Review Article

Dementia Therapeutics: Current Strategies and Potential Approaches for Its Treatment and Management

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ABSTRACT

Dementia is one of the major causes of disability in later life. It is devastating not only for those persons who have it, but also for their caregivers and families. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation. The continuing expansion of life expectancy, leading to a fast growing number of patients with dementia, particularly AD, has led to an enormous increase in research focused on the discovery of drugs for primary, secondary or tertiary prevention of the disease. The goals of current treatments are to reduce the severity or slow the progression of the cognitive and behavioural symptoms associated with dementia. In this review, current symptomatic treatments and new potential disease-modifying therapies for dementia are discussed.

Keywords: Dementia, Ageing, Amyloid hypothesis, Immunisation.

INTRODUCTION

Dementia is a syndrome due to disease of the brain – usually of a chronic or progressive nature – in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Alzheimer's disease is the most common form of dementia and possibly contributes to 60–70% of cases[1]. Other types of dementia includes Alzheimer's disease, Vascular dementia, Fronto temporal dementia and Dementia with Lewy Bodies, Behaviour variant, Mixed dementia, Parkinson's disease, Creutzfeldt-Jakob disease, Primary progressive aphasia or any cognitive/behavioural changes with neuropsychiatric symptoms[2].

Dementia: Epidemiology

It was estimated that 35.6 million people lived with dementia worldwide in 2010, with numbers expected to almost double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050[3]. In 2010, the global societal economic cost of dementia is US$ 604 billion, of which 89% is incurred in high-income countres[4]. It estimated that that the numbers of people with dementia in India is 3.7 million and this number is set to double in the next 20 years[4].

Dementia: Risk factor

The risk factor for progressive dementia includes vascular disease predisposes to Alzheimer's disease as well as to vascular dementia[5]. In short[6-8] and longer latency[9-10] incidence studies, smoking increases the risk for Alzheimer's disease. Diabetes is also a risk factor[11] in longer-term cohort studies; midlife hypertension[12] and raised cholesterol[13] are associated with the onset of Alzheimer's disease in later life. Aggregated cardiovascular risk indices incorporating hypertension, diabetes, hypercholesterolemia and smoking increase risk for dementia incidence incrementally whether exposure is measured in midlife[10] or a few years before onset of dementia.

Dementia: Pathology

There are a number of common features in the pathomechanisms of neurodegenerative processes, including mitochondrial disturbance[14,15], neuroinflammation[16], glutamate excitotoxicity[17] and oxidative stress[18] . Excitotoxic damage to neuronal cells is caused by the overactivation of glutamate receptors, inhibition of which could therefore be a promising neuroprotective strategy[19].

Dementia: Diagnosis

Clarity of diagnosis is critical in case of dementia in order to enable the timely intervention and unnecessary distress and most important incorrect diagnosis can lead to incorrect treatment with antipsychotics drugs can be harmful and even fatal for those with dementia and appropriate treatments can slow the course of vascular dementia and assist in the treatment of Alzheimer's disease[20]. Therefore clarity of diagnosis must be in a priority with dementia patients through the process of assessment with them which includes medical, psychiatric, social and developmental history, history of presenting concern, risk assessment ,support available , current medical factor and living, clinical interview/ mini state medical examination and the use of screening measures[21].

Ageing and Dementia

Dementia is not a part of normal ageing. Ageing is a progressive, predictable process that involves the evolution and maturation of living organism[22] .Higher

brain functions comprise abilities like language, learning, memory, planning, abstract reasoning and self-awareness; most of these are impaired as age-related cognitive decline progresses to dementia[23]. Brain areas that provide higher functions appear most susceptible to the effects of ageing and Alzheimer's disease[23]. Dementia is now applied to older adults of any age who shows a pattern of progressive mental deterioration coupled with personality changes in a state of clear consciousness associated with a specific configuration of neupathological changes in the brain. Severe and rapid memory loss is definitely not a part of normal aging. In fact, many people preserve their brainpower as they get older by staying mentally and physically active and making other healthy lifestyle choices[24].

Dementia and its treatment

Treatment of dementia includes drug, a nutraceutical, or a dietary supplement that protects nerve cells from damage, either from pathological events, like the excitotoxicity that attends stroke or brain injury, or from normal biological stressors, for example, the generation of free oxygen radicals[25]. Interventional studies on dementia and AD prevention have tested different medications, including statins, antihypertensive drugs, estrogens alone or in combination with progestin (hormone replacement therapy, or HRT), non-steroidal anti-infl ammatory drugs (NSAIDs), and nutraceuticals (folate, Ginkgo biloba, and vitamins B12, C, and E). For all of these compounds, the protective effects suggested by observational studies have not been confirmed in randomized controlled trials (RCTs), the results of which are inconsistent or even suggest a detrimental effect on cognition for example, NSAIDs and HRT[26-29].

