflammation. PPAR gamma agonists, estrogen, heavy metal chelators, 5HT₆ antagonists and nicotinic receptor agonists are other therapeutic strategies likely to alter the current treatment paradigm of Alzheimer's disease. The behavioral abnormalities are best treated first by non-pharmacologic interventions. The pharmacological agents used for treatment of Neuropsychiatric illnesses include antipsychotics, antidepressants and mood stabilizers. Treatment of Alzheimer's disease also includes health maintenance activities and proper nursing care of the patients.

Key words: Alzheimer's disease, therapy of Alzheimer's disease, cholinesterase inhibitors, neuroprotective agents, gamma secretase inhibitors.

INTRODUCTION

Alzheimer's disease (AD) is a devastating neurodegenerative disorder manifested by deterioration in memory and cognition, impairment in performing activities of daily living, and many behavioral and neuro-psychiatric illnesses (Cummings, 2004). Alzheimer's disease is the most common form of dementia in the old age. The percentage of persons with Alzheimer disease increases by a factor of 2 with every 5 years of age, so 1% of 60 year old and 30% of 85 year old have the disease. By 2050, the number of cases in US is predicted

to rise to 13.2 million (Herbert et al., 2003). An Indo-US study assessed prevalence of Alzheimer disease in a setting of rural India.

They found that the prevalence of Alzheimer disease was low, increased with age and was not associated with gender and literacy (Chandra et al., 1998). In 2000, India had 3.5 million patients with Alzheimer disease as against US, which had 4.5 million patients with Alzheimer disease. But with an increase in the geriatric population in India, number of AD patients is growing at a phenomenal rate. In 2005, the geriatric population was 10% of the whole population. By the year 2021, every seventh Indian will be a senior citizen (www.alzheimerdiseaseinindia.blogspot.com). (What happens in Indian Scenario?)

The course of Alzheimer disease is unique for every patient, but there are many common symptoms. The earliest stages are characterized mainly by short term

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Abbreviation: AD, Alzheimer disease.

memory loss. As the disease advances, there is progressive disablement in doing higher level activities to basic activities of daily living. In advanced stages, symptoms include confusion, aggression, mood changes, long term memory loss and social withdrawal (Mega et al., 1996; Galasko et al., 1997; Waldemar et al., 2007; Tabert et al., 2005).

Alzheimer disease is diagnosed clinically from the patient's history, history from the relatives and clinical observation. Advanced medical imaging with Computed Tomography (CT), Magnetic Resonance Imaging (MRI), with Single Photon Emission Computed Tomography (SPECT), or Positron Emission Tomography (PET) can be used to exclude other cerebral pathologies (Mendez, 2006). Neuropsychological tests such as Mini Mental Status Evaluation (MMSE) are used to evaluate the cognitive impairment and to confirm the diagnosis of Alzheimer disease (Tombaugh, 1992).

Research indicates that Alzheimer disease is associated with amyloid plaques and neurofibrillary tangles in the brain (Tiraboschi et al., 2004). Currently approved therapies offer symptomatic benefit. Drugs, which delay or halt the progression of the disease, are still under experimental phase. In Alzheimer disease, health maintenance and general care of the patient is very essential. The role of the main caregiver is an integral part of the treatment (Thompson et al., 2007).

The present review aims to study the approved as well as experimental therapies for Alzheimer disease. A short overview of future perspectives is also noted.

PATHOPHYSIOLOGY

Alzheimer's disease is characterized by atrophy of cerebral cortex and loss of hippocampal and neocortical neurons. The pathological hallmark of Alzheimer's disease is widespread neuritic plaques which are accumulations of amyloid beta (A β) protein (Braak et al., 1994). Production and accumulation of A β appears to be central to the pathogenesis of Alzheimer's disease (Hardy et al., 2002). A β is a short polypeptide of about 42 amino acids produced by the abnormal proteolytic cleavage of amyloid precursor protein (APP), which involves enzymes like gamma-secretase (Suh, 1997). Production and deposition of A β is the central event triggering oxidation, lipid peroxidation, excessive excitotoxicity of glutamatergic neurons, inflammation, apoptotic cell death and formation of neurofibrillary tangles (Hardy et al., 2002). Neurofibrillary tangles are paired helical filaments composed of tau protein which in normal cells are essential for axonal growth and development (Avila et al., 2004). However, when hyperphosphorylated, the tau protein forms tangles that are systematically deposited within neurons located in the hippocampus and medial temporal lobe, the parieto-

temporal region, and the frontal association cortices leading to cell death (Brion, 1998; Hernández et al., 2007; Chun et al., 2007). The cell death in the basal forebrain (Nucleus basalis of Meynert) leads to deficit in neurotransmitter systems of acetylcholine (ACh), serotonin and norepinephrine. Studies report that deficit in cholinergic system is responsible for cognitive decline and memory loss in patients with Alzheimer's disease (Pappas et al., 2000). The disturbances in neurotransmitter systems also lead to a variety of behavioral abnormalities including depression, psychosis and agitation (Mega et al., 1996).

TREATMENT

Based on the pathophysiology, various pharmacologic approaches are developed for the treatment of Alzheimer's disease. (Figure 1) The approved treatment strategies give symptomatic benefit in Alzheimer disease. The therapies under evaluation for the treatment of Alzheimer's disease have disease modifying and neuroprotective approaches (Giacobini, 1994). (Figure 2) The behavioural abnormalities are best treated first by non-pharmacologic interventions. Pharmacological agents used for treatment of Neuropsychiatric illnesses include antipsychotics, antidepressants and mood stabilizers (Zec et al., 2008). Treatment of Alzheimer's disease also includes health maintenance activities and proper nursing care of the patients (www.searo.who.int).

APPROVED DRUGS

Acetyl cholinesterase inhibitors (AChEI)

Degeneration of cholinergic neurons and decrease in ACh levels in neocortex, hippocampus and basal forebrain play a major role in the pathophysiology of AD. Various therapeutic approaches are proposed to elevate cholinergic transmission like increasing the amount of ACh precursors, blocking hydrolysis with AChE inhibitors, stimulating nicotinic and muscarinic receptors or using cholinomimetic substances. Animal and human data suggest that AChEI are the most efficacious drugs for increasing ACh levels in brain and ameliorating symptoms of AD (Krall et al., 1999).

AChEI are approved for the treatment of mild to moderate AD (Small et al., 1997). Four AChEI are approved by FDA. They are Tacrine, Donepezil, Rivastigmine and Gallantamine. Introduction of Tacrine was a significant breakthrough in the treatment of AD. In a randomized controlled trial of Tacrine, hepatotoxicity and cholinergic adverse effects were reported (Knapp et al., 1994). Also, Tacrine has a short half life (Watkins et al., 1994). Since then, Tacrine has been replaced by

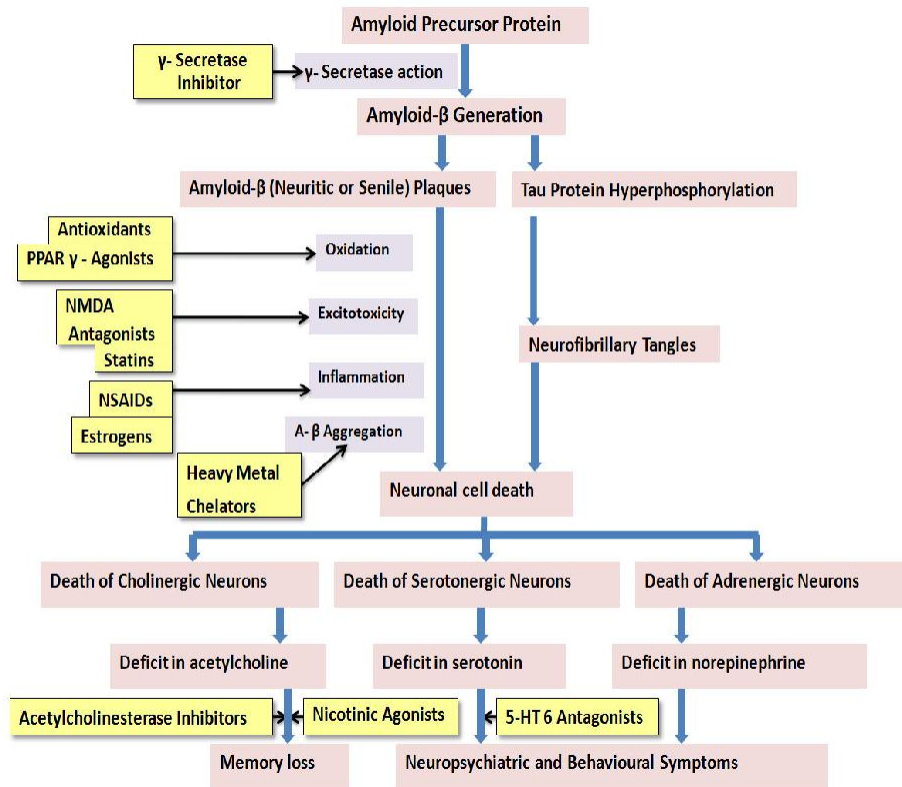


Figure 1. Pathophysiology of Alzheimer's disease and the targets of drug action.