PHARMACOLOGICAL TREATMENT

Cholinergic drugs

Acetylcholine is widely distributed in the nervous system and has been implicated to play a critical role in cerebral cortical development, cortical activity, controlling cerebral blood flow and sleep-wake cycle as well as in modulating cognitive performances and learning and memory processes[30]. It has been suggested that this decrease in cholinergic activity is related to the cognitive symptoms of AD; therefore, enhancing the remaining acetylcholine is believed to improve cognition. The first class of drugs introduced to treat Alzheimer's is referred to as acetylcholinesterase or cholinesterase inhibitors, and are characterized as a symptomatic treatment. Cholinesterase inhibitors are able to prolong the action of the neurotransmitter acetylcholine by reducing its metabolism at the synaptic cleft[31]. This treatment was able to slow the progression of cognitive deterioration in AD patients; however, the clinical significance was not well established[32]. All of these cholinesterase inhibitors have been shown to improve cognition over placebo conditions[33], and they have been found to delay cognitive impairment for up to 6-months in patients with mild to moderately severe AD[34]. Five therapies have been approved for AD. Four of these medications are classified together as cholinesterase inhibitors (CIs); these are approved for dementia of the Alzheimer's type in the mild-to-moderate stage. These include Tacrine (Cognex, First Horizon), Donepezil (Aricept, Eisai/Pfizer), Rivastigmine (Exelon, Novartis), and Galantamine (Razadyne, formerly Reminyl, Ortho-McNeil). Donepezil also carries an approval for severe or late-stage disease.

Donepezil provide symptomatic treatment of AD. Treatment with this drug can delay nursing home replacement[35], reduces the caregiver burden and the time spent caring[36] and possibly reduce mortality for patient living in nursing home[37] and community[38] and the safety and tolerability of donepezil in AD showed a low incidence of GI and cardiovascular adverse events (including bradycardia), comparable to the rates for placebo. In various studies, donepezil was found to be safe in patients with hepatic impairment as well as in those with moderately to severely impaired renal function. Donepezil may have a negative effect on aspiration pneumonia due to a side effect of nausea. An increased gastro-esophageal reflex may induce pneumonia[39]. **Tacrine** The first cholinesterase inhibitor approved by the Food and Drug Administration (FDA) for the treatment of Alzheimer's was tacrine[40]. This treatment was able to slow the progression of cognitive deterioration in AD patients; however, the clinical significance was not well established. Tacrine is now rarely used because of the increased risk of hepatoxicity, and the development of safer cholinesterase inhibitors[40].

Rivastigmine: Rivastigmine (Novartis Pharmaceuticals Corporation, NJ, USA) is a dual acting inhibitor that targets both acetylcholinesterase and butyrylcholinesterase. Treatment with rivastigmine has been shown to provide therapeutic benefit for cognitive symptoms associated with AD[41]. Such an outcome along with less cortical atropy in a temporal pariental area was observed in mild AD patient over a 20-week period[42]. A post hoc analysis of several studies suggests that rivastigmin slows the rate of decline as long as 5 years[43].

Memantine: Memantine is an antagonist of the N-methyl-D-aspartate (NMDA) receptor that interferes with glutamate, a neurotransmitter believed to overstimulate the NMDA receptors in AD, causing neuronal death and subsequent cognitive impairment. Memantine stop the overstimulation by binding with NMDA receptor which inhibit the influx of Ca2+ and results in a small improvement in a cognition and behaviour[44]. Memantine use in moderate-to-severe AD and mild-to-moderate AD was evaluated in a 2009 Cochrane review[41]. Evidence exists supporting the use of combination therapy of memantine and a ChEI for moderate-to-severe AD[42-43]. The American College of Physicians /American Academy of Family Physicians clinical practice guidelines do not specifically address combination therapy and recommend the choice of pharmacologic agents based on individual

tolerability, ease of use, and cost[44]. Combination therapy has been shown to be effective in improving cognition, activities of daily living, and behavior compared with ChEIs alone in patients with moderate-to-severe AD[45-46], the most common ADRs reported with memantine are headache, constipation, and dizziness[47-48]. This medication can have antagonistic effects on serotonin receptor-type 3, which may protect against the gastrointestinal effects of ChEIs when used in combination therapy[45].