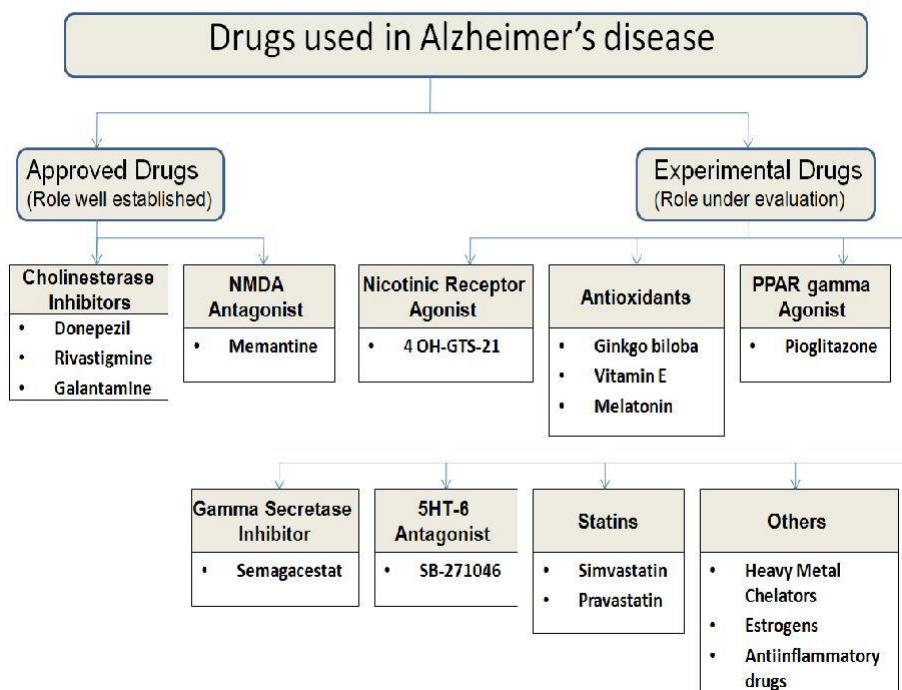


Figure 2. Drugs used in Alzheimer's disease.

Donepezil. Donepezil is a reversible inhibitor of AChEI with a long plasma half life of 70 h. It is not hepatotoxic. (Kosasa et al., 2000) Donepezil is found to bring significant benefit in patients receiving 5 and 10 mg Donepezil versus placebo as measured by Alzheimer Disease Assessment Scale (ADAS-cog) and Clinician Based Impression of Change Scale with Caregiver Input (CIBIC-Plus) (Rogers et al., 1998). Patients with mild, moderate and severe Alzheimer disease treated with donepezil for periods of 12, 24 and 52 weeks experienced benefit in cognition, activities of daily living and behavior. Better tolerability of 5mg/day dose as compared to 10 mg/day dose, lower cost make it the preferable option in AD (Birks, 2006). Another study evaluated effect of donepezil after 3 years of treatment. The mean MMSE change from baseline was positive for more than 6 months and in subgroups of patients for 12 months. After 3 years of treatment the mean change from baseline in MMSE-score was 3.8 points (95% CI, 3.0 - 4.7) and the ADAS-cog rise was 8.2 points (95% CI, 6.4 - 10.1) (Wallin et al., 2007). Several controlled studies have shown modest benefits in cognition and/or behavior (Steele et al., 1999). Therefore, many neurologists, psychiatrists and primary care physicians use donepezil in patients with mild to moderate Alzheimer's disease. In 2005, the UK National institute for clinical excellence (NICE) withdrew its recommendation for use of the drug for mild-to-moderate AD, on the basis that there is no significant improvement in functional outcome; of quality of life or of behavioral symptoms. However, NICE revised its guidelines to suggest that donepezil be used in moderate stage patient. It is currently not licensed for Alzheimer's disease in the UK at any other stage (Xiong et al., 2005). The U.S. Food and Drug Administration have approved the first generic versions of Aricept (donepezil hydrochloride) orally disintegrating tablets (www.fda.gov). Recently, the FDA has also approved 23 mg extended release tablet Donepezil for the treatment of moderate to severe

Alzheimer's disease (www.clinicaltrials.gov/NCT00478205).

Rivastigmine is a reversible AChEI with higher affinity for brain ACh than peripheral ACh. It inhibits both butyrylcholinesterase and acetylcholinesterase (Camps et al., 2002). It has a plasma half life of 2 h (Jann et al., 2000). Rivastigmine was found to have a statistically significant benefit in a randomized controlled trial after 2 - 6 weeks as measured by ADAS-cog and CIBIC-Plus scores (Corey-Bloom, 1998). Rivastigmine is started at a dose of 1.5 mg BD, then increased to 3 mg BD and then to 4.5 mg BD and to a maximum dose of 6 mg BD. Rivastigmine has demonstrated significant treatment effects on the cognitive (thinking and memory), functional (activities of daily living) and behavioral problems that are commonly associated with Alzheimer disease (Finkel, 2004). In comparisons with placebo, improvements were seen in the rate of decline of cognitive function, activities

of daily living and severity of dementia with daily doses of 6 to 12 mg (Birks et al., 2009). The US FDA has approved Rivastigmine capsules and the Rivastigmine patch for the treatment of mild to moderate dementia of the Alzheimer disease (www.fda.gov). In a large clinical trial of the rivastigmine patch in 1,195 patients with Alzheimer's disease, the target dose of 9.5 mg/24 h patch provided similar clinical effects (e.g. memory and thinking, activities of daily living, concentration) as the highest doses of rivastigmine capsules, but with three times fewer reports of nausea and vomiting (Winbald et al., 2007). When given by once-daily transdermal patch, the pharmacokinetic profile of rivastigmine is much smoother, compared with capsules, with lower peak plasma concentrations and reduced fluctuations. The 9.5 mg/24 h rivastigmine patch provides comparable exposure to 12 mg/day capsules (the highest recommended oral dose (Cummings et al., 2007)).

Galantamine is a reversible and selective AChEI having 50 times more selectivity for human Acetylcholinesterase than for human butyrylcholinesterase. Galantamine also acts as a nicotinic receptor agonist in the brain (Coyle et al., 2001). Galantamine was found to be efficacious in a randomized controlled trial of 636 patients of Alzheimer disease, as measured by CIBIC-Plus scores (Raskind et al., 2000).

The US Food and Drug Administration (FDA) and International health authorities have published an alert based on data from two studies during the treatment by galantamine of mild cognitive impairment; higher mortality rates were seen in drug-treated patients (www.fda.gov). On April 27, 2006, FDA approved labeling changes concerning all form of galantamine preparations (liquid, regular tablets and extended release tablets) warning of the risk of bradycardia and sometimes atrioventricular block, especially in predisposed persons). At the same time, the risk of syncope seems to be increased relative to placebo (www.archive.org). These side effects have not been reported in any other studies except in mild cognitive impairment. Huperizine A, a natural lycopodium alkaloid, isolated from herb *Hypersia serrata*, is a centrally active cholinesterase inhibitor. Preliminary studies have shown it to be of benefit in Alzheimer disease (Ott et al., 1998)

NMDA receptor antagonist

Glutamate is an excitatory neurotransmitter and acts on a variety of receptors. NMDA is one such receptor. NMDA receptor on activation causes potentiation of neuronal activity, but in Alzheimer's disease, excessive glutamatergic excitotoxicity causes apoptotic cell death and defects in cognition and memory (Danysz et al., 2003). Memantine, a NMDA receptor antagonist is recently approved by FDA for the treatment of moderate to severe

Alzheimer's disease, as it is found to interfere with the glutamate excitotoxicity (Parsons et al., 1999). A study reviews the molecular mechanism of Memantine action and the basis for Memantine used in Alzheimer disease. Excitotoxic cell death is mediated by over activation on NMDA glutamate receptors, which results in excessive Ca^{++} influx through the receptors associated ion channel. Memantine acts as an uncompetitive, low affinity open channel blocker (Lipton SA, 2004). Memantine is found to be superior to placebo as indicated by Neuropsychological Tests like Activities of Daily Living Inventory (ADLI) and Severe Impairment Battery (SIB), but not on Global Deterioration Scale (Reisberg et al., 2003). In patients receiving Donepezil, Memantine improved cognition, activities of daily living and reduced frequency of behavioural symptoms as compared to placebo (Tariot et al., 2004; Farlow et al., 2003).

EXPERIMENTAL DRUGS

Nicotinic receptor agonist

Another therapeutic approach to enhance cholinergic function is to administer nicotinic receptor agonists. Nicotinic receptor types 4 2 and 7 are localized in areas of brain associated with dementia and memory loss. A selective partial 7 nicotinic receptor agonist 4 OH-GTS-21 is shown to have protective action on cholinergic neurons, but not protective for the amyloid over expressing transgenic mice (Ren et al., 2007). A study reported that chronic treatment with RJR -2403 and 17 beta-estradiol had marked anti-amnesic effect in middle aged ovariectomized rats with experimental Alzheimer type dementia (Sapronov et al., 2006). A novel compound Alpha - 7 nicotinic receptor agonist EVP-6124 is currently in phase II ([www.clinicaltrials.gov/ NCT01073228](http://www.clinicaltrials.gov/NCT01073228)). More research is needed to unravel the full potential of nicotinic ACh agonists.