Antioxidants

Antioxidants play a major role in the treatment free radical-induced neural damage of dementia. For examples Gallic acid has beneficial activity against induced by permanent bilateral common carotid artery occlusion (2VO) as an animal model of vasculardementia (VD).2VO-induced cognitive deficits via enhancement of cerebral antioxidant defense[49] and Melatonin improved learning and spatial memory in Al-exposed transgenic mice[50] Vitamin E is a major lipid-soluble antioxidant, and is the most effective chain-breaking antioxidant within the cell membrane where it protects membrane fatty acids from lipid peroxidation. Beta-carotene and other carotenoids also provide antioxidant protection to lipid rich tissues[51]. Fruits and vegetables are major sources of vitamin C and carotenoids, while whole grains, i.e., cereals and high quality vegetable oils are major sources of vitamin E[52-53]. Antioxidant vitamins protect against free radical oxidation, and free radicals might be involved in the etiology of the two major diseases that cause cognitive impairment in older people Alzheimer's disease and vascular dementia[54]. Oxidative damage to neuronal cell membranes and mitochondrial DNA could lead to Alzheimer's disease. Vit C plays a vital role in prevention of dementia[55].

Herbal drugs

Studies suggest that Ginkgo may stabilize or improve cognitive performance in patients with Alzheimer disease and multi-infarct dementia[56, 57]. Ginkgo appears to alter vasoregulation[58] act as an antioxidant[59] modulate neurotransmitter and receptor activity[60] and inhibit platelet-activating factor[61]. Desmodium gangeticum has been shown to produce anti-inflammatory action in rodents[62], and also possess anti-oxidant property[63]. The neuroprotective effect of DG may be attributed to its anti-oxidant effect by virtue of which susceptible brain cell get less exposed to oxidative stress resulting in reduced brain damage and improved neuronal function[64.] Gomisin A has an ability to improve or ameliorate spatial long-term memory and short-term memory, in part, via enhancement of cholinergic nervous system [65]. E-harpagoside and MCA-Hg showed potent cognitive-enhancing activities by the inhibition of acetylcholinesterase activity, and by the regulation of the antioxidant system[66]. As such, E-harpagoside and MCA-Hg might offer a useful therapeutic choice in either the prevention or the treatment of Alzheimer's disease. The Edaravone prevents long-term memory impairment induced by Alzheimer's disease using Morris water maze procedure[67-68]

ADVANCED TREATMENT

Amyloid hypothesis

The leading hypothesis indicates that the Aβ peptides are what lead to the overall pathology of AD[69]. Two drugs, rosiglitazone and pioglitazone, decrease b-secretase expression by stimulating the nuclear peroxisome proliferator-activated receptor g[70] Pioglitazone easily crosses the blood-brain barrier and is currently undergoing phase 3 trial in patients with mild cognitive impairment. Two β-secretase inhibitors named as OM99-1 and OM99-2 were shown potent inhibitory effect on the β-secretase cleavage site in APP[71-72]. Demonstrated that β-secretase inhibitors had significant activity of A-beta clearance in Tg2576 transgenic AD mice model through intraperitoneal injection of the conjugated inhibitors of beta-secretase[73]. Drugs developed from β-secretase inhibitors are expected to possess high clinical efficacy and high blood brain barrier (BBB) permeability. Another γ-secretase inhibitor, LY450139, has been reported to inhibit A-gamma formation in whole cell assays, in transgenic mice and in beagle dogs[74]. In clinical trial, LY450139 causes a dose-dependent A-gamma reduction in plasma and cerebrospinal fluid. This drug is well tolerated and safe at a dose of 50mg per day[75]. Phase 1 testing of the investigational compound etazolate (EHT-0202), which modulates the gamma aminobutyric acid receptor thus stimulating a-secretase, has begun phase 2 testing for mild to moderate AD. Epigallocatechin-3-gallate, developed as Sunphenon EGCg, is a polyphenol extract from green tea, which induces α-secretase while decreasing Ab aggregation. Studies are currently recruiting patients with early mild AD. One such medication was tramiprosate (Alzhemed), which did not change Ab protein levels or have clinical effects on cognition in the phase 3 Alphase trial because of low CNS penetrability and weak potency[75]. There are many potentially disease modifying drugs for alzheimers disease treatment that have successfully reached to later-stage clinical trials.

Immunisation

Active and Passive immunization in alzheimers disease theoretically increase amyloid clearance via phagocytosis and or increase efflux of A-beta from the brain.[76] The vaccine AN-1792 reached phase II clinical trials; however, the study was halted after 18 of the 298 (6%) patients that were vaccinated developed meningoencephalitis[77] and patients that developed Aβ antibodies demonstrated an improvement in memory and cognition[78]. A phase 3 trial of bapineuzumab, a humanized anti-Ab monocloncal antibody, is actively recruiting. Also recruiting are phase 2 trials of solanezumab, ponezumab (PF-04360365), gantenerumab (R-1450), GSK-933776, and MABT-5102A for either prodromal AD or mild-to-moderate AD[79].

Estrogens therapy

There are estrogen receptors in hypothalamus, the preoptic area, anterior pituitary, CA 1 region of hippocampus, and several other brain regions[80].The role of these receptors might useful in cognition functions. Estradiol administration to oophorectimised is associated with an increase in choline acetyltransferase and potassium stimulated acetylcholine release in certain brain region[81-82]. Many plant-derived phytoestrogens (which possess the physiological properties of animal-derived estrogen) have been acted as potential replacements for estrogen. Consequently phytoestrogens can interact with estrogen receptors (ER) and mediate estrogenic responses[83]. For example a-ZAL exerted an in vivo improvement in estrogen deficiency induced spatial learning and memory impairment and the neuroprotection afforded by a-ZAL may be mediated through the regulation of antioxidase activities to improve oxidative stress and expression of MTH1 to decrease neuronal oxidative damage, in a manner similar to that of E2[83] But still there are studies that provide little evidence in preventive measure of phytoestrogen as a cognitive enhancers. Studies suggested that progestine added to the estrogen regimen might protect against MCI. But According to WHIMS results demonstrate that estrogen and progestine increases older women's risk for probable dementia. Thus estrogen plus progestin should not be prescribed with an expectation that it will enhance cognitive performance in postmenopausal women[84].

Statins

Some epidemiology studies have suggested that elderly patients treated with long term statin therapy have lower rate of incident alzheimers disease. Lipid-lowering agents (LLAs), particularly HMG CoA-reductase inhibitors (statins), seem to be beneficial in protecting against certain arterial disorders. Since dementia may at least in part to be associated with vascular disorders[85]. In Alzheimer's disease cerebral perfusion is decreased in affected areas of brain[86] capillary endothelium shows pathologic changes [87] and eNOS is decreased in capillaries in the brains[88-89]. The effect of statins in reducing the risk for dementia may involve such beneficial effects on the cerebral capillary endothelium, or other properties of the drugs. In addition, regulation of systemic cholesterol by statins might play important roles on prevention of AD by the reduction of cerebrovascular atherosclerosis, which is reported to correlate with AD pathology, including senile plaques and CAA. These studies suggest that one of the important actions of statins with regards to AD could involve blood vessels in the brain.

NON-PHARMACOLOGICAL TREATMENTS

Exercises & lifestyle intervention

There are several factors which directly or indirectly affects the cognition performance.

It is suggested that physical activity is a treatment modality which may have positive effects on dementia patients' cognitive and physical function and therefore could favourably influence the disease progression in institutionalized patients with dementia[90-91]. For example: inborn physical attributes, factors such as illiteracy and lack of early education, environmental stress, as well as fortuitous circumstances including accidents and traumas that have been associated with increased risk for dementia[92-93]. The reduced loss of hippocampal brain tissue in the aging brain is related to the level of physical fitness, in agreement with animal studies also showing increased brain cortical thickness with voluntary exercise[94-95] Aerobic and strength training each can positively affect the levels of insulin like growth factor-1 and brain derived neurotrophine factors[96-97]. These proteins mediate neuronal cell growth, proliferation, survival, and differentiation and also increase blood supply in the brain, thus facilitating nerve growth and nerve function[98]. In animal models, these vascular changes appear to promote plasticity in the cortex, most profoundly in the hippocampus, and enhance growth and protection of neural structures[99].

Music Therapy

There are more finding related to cognition in which older musicians showed greater auditory working memory relative to non-musicians, and suggested that musical training might reduce the impact of age-related declines. Results from these studies suggest that music therapy might be useful for maintaining cognitive function in normal elderly adults and dementia patients[100].

Symptomatic treatment:

The more cognitively impaired the patient, the more likely it is that the patient will evidence agitated behaviour[101-102]. In dementia there are different kinds of behavioural changes were noticed like aggression, verbal screaming, physical wandering, pacing, anxiety, depression symptoms, sexual disinhibition, apathy, hallucination, insomnia[103]. These symptoms present severe problems to all those who interact with the patients as well as to the patients themselves, and to society and its health service[104]. Neuropsychiatric symptoms are also associated with increased hospital lengths of stay [105] and commonly lead to nursing home placement [106-107] and greater impairment in activities of daily living, more rapid cognitive decline[108] worse quality of life[109], earlier institutionalization[110] and greater caregiver depression[111]. Federal expenditures for dementia are expected to triple in the next 10 years. There are many strategies to overcome with these behavioural symptoms include one-to-one interactions, aroma therapy, proper sleeping. There is also research showing that Music therapy is effective to reduce behavioural and psychologic symptoms (BPSD) in patients with moderate-severe dementia[112]. Exploration of the relationship of behavioural and psychological signs and symptoms of dementia with respect to environments in

which they occur and the underlying biological and psychological sub-strates[113].