Antioxidants

Oxidative damage is present within the brains of patients with Alzheimer disease. Treatment with antioxidants is a promising approach for reducing disease progression. Recent research has found a link between antioxidant intake and reduced incidence of dementia (Grundman et al., 2002). A review of antioxidants has suggested agents like aged garlic extract, curcumin, melatonin, resveratrol, ginkgo biloba extract, green tea and Vitamin C and E in patients with Alzheimer's disease (Frank et al., 2005). Ginkgo biloba extract is known to be neuroprotective. It inhibits lipid peroxidation (Oyama et al., 1996). Ginkgo biloba had shown small, but significant effect in comparison to placebo in patients with Alzheimer's disease

(Oken et al., 1998). An extract of Ginkgo biloba, Eqb 761, was tested in Alzheimer's disease patients for 52 weeks and it showed significant improvement on the ADAS-cog scale (Le Bars et al., 1997). Another antioxidant showing promise is Vitamin E or Alpha tocopherol. A study compared the effect of Vitamin E and Selegiline alone, together and placebo in patients with Alzheimer's disease. It was observed that delay to one of the primary outcomes like time to death, confinement or development of severe dementia was significantly more in Vitamin E groups as compared to placebo (Sano et al., 1997). Many practitioners have added Vitamin E supplements to the standard treatment regimen of Alzheimer's disease. Future development of antioxidant drugs to the mitochondria like Acetylcarnitine should pave the way to a new treatment paradigm (Mancuso et al., 2007).

PPAR agonists

Peoxisome Proliferator Activated Receptors (PPAR) are a family of nuclear receptors and play an important role in lipid peroxidation, cellular proliferation and differentiation (Willson et al., 2000). PPAR is a ligand activated transcription factor which regulates lipid metabolism and inflammation. PPAR agonists inhibit inflammatory gene expression, alter A beta homeostasis and exhibit neuro-protective effects (Landreth, 2007). They also induce apoptotic cell death in glioma cells (Chattopadhyaya et al., 2000).

A study demonstrated the effect of 15 - 30 mg of pioglitazone daily in patients with mild Alzheimer's disease. The pioglitazone group improved agitation and regional cerebral blood flow in the parietal lobe. The study demonstrated that pioglitazone exhibited cognitive and functional improvement (Sato et al., 2009). It may offer a novel strategy to the already existing treatment paradigm. However, several issues like metabolic effects, genomic effects and toxic effects of PPAR agonists need to be addressed

Gamma secretase inhibitors

Gamma Secretase inhibitors are disease modifying agents in Alzheimer's disease. Any drug which can significantly address underlying disease pathology and slow the disease progression would constitute a major advance in the therapy of Alzheimer's disease. Sufficient evidence is provided by genetic and biological studies that production and deposition of A amyloid contributes to Alzheimer's disease. Gamma secretase plays a pivotal role in production of C terminus of A, which determines its aggregability and tendency for deposition. Inhibition of gamma secretase by drugs can be an effective therapeutic strategy for Alzheimer's disease (Tomita et

al., 2006; Evin et al., 2006). A randomized controlled trial of LY450139 dihydrate, a gamma secretase inhibitor resulted in decrease in plasma and CSF A concentration (Siemers et al., 2006). Semagacestat (LY450139) is a gamma secretase inhibitor under development by Eli Lilly as an Anti Alzheimer's disease. Phase III double-blind clinical trials started in March 2008 with the IDENTITY study (Interrupting Alzheimer's dementia by evaluating treatment of amyloid pathology), including 1500 patients from 22 countries. This study will be running until May 2011 (<http://www.clinicaltrials.gov/show/NCT00594568>). The successor trial with further 1500 patients, IDENTITY-2, started in September 2008 (<http://www.clinicaltrials.gov/show/NCT00762411>). The open label study IDENTITY-XT, which includes patients who have completed one of the two studies has started in Dec 2009 (<http://www.clinicaltrials.gov/show/NCT00762411>).

5HT₆ receptor antagonist

Evidences supporting the role of serotonergic transmission in the pathophysiology of Alzheimer's disease have suggested the use of 5HT₆ receptor antagonists as a novel therapeutic strategy. An animal study with rats on Morris water maze tested the effect of SB-271046 and RO-04-6790 on learning and memory. The two compounds enhanced retention of learned position, but had no effect on learning during training phase (Reavill et al., 2001). Another study was done to evaluate the effect of SB-271046 on neuronal cell adhesion molecular (NCAM) polysialylation in rat brain. NCAM polysialylation contributes to learning and increases dendritic remodeling in CNS. It was observed that SB-271046 increased the NCAM polysialylation in the CNS in response to water maze spatial learning.

So it is inferred that 5HT₆ receptor antagonists have a favourable effect on synaptic plasticity (Regan et al., 2003). Dimebolin is a non selective anti-histaminic approved in Russia for the treatment of allergic disorders. This drug has been found to antagonize 5HT₆ receptor and also interacts with NMDA receptors, acetyl cholinesterase and voltage gated calcium channels. In a study, it was noted that Dimebolin produces an acute enhancement of short term social recognition memory (Schaff-Hanser et al., 2009). However, a phase III CONNECTION study of Dimebolin in mild to moderate Alzheimer's disease failed to meet the co-primary and secondary efficacy endpoints as compared to placebo (www.clinicaltrials.gov/NCT00675623).

Statins

Higher cholesterol levels are a risk factor not only for

cardiovascular diseases, but also for the development of Alzheimer's disease. Nerve cells die because of excitotoxicity and oxidation. In animal experiments, it was demonstrated that treatment with Lovastatin prevented the death of nerve cells. It also prevented the loss of memory capacity and stimulated the protective capacity of TNF-alpha (Dolga et al., 2009). However, a review of several studies has shown that statins (HMG CoA reductase inhibitor) do not prevent Alzheimer's disease. Two major studies, that is, HPS (Simvastatin given in 20,536 patients for 5 years) and PROSPER trial (Pravastatin given in 5,084 patients for 3.2 years) showed no difference in the drug and control group in terms of dementia, cognitive function and specific neuropsychological tests. Although, this review reported that statins do not prevent Alzheimer's disease, if given in late life, it could not comment on the effect of statins on dementia in late life, if they are given in early and middle life (McGuinness et al., 2009). Another study demonstrated an association between antecedent exposure of statins and formation of Neuritic Plaques or Neurofibrillary tangles in human subjects (Li et al., 2007). However, additional studies are required to assess the causal association between statin use and decreased development of Alzheimer disease.

Heavy metal chelators

There is increasing evidence that biometals like aluminium, iron, zinc and copper increase aggregation of A₂ and toxicity in Alzheimer's disease (Bush et al., 1994). Structural analysis of A₂ acrylid showed that there is a direct biochemical interaction between aluminum and A₂ (Holloosi et al., 1994). Some studies have shown higher mercury concentrations in brains of deceased and in blood of living patients with Alzheimer's disease. Experimental studies have found that even smallest amounts of mercury but no other metals in low concentrations were able to cause all nerve cell changes, which are typical for Alzheimer's disease (Mutter et al., 2004). It has been seen that levels of iron and zinc are abnormally elevated in brain in patients with AD. This evidence supports the hypothesis that metal chelators may be a possible therapeutic approach for AD (Cornett et al., 1998). In a clinical trial in which desferrioxamine was used, there was a decrease in dementia (Crappier-Malachlan et al., 1991). After 2 years, it was noted that the aluminium concentrations reduced to near control concentrations. A review proposes a novel system for the delivery of chelating agents through the use of nanoparticles. Nanoparticles conjugated to chelators have a unique ability to cross Blood brain barrier, chelate metals and exit thoroughly the BBB with the complex. This novel technique may be able to stave off the harmful effect of oxidative damage done by metal ions in Alzheimer

disease (Liu et al., 2005). However, more clinical trials need to be done to throw light on the future role of chelating agents in Alzheimer disease therapy (www.fda.gov; www.clinicaltrials.gov)

Estrogens

Several pharmacoepidemiologic studies have reported that Alzheimer disease is more common in postmenopausal women than men (Henderson, 1997). These occurrences have led to the hypothesis that estrogen loss in postmenopausal women may contribute to the development of Alzheimer's disease. Estrogen is known to reduce the risk of developing dementia. There are various biological and neurophysiologic mechanisms which support this hypothesis. Estrogen is known to modulate Apo E gene, increase the metabolism of APP, protects against oxidative stress and causes direct modulation of neurotransmitters (Yaffe et al., 1998). Estrogen is found to increase cerebral blood flow and prevent neuronal atrophy (Burns et al., 1996). However, the reports of various studies are inconclusive. The Women's Health Initiative study of Estrogen and Pro-gesterone showed an increase in the risk of dementia in study group (Shumaker et al., 2003). Another trial was conducted on women in the age group of 75 - 79 years. They received 1.25 mg/d of conjugated estrogen. It was seen at the end of 16 weeks that ADAS-cog score of patients in estrogen group had in fact decreased by 1.8 points, whereas it reduced by 0.5 points in placebo group (Henderson et al., 2000). Observational data link use of hormone therapy to reduction in Alzheimer's risk, but experimental evidence from clinical trials demonstrate that estrogen increases the incidence of dementia. Bias and confounding factors are the leading cause of dis-crepancy between observational studies and clinical trials (Henderson, 2006) . Several studies are of the view that hormone therapy initiated closer to the time of menopause may reduce the incidence of Alzheimer's dementia. The time at which estrogen therapy is initiated (critical window hypothesis), the neurological status at the time of therapy initiation and the type of progesterone used, all contribute to the efficacy of estrogen in Alzheimer's disease (Henderson, 2007; Brinton, 2004) Although there is no clinical trial evidence, yet it needs to be determined, whether initiation of hormone therapy in relation to menopause modifies the treatment outcomes.