CONCLUSION

Dementia is distressing for patients, their families, and their careers. There are many treatment options discussed above showing positive results to treat dementia like statins, estrogen therapy, antioxidants, immunization, music therapy social interactions, environmental changes are showing promising role in future treatments. Epidemiological research suggests that the most effective strategy may be to encourage the implementation of multiple preventive measures throughout the life course, including high educational attainment in childhood and early adulthood, active control of vascular factors and disorders over adulthood, and maintenance of mentally, physically, and socially active lifestyles during middle age and later in life. Multiple strategies should be targeted to prevent the development and the progression of the disease.

REFERENCES

1. World Health Organization and Alzheimer's disease international: Dementia: a public health priority, Geneva, 2012.
2. Mitran SL, Catalin B, Sfredel V, Balseanu TA, Neuroregeneration and dementia: new treatment options, Journal of Molecular Psychiatry, 1, 2013, 12.
3. WHALLEY LJ, Brain ageing and dementia: what makes the difference? , British journal of psychiatry, 181, 2002, 369-371.
4. World Health Organization and Alzheimer's disease international: Dementia: a public health priority, Geneva, 2012.
5. Hofman A, Otto A, Breteler MMB, Bots ML, Slooter AJC, Harskamp FV, Duijn CNV, Broeckhoven CV, Grobbee DE, Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study, Lancet, 349, 1997, 151–154.
6. Ott A, Slooter AJC, Hofman A, van Harskamp F, Witteman JCM, Van Broeckhoven C, van Duijn CM, Breteler MMB, Smoking and risk of dementia and Alzheimer's disease in a population based cohort study: the Rotterdam Study, Lancet, 351, 1998, 1841–1843.
7. Juan D, Zhou DH, Li J, Wang JY, Gao C, Chen M, A 2-year follow-up study of cigarette smoking and risk of dementia, European Journal of Neurology, 11, 2004, 277–282.
8. Luchsinger JA, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R, Aggregation of vascular risk factors and risk of incident Alzheimer disease, Neurology, 65, 2005, 545–551
9. Tyas SL, White LR, Petrovitch H, Webster RG, Foley DJ, Heimovitz HK, Launer LJ, Mid-life smoking and late-life dementia: the Honolulu-Asia Aging Study, Neurobiology of Aging, 24, 2003, 589–596.
10. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K, Midlife cardiovascular risk factors and risk of dementia in late life, Neurology, 64, 2005, 277–28.
11. Ott A, Stolk RP, van HF, Pols HA, Hofman A, Breteler MM, Diabetes mellitus and the risk of dementia: the Rotterdam Study, Neurology, 53, 1999, 1937–1942.
12. Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L, Persson G, Oden A, Svanborg A, 15-year longitudinal study of blood pressure and dementia. Lancet, 347, 1996, 1141–1145.
13. Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A, Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study, British Medical Journal, 322, 2001, 1447–1451.
14. Karbowski M, Neutzner A, Neurodegeneration as a consequence of failed mitochondrial maintenance, Acta Neuropathol., 123, 2012, 157–171.
15. Szalardy L, Klivenyi P, Zadori D, Fulop F, Toldi J, Vécsei L, Mitochondrial disturbances, tryptophan metabolites and neurodegeneration: medicinal chemistry aspects, Curr Med Chem, 19, 2012, 1899–1920.
16. Glass C, Saijo K, Winner B, Marchetto M, Gage F, Mechanisms underlying inflammation in neurodegeneration, Cell, 140, 2010, 918–934.
17. Lau A, Tymianski M, Glutamate receptors, neurotoxicity and neurodegeneration, Pflugers Arch, 460, 2010, 525–542.
18. Gandhi S, Abramov A, Mechanism of oxidative stress in neurodegeneration, Oxid Med Cell Longev, 11, 2012, 428010.
19. Majláth Z, Tajti J, Vécsei L, Kynurenines and other novel therapeutic strategies in the treatment of dementia, Ther Adv Neurol Disord, 6, 2013, 386–397.
20. Thomas AJ, & O Brien JT, Alzheimers disease, In Jacoby R, & Oppenheizer C, eds., Psychiatry in the elderly, 3 ed, Oxford, Oxford University,2002, Press.
21. O'Reilly O, Lavin D, B, Coughlan BJ, Ageing and dementia: Assessment and intervention, Routledge, 2013, 296
22. Dalton AJ, Janicki MP, Ageing and dementia: A Handbook, Psychology press, 1999, 488.
23. WHALLEY LJ, Brain ageing and dementia: what makes the difference?, British journal of psychiatry, 181, 2002, 369-371.
24. Wayne M, White M, Smith M, Understanding dementia [online], February 2014. Available from URL www.helpguide.org/elder/alzheimers_dementias_types.htm
25. T Gualtieri, Cognitive enhancers and neuroprotectants In: Brain Injury & Mental Retardation : Neuropsychiatry & Psychopharmacolog, Lippincott, 2004
26. Daviglus ML, Bowen PE, Connolly ES Jr, Cox NJ, Dunbar-Jacob JM, Granieri EC, Hunt G, McGarry K, Patel D, Potosky AL, Sanders Bush E, Silberberg D, Trevisan M, National Institutes of Health State-of-the- Science Conference statement: preventing alzheimer disease and cognitive decline, Ann Intern Med, 153, 2011, 176-181.
27. Solomon A, Kivipelto M, Cholesterol-modifying strategies for Alzheimer's disease, Expert Rev Neurother , 9, 2009,695-709.
28. Malouf R, Grimley Evans J, Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people, Cochrane Database Syst Rev, 4, 2008, CD004514.
29. Wald DS, Kasturiratne A, Simmonds M, Effect of folic acid, with or without other B vitamins, on cognitive decline: meta-analysis of randomized trials, Am J Med, 123, 2010, 522-527.
30. Schliebs R, Arendt T, The significance of the cholinergic system in the brain during aging and in Alzheimer's disease, J Neural Transm, 113, 2006, 1625–1644.
31. Husain MM, Trevino K, Siddique H, McClintock SM, Present and prospective clinical therapeutic regimens for Alzheimer's disease, Neuropsychiatric Disease and Treatment, 4, 2008, 765–777.
32. Qizilbash N, Birks J, López-Arrieta J, Lewington S, Szeto S, Tacrine for Alzheimer' disease, Cochrane Database Syst Rev, 3, 2002, CD000202.
33. Ritchie CW, Ames D, Meta anlysis of randomized trials of the efficacy and safety of donepezil, galantamine, and rivastigmine for

the treatment of Alzheimer disease, Am J of Geriatr Psychiatry, 12, 2004, 358–69.

34. Takeda A, Loveman E, Clegg A, Kirby J, Picot J, Payne E, Green C, A systematic review of the clinical effectiveness of donepezil, rivastigmine and galantamine on cognition, quality of life and adverse events in Alzheimer's disease, Int J Geriatr Psychiatry,21, 2006,17–28.

35. Geldmacher DS, Provenzano G, McRae T, Mastey V, Ieni JR, Donepezil is associated with delayed nursing home placement in patients with Alzheimer's disease, J Am Geriatr Soc, 51, 2003,937–944.

36. Linger JH, Martire LM, Schulz R, Caregiver-specific outcomes in anti dementia clinical drug trials: A systematic review and meta-analysis, J Am Geriatr Soc, 53, 2005, 983–990.

37. Gasper MS, Ott BR, Lapane KL, Is Donepezil Therapy associated with reduced mortality in nursing home residents with dementia?, Am J Geriatr Pharmacother., 3, 2005, 1–7.

38. Lopez OL, Becker JT, Wisniewski S, Saxton J, Kaufer DI, DeKosky ST, Cholinesterase inhibitor treatment alters the natural history of Alzhimer's disease, J Neurol Neurosurg Psychiatr., 72, 2002, 310–314.

39. Meguro K, Kasai M, Akanuma K, Meguro M, Ishii H, Yamaguchi S, Donepezil and life expectancy in Alzheimer's disease: A retrospective analysis in the Tajiri Project, Bio med central Neurology, 14, 2014,83.

40. Husain MM, Trevino K, Siddique H, McClintock SM, Present and prospective clinical therapeutic regimens for Alzheimer's disease, Neuropsychiatric Disease and Treatment, 4, 2008,765–777.

41. McShane R, Aerosa Sastre A, Minakaran N, Memantine for dementia, Cochrane Database Syst Rev, 2006, Issue 2. Art. No. :CD003154**.**

42. Schmitt B, Bernhardt T, Moeller HJ, Heuser I, Frolich L, Combination therapy in Alzheimer's disease: a review of current evidence, CNS Drugs, 18, 2004, 827-844.

43. Fillit HM, Doody RS, Binaso K, Crooks GM, Ferris SH, Farlow MR, Leifer B, Mills C, Minkoff N, Orland B, Reichman WE, Salloway S, Recommendations for best practices in the treatment of Alzheimer's disease in managed care. Am J Geriatr Pharmacother, 4, 2006, 9-24.