Anti-inflammatory agents (NSAIDs)

Alzheimer's disease is characterized by neuritic plaques and neurofibrillary tangles. Along with them, there is also evidence of inflammation in the form of cytokines and microglial activation (Flynn, 1999; Finch, 2001). These

observations led to a series of clinical trials with NSAIDs to ascertain their role in Alzheimer's disease. The mechanism by which NSAIDs affect the pathology of Alzheimer's disease is by inhibition of COX enzymes resulting in decreased production of cytokines, decreased platelet aggregation and decreased release of factors which prevent free radical damage (Flynn, 1999). Several studies with Prednisolone, Diclofenac and Rofecoxib have given negative outcomes (Aisen, 2000; Scharf, 1999; Aisen, 2003). A meta analysis evaluated 17 studies, in which each study had brought forth the conclusion that NSAIDs have a protective role in Alzheimer's disease (McGeer, 1996). A longitudinal study evaluated whether there was reduced risk of Alzheimer's disease in users of Aspirin or any other NSAID. In a total of 1686 patients, only 51 patients were found to be suffering from Alzheimer's disease, thus indicating that NSAID use reduces the risk of AD. It was also observed that the relative risk for Alzheimer's disease decreased with increasing duration of NSAID use (Stewart, 1997). A recently published study has tested the effect of NSAID use for more than 5 years on AD. It reported that the long term use of NSAID use was protective against Alzheimer's disease. Maximum effect was seen with the use of Ibuprofen (Vlad et al., 2008). Another study reported 7 days treatment of APPV7171 mice with pioglitazone and Ibuprofen. The drug treatment reduced the expression of the proinflammatory enzyme COX-2 and iNOS and Beta secretase (Heneka et al., 2005). Two other studies also demonstrate that Ibuprofen reduces microglial activation and cytokine production in transgenic mice overexpressing APP (Lim, 2000; Yan et al., 2003).

Health maintenance and general medical treatment

As soon as the diagnosis of Alzheimer disease is made, it is essential to develop a daily routine for the patient. Maintaining a daily routine includes drawing up a fixed timetable for the patient for getting up in the morning, toilet, exercise and meals. This gives the patient a sense of security. Patients often deteriorate after dark, a phenomenon known as 'sundowning'. Additional care must be taken during the evening and at night. Patient should be provided a well balanced diet, rich in protein, high in fibre and with adequate calories. The safest diet is a semi-solid one with the consistency of a purée. Liquids are the most dangerous type of food, as these can be easily aspirated into the lungs. Toilet habits should be established as soon as possible and maintained as a rigid routine. This includes conditioned behaviour such as going for bowel movement immediately after a cup of tea. The patient should be taken to urinate at fixed intervals. Particular care should be taken about personal hygiene such as, brushing teeth, taking baths etc. Great care should be taken to avoid accidents caused by tripping

over furniture, falling down the stairs or slipping in the bathroom. Patients of Alzheimer disease need continuous monitoring for coexisting medical disorders like pneumonia, fractures, urine infections and stomach upsets. Aspiration of food into lungs is the most common cause of pneumonia. Minor falls can cause fractures and infections can occur due to unhygienic conditions. Great care should be taken to avoid accidents caused by tripping over furniture, falling down the stairs or slipping in the bathroom. (Chandra et al., 1986., www.searo.who.int).

Management of neuropsychiatric and behavioral symptoms

Along with cognitive decline, patients with Alzheimer's disease have a varied range of non-cognitive symptoms, which can be very disturbing. They include neuropsychiatric and Behavioral symptoms, such as agitation, psychosis, hallucinations, aggression, aimless vocalization and wandering. These symptoms appear in 90% of people with AD (McShane et al., 2007; Ballard et al., 2006). They are also the root cause of morbidity, higher cost of care and reduced quality of life (Yaffe et al., 2002). Food and Drug Administration (FDA) has not approved any medication for the treatment of neuropsychiatric and behavioral symptoms in patients with AD. However, off label medication use is rampant worldwide. The first line therapy of neuropsychiatric and behavioral symptoms should be non pharmacologic interventions. Pharmacological treatment of these symptoms is usually undertaken in advanced stages of Alzheimer disease (Zec et al., 2008)

Non pharmacological treatment

There are several non pharmacological strategies, which manage the functional and behavioral deterioration (www.gmhfonline.org). A recent review has suggested that there is evidence to support the efficacy of activity programs, music, behavior therapy, light therapy and changes to the physical environment (Opie et al., 1999).

(1) Independence promoting strategies: Usage of incentives, verbal and physical prompting and physical guidance. Helps the patient in maintaining hygiene, dressing, grooming etc.

(2) Exercise: Simple exercises like walking and cycling can improve sleep and decrease agitation.

(3) Incontinence management: By monitoring incontinence and scheduling bathroom time or by putting reminders.

(4) Sleep management: Enhance night time sleep by dark environment at night and limiting day time napping.

(5) White noise: Continuous background monotonous noise reduces agitation and is soothing. Music therapy also helps to stir memories.

(6) Visual cueing- Pasting pictures of bed on bedroom door can help the patient find his way around home.

(7) Counselling, reminiscence therapy, validation, simulated presence, pet therapy, recreational therapy and art therapy are other ways of reducing behavioral swings in a patient suffering from Alzheimer disease.

Pharmacological treatment

Atypical antipsychotics are the most commonly prescribed drugs for the treatment of neuropsychiatric symptoms in Alzheimer's disease (Sink et al., 2005). Several placebo controlled trials have examined the efficacy of atypical neuroleptics over a period of 6 -12 weeks in patients with Alzheimer's disease. Approximately two-third of the patients improved, but the response was modest and some did not benefit at all. Atypical neuroleptics have not shown consistent efficacy (Schneider et al., 1990) . Risperidone has the best evidence base for benefit in aggression at a dose of 2 mg, but not in agitation and psychosis (Ballard et al., 2006). Olanzapine was also effective at a dose of 5 - 10 mg/day (Street et al., 2000). Data for quetiapine, ziprasidone and aripiprazole are limited. Clozapine at 12.5 - 100 mg/day may improve psychosis or aggression (Schneider et al., 2001). A few trials have assessed the effect of neuroleptics over a period of more than 14 weeks, neither giving any positive effect (Ballard et al., 2005; Schneider et al., 2006; Ballard et al., 2008). However, Food and drug administration (FDA) has issued safety warnings against the off label use of neuroleptics in Alzheimer's disease. Neuroleptics are associated with several adverse effects like edema, chest infections, cerebrovascular accidents, metabolic syndromes and death (Schneider et al., 2005).

In some studies, neuro-leptics have even caused accelerated cognitive decline (Schneider et al., 2006). Other drugs for the treatment of neuropsychiatric symptoms are carbamazepine, sodium valproate and antidepressants like trazodone and citalopram. Carbamazepine is the drug best supported by trials (Tariot et al., 1998). A recent Cochrane review concluded that valproate is effective at higher doses (Lonergan et al., 2007). Antidepressant drugs are the therapy of choice for severe depression, but the evidence base from trials is far from clear. A Cochrane review concludes that the trials did not demonstrate any superiority of antidepressants over placebo (Bains et al., 2007). Studies of Trazodone have given mixed results (Sultzer et al., 1997; Teri et al., 2001). Citalopram was associated with improvement in symptoms and has equivalent efficacy to risperidone (Nyth et al., 1990; Pollock et al., 2007). No

study has evaluated the effect of antidepressants over long term use in Alzheimer's disease. Better designed trials are the need of hour to understand the efficacy of antidepressants in the treatment of neuropsychiatric and behavioral symptoms. Growing evidence suggests that neurobiological basis of neuropsychiatric and behavioral symptoms in AD is a loss of cholinergic neurons and a decline in Acetylcholine levels in limbic system, which regulates behavioral and emotional responses (Wang et al., 2005). This deficit can be corrected by Acetylcholinesterase inhibitors. Donepezil has shown efficacy for cognitive as well as behavioral symptoms in patients with Alzheimer's disease. Gallantamine has also shown to delay the onset of behavior and psychological symptoms (Trinh et al., 2003).

However, several studies have given negative results for the use of AChEI for neuropsychiatric symptoms (Howard et al., 2007; Holmes et al., 2004; Gauthier et al., 2002). It is unlikely that AChEI are going to be useful for the treatment of neuropsychiatric and behavioral symptoms. Emerging evidence indicates that Memantine may play a pivotal role in the treatment of agitation and aggression (Gauthier et al., 2005; Cummings et al., 2006; Wilcock et al., 2008). However, these data are based on retrospective posthoc analyses. Prospective studies are required to determine the role of memantine in the treatment of neuropsychiatric and behavioral symptoms in Alzheimer's disease.

Caregivers

The role of a caregiver is integral for the wellbeing of the patient. Patients with Alzheimer disease are usually cared for by a member of the family in their homes or by a hired nurse or a qualified caretaker. Physical exercise, social activities, as well as proper nutrition and health maintenance are important aspects of care. The caregiver should plan daily activities of the patient. The activities should be familiar, satisfying and should provide structure, meaning and sense of accomplishment to the patient. The care giver should also keep the patient out of harm's way by removing safety risks. (www.helpguide.org).

The responsibility of caring for the Alzheimer disease patient can take an enormous emotional and physical toll of the caregiver. Because of the burdens of care giving, the caregiver of the patient is also referred to as the hidden or the second patient. Caregiver stress can present serious health and psychological problems. The caregiver can develop anger, social apathy, anxiety, depression, sleeplessness, irritability, and other health problems. Emotional support from family and friends, self confidence and resources to help household chores were found to positively influence caregivers and protect them against stress. Several support groups, respite care and

skills training programmers help the family and the caregiver to cope up with and help an Alzheimer disease patient. (www.gmhf.org).

Future perspectives

As of 2010, more than 800 clinical trials are being investigated world wide, approximately a quarter of these are in Phase III (www.clinicaltrials.gov/term=alzheimer). One area of clinical research is focused on treating the underlying disease pathology. Reduction of Amyloid beta levels is a common target of compounds (such as apomorphine) under investigation (Lashuel et al., 2002). Immunotherapy or vaccination for the amyloid protein is one treatment modality under study (Dodel et al., 2010). It is based upon the concept of training the immune system to recognise, attack, and reverse deposition of amyloid, thereby altering the course of the disease (Hawkes et al., 2007; Solomon et al., 2007). An example of such a vaccine under investigation was ACC-001 (www.clinicaltrials.gov/NCT00498602), although the trials were suspended in 2008 (www.medpagetoday.com). In previous clinical trials for vaccination against human beta amyloid, called AN-1792, patients with Alzheimer's disease using active immunization had positive outcomes with removal of plaques, but 6% of subjects developed aseptic meningitis and the trial was stopped (Woodhouse et al., 2007). A vaccine AFFITOPE AD02 is entering phase II trials (www.clinicaltrials.gov/NCT00711321). Another similar agent is bapineuzumab, a humanized monoclonal antibody designed as identical to the naturally induced anti-amyloid antibody (www.clinicaltrial.gov/NCT00574132). Other approaches are neuroprotective agents, such as AL-108 (www.clinicaltrials.gov/NCT004222981) and metal-protein interaction attenuation agents, such as PBT2 (www.clinicaltrials.gov/NCT00471211). A TNF receptor fusion protein, etanercept has showed encouraging results (Griffin, 2008). In 2008, clinical trials showed positive results in modifying the course of disease in mild to moderate AD with methylthioninium chloride (trade name *rember*), a drug that inhibits tau aggregation (Wischik et al., 2008; Harrington et al., 2008). Another novel compound is LY2062430 (solanezumab), which is a humanized anti-A Beta peptide immunoglobulin G-1 (IgG1) monoclonal antibody being developed for the treatment of AD. Currently, two phase III studies EXPEDITION and EXPEDITION 2 are testing the efficacy of solanezumab on the slowing of cognitive and functional decline in Alzheimer's disease as compared to placebo (www.clinicaltrials.gov/NCT00905372/ [NCT00904683](http://www.clinicaltrials.gov/NCT00904683)).

Conclusion

Alzheimer disease is one of the most debilitating diseases

affecting the old age. A clear understanding of the natural history of Alzheimer disease has enabled us to develop appropriate trial designs and outcomes for the various stages of this condition. Clear benefit for the treatment of symptoms in mild to severe AD using AChEIs and Memantine is seen. Also, there is cautious optimism for successful disease modification using a number of agents currently under study. Guidelines for the treatment of Alzheimer disease have to be constantly updated to take into account new evidence for the ultimate benefit of patients and care-givers.

REFERENCES

- A Safety and Efficacy Study of Oral Dimebon in Patients With Mild-To-Moderate Alzheimer's Disease (CONNECTION). Clinical Trial. US National Institutes of Health. Available from: <http://clinicaltrials.gov/ct2/show/NCT00675623>. Accessed on 15th June 2010.
- Aisen PS, Davis KL, Berg JD, Schafer K, Campbell K, Thomas RG (2000). A randomized controlled trial of prednisone in Alzheimer's disease. *Neurology*. 54: 588-93. Aisen PS, Schafer KA, Grundman M, Pfeiffer E, Sano M, Davis KL, et al (2003). Effects of rofecoxib or naproxen vs placebo on Alzheimer's disease progression: a randomized controlled trial. *J. Am. Med. Assoc.*, 289: 2819-26. provide other names, et al is not allowed in reference
- Alzheimer's disease in India. Available from: www.alzheimerdiseaseinindia.blogspot.com/.../rise-of-alzheimers-disease-cases-html-. Accessed on 15th June 2010.
- Alzheimer's disease in India. Available from: www.alzheimerdiseaseinindia.blogspot.com/.../demographic-transition-in-india-how-to.html-. Accessed on 15th June 2010.
- Alzheimer's Disease Vaccine Trial Suspended on Safety Concern. Medpage Today. 2008-04-18. <http://www.medpagetoday.com/MeetingCoverage/AAN/tb/9165>. Accessed on 14th June 2010.
- Alzheimer's Disease: FDA's Role In New Product Development. Available from: www.fda.gov/NewsEvents/Testimony/ucm110879.htm. Accessed on 14th June 2010.
- Avila J, Lucas JJ, P'erez M, Hern'andez (2004). Role of Tau protein in both physiological and pathological conditions. *Physiol. Rev.*, 84: 361-84.
- Bains J, Birks JS, Denning TD (2007). Antidepressants for treating depression in dementia, *Cochrane Database Syst. Rev.*, 3.
- Ballard C, Howard R (2006). Neuroleptic drugs in dementia: benefits and harm, *Nat. Rev. Neurosci.*, 7: 492-500.
- Ballard C, Lana MM, Theodoulou M, et al, Douglas S, McShane R, Jacoby R et al (2008). A Randomised, Blinded, Placebo-Controlled Trial in Dementia Patients Continuing or Stopping Neuroleptics (The DART-AD Trial), *PLoS Med.*, 5: e76.
- Ballard C, Margallo-Lana M, Juszcak E, Douglas S, Swann A, Thomas A et al (2005). Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial, *BMJ*, 330: 874-7.
- Bapineuzumab in Patients With Mild to Moderate Alzheimer's Disease/ Apo_e4 non-carriers. Clinical Trial. US National Institutes of Health. <http://clinicaltrials.gov/ct2/show/NCT00574132>. Accessed on 14th June 2010.
- Birks J, Grimly EJ, Lakovidou V, Tsolaki M, Holt FE (2009). Rivastigmine for Alzheimer disease. *Cochrane Database Syst Rev.* 15: CD001191. therapy and Alzheimer's disease. *Am. Acad. Neurol.*, 48: S27-S35.
- Birks J, Harvey RJ (2006). Donepezil for dementia due to Alzheimer disease. *Cochrane database Syst. Rev.*, 25: CD001190.
- Braak H, Braak E (1994). Pathology of Alzheimer's disease. In: Calne D, ed. *Neurodegenerative Diseases*. Philadelphia: Saunders, 585-614.
- Brenner DE, Kukull WA, Stergachis A, Van Belle G, Bowen JD, McCormick WC, et al (1994). Postmenopausal estrogen replacement therapy and the risk of Alzheimer's disease: A population-based case-control study. *Am. J. Epidemiol.*, 140: 262-67.
- Brinton RD (2004). Impact of estrogen therapy on Alzheimer's disease: a fork in the road? *CNS Drugs*. 18: 405-22.
- Brion JP (1998). Neurofibrillary tangles and Alzheimer's disease. *Eur. Neurol.*, 40: 130-40.
- Burns A, Murphy D. (1996). Protection against Alzheimer's disease? [Commentary]. *Lancet.*, 348: 420-421.
- Bush AI, Pettingell WH, Paradis MD, and Tanze RE (1994). Modulation of a beta adhesiveness and secretase site cleavage by zinc. *J. Biol. Chem.*, 269: 12152-12158.
- Camps P. Munoz-Torrero D (2002). Cholinergic drugs in pharmacotherapy of Alzheimer's disease. *Mini. Rev. Med. Chem.*, 2: 11-25.
- Caring for the Alzheimer's disease patient. Geriatric mental health foundation. (Accessed on 7th May 2010) Available from: http://www.gmhfonline.org/gmhf/consumer/factsheets/caring_alzheimer_diseasecg.html.
- Chandra V, Bharucha NE, Schoenberg BS (1986). Conditions associated with Alzheimer's disease at death: case-control study. *Neurology*, 36: 209-211.
- Chandra V, Ganguli M, Pandav R, Johnston J, Belle S, Dekosky ST (1998). Prevalence of Alzheimer disease and other dementias in rural India. *Neurol.*, 51: 1000-8.
- Chattopadhyay N, Singh DP, Heese O, Godbole MM, Sinohara T, Black PM (2000). Expression of PPARs in human astrocytic cells: PPAR gamma agonists as inducers of apoptosis. *J Neurosci Res.* 61: 67-74.
- Chun W, Johnson GV (2007). The role of tau phosphorylation and cleavage in neuronal cell death. *Front Biosci.*, 12: 733-56.
- Clinical Trials: Found 801 studies with search of: alzheimer. (Accessed on 12th June 2010). Available from: <http://www.clinicaltrials.gov/ct2/results?term=alzheimer>.
- Comparison of 23 mg Donepezil Sustained Release (SR) to 10 mg Donepezil Immediate Release (IR) in Patients With Moderate to Severe Alzheimer's Disease. Clinical Trial. US National Institutes of Health. Available from: <http://clinicaltrials.gov/ct2/show/NCT00478205>. Accessed on 15th June 2010.
- Corey-Bloom J, Anand R, Veach J (1998). for the ENA 713 B352 Study Group: A randomized trial evaluating the efficacy and safety of ENA 713 (Rivastigmine Tartarate), a new Acetyl cholinesterase inhibitor, in Cornett CR, Markesbery WR, Ehmann WD (1998). Imbalance of trace elements related to oxidative damage in Alzheimer's disease brain. *Neurotoxicology*. 19: 339-345.
- Coyle J, Kershaw P (2001). Galantamine, a cholinesterase inhibitor that allosterically modulates nicotinic receptors: effects on the course of Alzheimer's disease. *Biol. Psychiatry.*, 49: 289-99.
- Crapper- Malachlan DR, Dalton AJ, Kruck TPA, Bell MY, Smith WL, Kalow W (1991). Intramuscular desferrioxamine in patients with Alzheimer's disease. *Lancet*. 337: 1304-1308.
- Cummings J, Lefevre G, Small G, Appel-Dingemans S (2007). Pharmacokinetic rationale for the rivastigmine patch. *Neurol.*, 69: S10-3.
- Cummings JL (2004). Alzheimer's disease. *N Engl J Med.* 351: 56-67.
- Cummings JL, Schneider E, Tariot PN, Graham SM (2006). Behavioural effects of memantine in Alzheimer's disease patients receiving donepezil treatment, *Neurol.*, 67: 57-63.
- Danzysz W, Parsons CG (2003). The NMDA receptor antagonist Memantine as a symptomatological and neuroprotective treatment for Alzheimer's disease: a preclinical evidence. *Int. J. Geriatr. Psychiatry*, 18: S23-32.
- Dodel R, Neff F, Noelker C, Pul R, Du Y, Bacher M Oertel W (2010). Intravenous Immunoglobulins as a Treatment for Alzheimer's Disease: Rationale and Current Evidence. *Drugs*. 70: 513-528.
- Dolga AM, Granic I, Nijholt IM, Nyakas C, VanDer Zee EA, Luiten PGM (2009). Pretreatment with Lovastatin prevents N-methyl-D-Aspartate induced neurodegeneration in the magnocellular Nucleus Basalis and Behavioral dysfunction. *J. Alzheimer. Dis.*, 17: 2.