44. Qaseem A, Snow V, Cross JT, Forciea MA, Hopkins R, Shekelle P, Adelman A, Mehr D, Schellhase K, Campos-Outcalt D, Santaguida P, Owens DK, Current pharmacologic treatment of dementia: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians, Ann Intern Med, 148, 2008, 370–378.

45. Thomas SJ, Grossberg GT, Memantine: a review of studies into its safety and efficacy in treating Alzheimer's disease and other dementias, Clin Interv Aging, 4, 2009, 367–377.

46. Tariot PN, Farlow MR, Grossber GT, Graham SM, McDonald S, Gergel I for the Memantine Study Group, Memantine treatment in patients with moderate to severe Alzheimer's disease already receiving donepezil: a randomized, controlled trial, JAMA, 291, 2004, 317–324.

47. Faulkner JD, Bartlett J, Hicks P, Alzheimer's disease, McGraw-Hill, 2005, 1157–1173.

48. Panisset M, Roudier M, Saxton J, Boller F, Severe impairment battery: a neuropsychological test for severely demented patients, Arch Neurol, 51,1994,41-45.

49. Korani MS, Farbood Y, Sarkaki A, Fathi Moghaddam H, Taghi Mansouri M, Protective effects of gallic acid against chronic cerebral hypoperfusion-induced cognitive deficit and brain oxidative damage in rats, Eur J Pharmacol, 733, 2014, 62-7.

50. Paolo CD, Reverté I, Colomina MT, Domingo JL, Gómez M, Chronic exposure to aluminum and melatonin through the diet: Neurobehavioral effects in a transgenic mouse model of Alzheimer disease, Food Chem Toxicol, 69, 2014 ,320-329.

51. Singh RP, Sharad S, Kapur S, Free Radicals and Oxidative Stress in Neurodegenerative Diseases: Relevance of Dietary Antioxidants, JIACM, 5, 2004, 218-25.

52. Halliwell B, Free radicals, antioxidants and human disease: curiosity, cause or consequences?, Lancet, 344, 1994,721-4.

53. Block G, Patterson B, Subar A, Fruits, vegetables and cancer prevention: A review of epidemiological evidence. Nutr Cancer, 18, 1992, 1-29.

54. Smith CD, Carney JM, Starke-Reed PE, Oliver CN, Stadtman ER, Floyd RA, Markesbery WR, Excess brain protein oxidation and enzyme dysfunction in normal aging and in Alzheimer disease, Proc Natl Acad Sci U S A, 88, 1991,10540-3.

55. Paleologos M, Dimming GR, Lazarus R, Cohort Study of Vitamin C Intake and Cognitive Impairment, American Journal of Epidemiology, 148, 1998, No. 1.

56. Le Bars PL, Katz MM, Berman N, Itil TM, Freedman AM, Schatzberg AF, A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia: North American EGb Study Group, JAMA, 278, 1997,1327-1332.

57. Oken BS, Storzbach DM, Kaye JA, The efficacy of Ginkgo biloba on cognitive function in Alzheimer disease, Arch Neurol, 55, 1998,1409-1415.

58. Jung F, Mrowietz C, Kiesewetter H, Wenzel E, Effect of Ginkgo biloba on fluidity of blood and peripheral microcirculation in volunteers, Arzneimittelforschung, 40, 1990,589-593.

59. Maitra I, Marcocci L, Droy-Lefaix MT, Packer L, Peroxyl radical scavenging activity of Ginkgo biloba extract EGb 761, Biochem Pharmacol, 49, 1995,1649-1655.

60. Hoyer S, Lannert H, Noldner M, Chatterjee SS, Damaged neuronal energy metabolism and behavior are improved by Ginkgo biloba extract (EGb 761), J Neural Transm, 106, 1999,1171-1188.

61. Chung KF, Dent G, McCusker M, Guinot P, Page CP, Barnes PJ, Effect of a ginkgolide mixture (BN 52063) in antagonizing skin and platelet responses to platelet activating factor in man, Lancet, 1, 1987,248-251.

62. Rathi A, Rao Ch V, Ravishankar B, Des , Mehrotra S, Anti-inflammatory and anti-nociceptive activity of the water decoction Desmodium Gangeticum, J. Ehanopharmacol., 95, 2004,259-263.

63. Govindarajan R, Rastogi S, Vijayakumar M ,Shirwaikar A, Rawat AK, Mehrotra S, Pushpangadan P, Studies on the anti-oxidant activities of Desmodium Gangeticum, bio Pharm.Bull , 26, 2003, 1424-1427.

64. Joshi H, Parle M, Zassi Y, Antiamnesic effect of Desmodium Gangeticum in mice, The pharmaceutical society of japan, 126, 2006,795-804.