- Effect of LY2062430 on the Progression of Alzheimer's Disease (EXPEDITION). Clinical Trial. US National Institutes of Health. Available from: <http://clinicaltrials.gov/ct2/show/NCT00905372>. Accessed on 15th June 2010.
- Effect of LY2062430 on the Progression of Alzheimer's Disease (EXPEDITION2). Clinical Trial. US National Institutes of Health. Available from: <http://clinicaltrials.gov/ct2/show/NCT00904683>. Accessed on 15th June 2010.
- Effect of LY450139 on the Long Term Progression of Alzheimer's Disease. Available from: <http://www.clinicaltrials.gov/show/NCT00594568>. (Accessed on 12th June 2010).
- Effects of LY450139, on the Progression of Alzheimer's Disease as Compared With Placebo (IDENTITY-2). Available from: <http://www.clinicaltrials.gov/show/NCT00762411>. (Accessed on 12th June 2010)
- Evin G, Sernee MF, Masters CL (2006). Inhibition of gamma secretase as a therapeutic intervention for Alzheimer's disease: Prospects, limitations and strategies. *CNS drug*. 20: 351-72.
- Farlow MR, Tariot P, Grossberg GT, Gergel I, Graham S, Jin J (2003). Memantine/donepezil dual therapy is superior to placebo/donepezil therapy for treatment of moderate to severe Alzheimer Disease. *Neurology*, 60: A412.
- FDA ALERT: Galantamine hydrobromide (marketed as Razadyne, formerly Reminyl) - Healthcare Professional Sheet. Postmarket Drug Safety Information for Patients and Providers. Food and Drug Administration. May 2005. <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126138.pdf>. Accessed on 14th June 2010.
- FDA NEWS RELEASE- For Immediate Release: Dec. 15, 2009 FDA Approves Generic Aricept to Treat Dementia Related to Alzheimer's Disease. Available from <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm194173.htm> (Accessed on 12th June 2010).
- Finch CE, Longo V, Miyao A, et al (2001). Inflammation in Alzheimer's disease. In: Chesselet M-F, ed. *Molecular mechanisms of neurodegenerative diseases*. Totowa, N.J.: Humana Press. 87-110.
- Finkel SI (2004). Effects of rivastigmine on behavioral and psychological symptoms of dementia in Alzheimer's disease. *Clin. Ther.*, 26: 980-990.
- Flynn BL, Theesen KA (1999). Pharmacologic management of Alzheimer's disease, Part III: Nonsteroidal anti-inflammatory drugs-emerging protective evidence? *Ann. Pharmacother.*, 33: 840-849.
- Frank B, Gupta S (2005). A review of antioxidants and Alzheimer's disease. *Ann. Clin. Psych.*, 17: 269-86.
- Galasko D, Bennett D, Sano M, Ernesto C, Thomas R, Grundman M et al (1997). An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative study. *Alzheimer Dis. Assoc. Disord.*, 11: S33-S39.
- Gauthier S, Feldman H, Hecker J, Vellas B, Ames D, Subbiah P et al (2002). Donepezil MSAD Study Investigators Group. Efficacy of donepezil on behavioral symptoms in patients with moderate to severe Alzheimer's disease. *Int Psychogeriatrics*. 14: 389-404.
- Gauthier S, Wirth Y, Möbius HJ (2005). Effects of memantine on behavioural symptoms in Alzheimer's disease patients: an analysis of the Neuropsychiatric Inventory (NPI) data of two randomised, controlled studies. *Int. J. Geriatric Psych.*, 20: 459-64.
- Giacobini E (1994). Therapy for Alzheimer disease. Symptomatic or Neuroprotective. *Mol Neurobiol.*, 9: 115-8.
- Griffin WS (2008). Perispinal etanercept: potential as an Alzheimer therapeutic. *J. Neuroinfl.*, 5: 3.
- Grundman M, Grundman M, Delaney P (2002). Antioxidant strategies for Alzheimer disease. *Proc Nutr Soc.* 61: 191-202.
- Hardy J, Selkoe DJ (2002). The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*. 297: 353-6. (Erratum, *Science* 2002;297:2209.)
- Harrington C, Rickard JE, Horsley D, et al. (2008). Methylthioninium chloride (MTC) acts as a Tau aggregation inhibitor (TAI) in a cellular model and reverses Tau pathology in transgenic mouse models of Alzheimer's disease. *Alzheimer's and Dementia (Alzheimer's Association)* 4: T120-T121.
- Hawkes CA, McLaurin J (2007). Immunotherapy as treatment for Alzheimer's disease. *Expert Rev. Neurother.*, 7: 1535-48.
- Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA (2003). Alzheimer disease in the US population: prevalence estimates using the 2000 Census. *Arch Neurol.*, 60: 1119-22.
- Henderson VW (2006). Estrogen-containing hormone therapy and Alzheimer's disease risk: understanding discrepant inferences from observational and experimental research. *Neurosci.*, 138: 1031-9.
- Henderson VW (2007). Alzheimer's disease and other neurological disorders. *Climacteric*, 10: 92-6.
- Henderson VW, Paganini-Hill A, Miller BL, Eible BL, Reyes PF, Shoupe D, et al (2000). Estrogen for AD in women-randomized, double blind placebo controlled trial. *Neurol.*, 54: 295-301.
- Henderson, V.W. (1997). The epidemiology of estrogen replacement therapy and Alzheimer's disease. *Am. Acad. Neurol.*, 48: S27-S35.
- Heneka MT, Sastre M, Ozimek LD, hanke A, Dewachter I, Kuiperi C (2005). Acute treatment with the PPAR agonist pioglitazone and ibuprofen reduces glial inflammation and A β 1-42 levels in APPV7171 transgenic mice. *Brain*. 128: 1442-53.
- Heneka MT, Sastre M, Ozimek LD, hanke A, Dewachter I, Kuiperi C (2005). Acute treatment with the PPAR agonist pioglitazone and ibuprofen reduces glial inflammation and A β 1-42 levels in APPV7171 transgenic mice. *Brain*. 128: 1442-53.
- Hernández F, Avila J (2007). Tauopathies. *Cell. Mol. Life Sci.*, 64: 2219-33.
- Hollosi M, Shen ZM, Perczel A, Fasman GD (1994). Stable Intrachain and interchain complexes of neurofilament peptides: a putative link between A1⁺⁺⁺ and Alzheimer's disease. *Proc Natl Acad Sci USA*. 91: 4902-4906.
- Holmes C, Wilkinson D, Dean C, Vethanayagam S, Olivieri S, Langley A (2004). The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. *Neurol*. 63: 214- 19.
- Howard RJ, Juszcak E, Ballard CG, Bentham P, Brown RG, Bullock R (2007). Donepezil for the treatment of agitation in Alzheimer's disease. *N Engl J Med*. 357:1382-1392.
- Jann MW (2000). Rivastigmine, a new generation cholinesterase inhibitor for the treatment of Alzheimer's disease. *Pharmacotherapy*. 20: 1-12.
- Kawas C, Resnick S, Morrison A, Brookmeyer R, Corrada M, Zonderman A (1997). A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease. *Neurology*. 48: 1517-1521.
- Knapp MJ, Knopman DS, Solomon PR, Pendlebury WW, Davis CS, Gracon SI (1994). A 30 week randomized controlled trial of high dose Tacrine in patients with Alzheimer's disease. *J. Am. Med. Assoc.*, 271: 985-91.
- Knopman DS, DeKosky ST, Cummings JL, Chui H, Corey-Bloom J, Relkin N (2001). Practice parameter: diagnosis of dementia (an evidence based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, 56: 1143-53.
- Kosasa T, Kuriya Y, Matsui K, Yamanish Y (2000). Inhibitory effect of orally administered Donepezil hydrochloride (E2020), a novel treatment for Alzheimer's disease on cholinesterase activity in rats. *Eur. J. Pharmacol.*, 389: 173-9.
- Krall WJ, Sramek JJ, Cutler NR (1999). Cholinesterase Inhibitors: a therapeutic strategy for Alzheimer's disease. *Ann. Pharmacother.* 33: 441-50.
- Landreth G (2007). Therapeutic use of agonists of the nuclear receptor PPARgamma in Alzheimer's disease. *Curr. Alzheimer Res.*, 4: 159-64.
- Lashuel HA, Hartley DM, Balakhaneh D, Aggarwal A, Teichberg S, Callaway DJE (2002). New class of inhibitors of amyloid-beta fibril formation. Implications for the mechanism of pathogenesis in Alzheimer's disease. *J. Biol. Chem.*, 277: 42881-90.
- Le Bars PL, Katz MM, Berman N, Itil TM, Freedman AM, Schatzberg AF

- (1997). A placebo controlled, double blind, randomized trial of an extract of Ginkgo biloba for dementia. North American EGB study group. *J. Am. Med. Assoc.*, 278: 1327-32.
- Li G, Larson EB, Sonnen JA, Shofer JB, Petrie EC, Schantz A et al (2007). Statin therapy is associated with reduced neuropathologic changes of Alzheimer disease. *Neurology*, 69: 878-85.
- Lim GP, Yang F, Chu T, Chen P, Beech W, Teter B (2000). Ibuprofen suppresses plaque pathology and inflammation in a mouse model for Alzheimer's disease. *J. Neurosci.*, 20: 5709-14
- Lipton SA (2004). Paradigm shift in NMDA receptor antagonist drug development: molecular mechanism of uncompetitive inhibition by memantine in the treatment of Alzheimer's disease and other neurologic disorders. *J. Alzheimers Dis.*, 6: S61-74.
- Liu G, Garrett MR, Men P, Zhu X, Perry G, Smith MA (2005). Nanoparticle and other metal chelation therapeutics in Alzheimer disease. *Biochem. Biophys. Acta.* 1741: 246-52.
- Loneragan ET, Luxenberg J (2007). Valproate preparations for agitation in dementia, *Cochrane Database Syst. Rev.*, 3.
- Long-term Safety and Tolerability of AFFITOPE AD02. Clinical Trial. US National Institutes of Health. Available from: <http://clinicaltrials.gov/ct2/show/NCT00711321>. Accessed on 15th June 2010.
- Magenheim MJ (1998). Preventive health maintenance. In: Duthie EH Jr, Katz PR, eds. *Practice of Geriatrics*. 3rd ed. Philadelphia: W.B. Saunders : 115-29.
- Mancuso C, Bates TE, Bulterfield DA, Calafato S, Cornelius C, Lorenzo AD et al (2007). Natural antioxidants in Alzheimer's disease. *Expert Opin. Investig. Drugs*. 16: 1921-31.
- McGeer PL, Schulzer M, McGeer EG (1996). Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: A review of 17 epidemiologic studies. *Neurology*, 47: 425-432.
- McGuinness B, Craig D, Bullock R, Passmore P (2009). Statins for the prevention of dementia. *Cochrane Database of Systematic Reviews*, Issue 2.
- McShane R, Areosa Sastre A, Minakaran N (2007). Memantine for dementia, *Cochrane Database Syst. Rev.*, 3.
- Mega MS, Cummings JL, Fiorello T, Gornbein J (1996). The spectrum of behavioral changes in Alzheimer's disease. *Neurology*. 46: 130-5.
- Mendez MF (2006). The accurate diagnosis of early-onset dementia. *Intl J Psych Med*. 36: 401-12.
- Mental health and substance abuse. Alzheimer's disease: The brain killer. Available from: http://www.searo.who.int/en/Section1174/Section1199/Section1567/Section1823_8068.htm. Accessed on 15th June 2010.
- Mutter J, Naumann J, Sadaghiani C, Schneider R, Walach H (2004). Alzheimer disease: Mercury as pathogenetic factor and apolipoprotein E as a moderator. *Neuroendocrinol. Lett.*, 25: 331-39.
- Nyht AL, Gottfries CG (1990). The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders, *Br. J. Psych.*, 157: 894-901.
- Oken BS, Storzbach DM, Kaye JA (1998). The efficacy of Ginkgo biloba on cognitive function in Alzheimer disease. *Arch Neurol*. 55: 1409-15.
- Opie J, Rosewarne R, O'Connor DW (1999). The efficacy of psychosocial approaches to behaviour disorders in dementia: a systematic literature review. *Aust N Z J. Psych.* 33: 789-99.
- Ott BR, Owens NJ (1998). Complementary and alternative medicines for Alzheimer's disease. *J. Geriatr. Psychiatry Neurol.*, 11: 163-73.
- Oyama Y, Chikahisa L, Ueha T, Kanemaru K, Noda K (1996). Ginkgo biloba extract protects brain neurons against oxidative stress induced by hydrogen peroxide. *Brain Res.*, 412: 349-352.
- Paganini-Hill A, Henderson VW (1994). Estrogen deficiency and risk of Alzheimer's disease in women. *Am. J. Epidemiol.*, 140: 256-61.
- Paganini-Hill A, Henderson VW (1996). Estrogen replacement therapy and risk of Alzheimer's disease. *Arch In. Med*. 156: 2213-2217.
- Pappas BA, Bayley PJ, Bui BK, Hansen LA, Thal LJ (2000). Choline acetyltransferase activity and cognitive domain scores of Alzheimer's patients. *Neurobiol. Aging*. 21: 11-7.
- Parsons CG, Danysz W, Quack G (1998). Memantine is a clinically well tolerated NMDA receptor antagonist- a review of preclinical data. *Neuropharmacology*, 38: 735-67.
- patients with mild to moderate severe Alzheimer's disease. *Int. J. Geriatr. Psychopharmacol.*, 1: 55-6.
- Pollock BG, Mulsant BH, Rosen J, Mazumdar S, Blakesley RE, Houck PR (2007). A double-blind comparison of citalopram and risperidone for the treatment of behavioral and psychotic symptoms associated with dementia, *Am J Geriatric Psych.*, 15:942-52.
- Raskind MA, Peskind ER, Wessel T, Yuan W (2000). Galantamine in AD: a 6 month randomized, placebo controlled trial with a 6 month extension. *Neurol.*, 54: 2261-8.
- Reavill C and Rogers DC (2001). The therapeutic potential of 5-HT₆ receptor antagonist. *Curr. Opin. Invest. Drugs*. 2: 104-109.
- Regan CM, Foley AG, Murphy KJ, Hirst WD, Gallagher HC, Hagan JJ (2003). The 5 HT₆ receptor antagonist SB-271046 and SB-399885 increase basal and learning induced NCAM-polysialylation in the rat dentate gyrus. Society for Neuroscience, 33rd Annual Meeting, New Orleans, USA (Abstract no. 835.21).
- Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius HJ (2003). Memantine in moderate to severe Alzheimer's disease. *N Engl. J. Med.*, 348: 1333-41.
- Ren K, King MA, Liu J, Siemann J, Altman M, Meyers C (2007). The alpha 7 nicotinic receptor agonist 4OH-GTS-21 protects axotomized septohippocampal cholinergic neurons in wild type but not amyloid-overexpressing transgenic mice. *Neuroscience*. 148: 230-7.
- Rogers SL, Doody RS, Mohs RC, Friedhoff LT (1998). Donepezil improves cognition and global function in Alzheimer's disease: a 15 week, double blind, placebo controlled study. *Arch Int. Med.*, 158: 1021-31.
- Safety and Cognitive Function Study of EVP-6124 in Patients With Mild to Moderate Alzheimer's Disease. Clinical Trial. US National Institutes of Health. Available from: <http://clinicaltrials.gov/ct2/show/NCT01073228>. Accessed on 15th June 2010.
- Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER). MedWatch, The FDA Safety Information and Adverse Event Reporting Program. Food and Drug Administration. April 2006. Archived from the original on 2007-10-09. <http://web.archive.org/web/20071009145003/http://www.fda.gov/medwatch/safety/2006/apr06.htm>. Accessed on 14th June 2010.
- Safety, Tolerability and Efficacy Study to Evaluate Subjects With Mild Cognitive Impairment. Clinical Trial. US National Institutes of Health. Available from: on <http://clinicaltrials.gov/ct2/show/NCT00422981>. Accessed on 14th June 2010.
- Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M (1997). A controlled trial of selegiline, alpha tocopherol, or both as treatment for Alzheimer disease. *N Engl. J. Med.*, 336: 1216-22.
- Sapronov NS, Fedotova YO, Kuznetsova NN (2006). Anti-amnesic effect of 7-nicotinic receptor agonist RJR-2403 in middle-aged ovariectomized rats with Alzheimer type dementia. *Bull. Exp. Biol. Med.*, 142: 700-702.
- Sato T, Hanyu H, Hirao K, Kanetaka H, Sakurai H, Iwamoto T (2009). Efficacy of PPAR gamma agonist Pioglitazone in mild Alzheimer's disease. *Neurobiol Aging*. (Epub ahead of print). doi:10.1016/j.neurobiolaging.2009.10.009
- Schaff-hauser H, mathiasen JR, Dicamillo A, Huffman MJ, Lu LD, Mckenna BA (2009). Dimebolin is a 5HT₆ antagonist with acute cognition enhancing activities. *Biochem. Pharmacol.*, 78: 1035-42.
- Scharf S, Mander A, Ugoni A, Vajda F, Christophidis N (1999). A double-blind, placebocontrolled trial of diclofenac/misoprostol in Alzheimer's disease. *Neurology*, 53: 97-201.
- Schneider LS, Dagerman K, Insel PS (2006). Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials, *Am. J. Ger. Psych.* 14:191-210.
- Schneider LS, Dagerman KS, Insel P (2005). Risk of Death With Atypical Antipsychotic Drug Treatment for Dementia: Metaanalysis of Randomized Placebo-Controlled Trials, *JAMA*. 294:1934-43.
- Schneider LS, Pollock VE, Lyness SA (1990). A meta-analysis of controlled trials of neuroleptic treatment in dementia. *J. Am. Geriatr.*

- Soc., 38:553–563.
- Schneider LS, Tariot PN, Dagerman KS, Davis SM, Hsiao JK, Ismail MS (2006). Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl. J. Med.*, 355:1525–38.
- Schneider LS, Tariot PN, Lyketsos CG, Dagerman KS, Davis KL, Hsiao JK (2001) National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE): Alzheimer disease trial methodology. *Am. J. Geriatr. Psychiatry*, 9:346–360.
- Semagacestat- Gamma Secretase Inhibitor for Alzheimer's Disease Semagacestat- Gamma Secretase Inhibitor for Alzheimer's Disease (AD). (Accessed on 7th May 2010). Available from: <http://www.drugdevelopment-technology.com/projects/semagacestat>
- Shumaker SA, Legault C, Rapp SR (2003). Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. The Women's Health Initiative Memory Study: a randomized controlled trial. *J. Am. Med. Assoc.*, 289: 2651–62.
- Siemers ER, Quinn JF, Kaye J, Farlow MR, Porsteinson A, Tariot P (2006). Effects of a Gamma secretase inhibitor in a randomized study of patients with Alzheimer disease. *Neurology*, 6: 602–4.
- Silverman DH, Small GW, Chang CY, Lu CS, Kung De Aburto MA, Chen W et al (2001). Positron emission tomography in evaluation of dementia: Regional brain metabolism and long term outcome. *J. Am. Med. Assoc.*, 286: 2120–7.
- Sink KM, Holden KF, Yaffe K (2005). Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. *J. Am. Med. Assoc.*, 293:596–608.
- Small GW, Rabins PV, Barry PP, Buckholtz NS, DeKosky ST, Ferris SH (1997). Diagnosis and treatment of Alzheimer's disease and related disorders: consensus statement of the American Association of Geriatric psychiatry, the Alzheimer's Association and the American Geriatric Society. *J. Am. Med. Assoc.*, 278: 1363–71.
- Solomon B (2007). Clinical immunologic approaches for the treatment of Alzheimer's disease. *Expert Opin Investig Drugs* 16: 819–28.
- Steele LS, Glazier RH (1999). Is donepezil effective for treating Alzheimer's disease?. *Can. Fam. Physician*, 45: 917–9.
- Stewart WF, Kawas C, Corrada M, Metter EJ (1997). Risk of Alzheimer's disease and duration of NSAID use. *Neurology*, 48: 626–632.
- Street JS, Clark WS, Gannon KS, Cummings JL, Bymaster FP, Tamura RN et al (2000). Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer's disease in nursing care facilities. *Arch Gen. Psych.*, 57: 968–976.
- Study Evaluating ACC-001 in Mild to Moderate Alzheimer's Disease Subjects*. Clinical Trial. US National Institutes of Health. 2008-03-11. <http://www.clinicaltrials.gov/ct/show/NCT00498602>. Accessed on 14th June 2010.
- Study Evaluating Safety, Tolerability, and Immunogenicity of ACC-001 in Subjects With Alzheimer's Disease. US National Institutes of Health. <http://clinicaltrials.gov/ct2/show/NCT00479557>. Accessed on 14th June 2010.
- Study Evaluating the Safety, Tolerability and Efficacy of PBT2 in Patients With Early Alzheimer's Disease. Clinical Trial. US National Institutes of Health. Available from: <http://clinicaltrials.gov/ct2/show/NCT00471211>. Accessed on 14th June 2010.
- Suh YH (1997). An etiological role of amyloidogenic carboxyl-terminal fragments of the beta-amyloid precursor protein in Alzheimer's disease. *J. Neurochem.*, 68: 1781–91.
- Sultz DL, Gray KF, Gunay I, Berisford MA, Mahler ME (1997). A double-blind comparison of trazodone and haloperidol for treatment of agitation in patients with dementia. *Am. J. Geriatric Psych.* 5:60–69.
- Support for Alzheimer's and Dementia Caregivers. www.helpguide.org. (Accessed on 7th May 2010) Available from: http://www.helpguide.org/elder/alzheimers_disease_dementia_support_caregiver.htm.
- Tabert MH, Liu X, Doty RL, Serby M, Zamora D, Pelton GH (2005). A 10-item smell identification scale related to risk for Alzheimer's disease. *Ann. Neurol.*, 58: 155–160.
- Tang M, Jacobs D, Stern Y, Marder K, Schofield P, Gurland B (1996). Effect of estrogen during menopause on risk and age at onset of Alzheimer's disease. *Lancet*, 348: 429–32.
- Tariot PN, Erb R, Leibovici A, Podgorski CA, Cox C, Asnis J (1998). Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. *Am. J. Psych.*, 155:54–61.
- Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I (2004). Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *J. Am. Med. Assoc.*, 291: 317–24.
- Teri L, Logsdon RG, Peskind E, Raskind M, Weiner MF, Tractenberg RE (2000). Treatment of agitation in AD: a randomized, placebo-controlled clinical trial. *Neurol.* 55: 1271–8.
- Thompson CA, Spilbury K, Hall J, Birks Y, Barnes C, Adamson J (2007). Systematic review of information and support interventions for caregivers of people with dementia. *BMC Geriatr.* 7: 18.
- Tiraboschi P, Hansen LA, Thal LJ, Corey-Bloom J (2004). The importance of neuritic plaques and tangles to the development and evolution of AD. *Neurology*, 62: 1984–89.
- Tombaugh TN, McIntyre NJ (1992). The mini-mental state examination: a comprehensive review. *J. Am. Geriatr. Soc.*, 40: 922–35.
- Tomita T, Iwatsubo T (2006). Gamma secretase as a therapeutic target for treatment of Alzheimer disease. *Curr Pharm Des.* 12: 661–70.
- Trinh N-H, Hoblyn J, Mohanty S, Yaffe K (2003). Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer's disease. *J. Am. Med. Assoc.*, 289:210–216.
- Vlad SC, Miller DR, Kowall NW, Felson DT (2008). Protective effects of NSAIDs on the development of Alzheimer's disease. *Neurology*, 70: 1672–77.
- Waldemar G, Dubois B, Emre M, Georges J, McKeith IG, Rossor M (2007). Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. *Eur. J. Neurol.* 14: e1–26.
- Wallin AK, Andreasen N, Eriksson S, Batsman S, Nasman B, Ekdahl A (2007). Donepezil in Alzheimer disease: What to expect after 3 years of treatment in a routine clinical setting. *Demnt Geriatr Cogn Disord.* 23: 150–60.
- Wang PS, Schneeweiss S, Avorn J, Fischer MA, Mogun H, Solomon DH (2005). Risk of death in elderly users of conventional vs atypical antipsychotic medications. *N Eng. J. Med.*, 353:2335–2341.
- Watkins PB, Zimmerman HJ, Knapp MJ, Garcon SI, Lewis KW (1994). Hepatotoxic effect of Tacrine administration in patients with Alzheimer's disease. *J. Am. Med. Assoc.*, 271: 992–8.
- Wilcock GK, Ballard CG, Cooper JA, Loft H (2008). Memantine for agitation/aggression and psychosis in moderately severe to severe Alzheimer's disease: a pooled analysis of 3 studies. *J. Clin. Psych.*, 69: 341–8.
- Willson TM, Brown PJ, Sternbach DD, Henke BR (2004). The PPARs: from orphan receptors to drug discovery. *J. Med. Chem.*, 43: 527–550.
- Winblad B, Grossberg G, Frolich L, Farlow M, Zechner S, Nagel J, Lane R (2007). "IDEAL: a 6-month, double-blind, placebo-controlled study of the first skin patch for Alzheimer disease". *Neurol*, 69: S14–22.
- Wischik CM, Bentham P, Wischik DJ, Seng KM (2008). Tau aggregation inhibitor (TAI) therapy with rember™ arrests disease progression in mild and moderate Alzheimer's disease over 50 weeks. *Alzheimer's and Dementia (Alzheimer's Association)*. 4: T167.
- Woodhouse A, Dickson TC, Vickers JC (2007). Vaccination strategies for Alzheimer's disease: A new hope?. *Drugs Aging*. 24: 107–19.
- Xiong G, Doraiswamy PM (2005). Combination drug therapy for Alzheimer's disease: what is evidence-based, and what is not? *Geriatrics*, 60 (6): 22–6.
- Yaffe K, Fox P, Newcomer R, Sands L, Lindquist K, Dane K (2002). Patient and caregiver characteristics and nursing home placement in patients with dementia. *J. Am. Med. Assoc.*, 287: 2090–7.

Yaffe K, Sawaya G, Lieberburg I, Grady D (1998). Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. *J. Am. Med. Assoc.*, 279: 688-695.

Yan Q, Zhang J, Liu H, Babu-Khan S, Vassar R, Biere AL (2003). Antiinflammatory drug therapy alters beta Amyloid processing and deposition in an animal model of Alzheimer's disease. *J. Neurosci.*, 23: 7504-9.

Zec RF, Burkett NR (2008). Non Pharmacological and Pharmacological treatment of the cognitive and behavioral symptoms of Alzheimer disease. *NeuroRehab.*, 23: 425-38.