65. Kim DH, Hung MT, Bae HK, Sung HS, Kim YC, Jung JW, Lee S, Yoon BH, Cheong JH, Ko KH, Ryu JH, Gomisin A improves scopolamine-induced memory impairment in mice, European Journal of Pharmacology, 542 ,2006, 129–135.

66. Jeong JE, Lee YK, Kim HS, Sung HS, Kim YC, Cognitive-enhancing and antioxidant activities of iridoid glycosides from Scrophularia buergeriana in scopolamine-treated mice, European Journal of Pharmacology, 588, 2008, 78-84.

67. Yoshida, H, H Yanai, Y Namiki, K Fakatsu-Saaki, N Furutani, N Tada, Neuroprotective effect of edarvone: A novel free radical scavenger in cerebrovascular injury,CNS drug Rev, 12, 2006, 9-20.

68. Kaminda, T, M Fujiki, H Ooba, M Anan, T ABE, H Kobayashi. Neuroprotective effect of edarvone ,a free radical scavenger on

the rat hippocampus after pilocarpine induced status epilepticus , seizure, 18, 2009,71-75

69. Hardy J, Selkoe DJ, The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics, Science, 297, 2002,353–6

70. Mangialasche F, Solomon A, Winblad B, Mecocci P, Kivipelto M, Alzheimer's disease: clinical trials and drug development, Lancet Neurol., 9, 2010,702–716.

71. Ghosh AK, Shin D, Downs D, Koelsch G, Lin X, Ermolieff J, Tang J, Design of potent inhibitors for human brain Memapsin 2 (β-secretase), J. Am. Chem. Soc., 122, 2002, 3522-3523.

72. Hong L, Koelsch G, Lin X, Wu S, Terzyan S, Ghosh AK, Zhang XC, Tang J, Structure of the protease domain of memapsin 2 (β -secretase) complexed with inhibitor, Science (Wash DC), 290, 2000, 150-153.

73. Chang WP, Koelsch G, Wong S, Downs D, Da H, Weerasena V, Gordon B, Devasamudram T, Bilcer G, Ghosh AK, Tang J. Invivo inhibition of Abeta production by memapsin 2 (β -secretase) inhibitors. J. Neurochem, 89, 2004, 1409-16.

74. Siemer E, Skinner M, Dean RA, Safety tolerability, and changes in amyloid beta concentration after administration of a gamma-secretase inhibitor in volunteers, Clin. Neuropharmacol, 28, 2005, 126-32.

75. Mangialasche F, Solomon A, Winblad B, Mecocci P, Kivipelto M, Alzheimer's disease: clinical trials and drug development, Lancet Neurol, 9, 2010,702–716.

76. Gelinas DS, Dasilva K , Fenili D, Immunotherapy for alzheimers disease, Acad Sci USA, 101, 2004, 14657-14662.

77. Orgogozo JM, Gilman S, Dartigues JF, Laurent B, Puel M, Kirby LC, Jouanny P, Dubois B, Eisner L, Flitman S, Michel BF, Boada M, Frank A, Hock C, Subacute meningoencephalitis in a subset of patients with AD after A 42 immunization, Neurology, 61, 2003,46–54.

78. Gilman S, Koller M, Black RS, Jenkins L, Griffith SG, Fox NC, Eisner L, Kirby L, Rovira MB, Forette F, Orgogozo, Clinical effects of A immunization (AN1792) in patients with AD in an interrupted trial, Neurology, 64, 2005,1553–62.

79. Mangialasche F, Solomon A, Winblad B, Mecocci P, Kivipelto M, Alzheimer's disease: clinical trials and drug development, Lancet Neurol, 9, 2010,702–716.

80. McEwen BS, Woolley CS, Estradiol and progesterone regulate neuronal structure and synaptic connectivity in adults as well as developing brain, Exp Gerontol, 29, 1994, 431-436.

81. Luine VN, Estradiol increase choline acetyl-transferase activity in specific basal forebrain nuclei and projections areas of female rats, Exp Neurol, 89, 1985, 484-490.

82. O' Malley CA, Hautamaki RD, Kelly M, Meyer EM, Effect of ovariectomy and estradiol benzoate on high affinity choline uptake, Ach synthesis , and release from rat cerebral cortical synaptosomes, Brain Res., 403, 1987, 389-392.

83. Dong Y, Wang Y, Liu Y, Yang N, Zuo P, Phytoestrogen a-zearalanol ameliorates memory impairment and neuronal DNA oxidation in ovariectomized mice, CLINICS, 68, 2013,1255-1262.

84. Shumarker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, Hendrix SL, Jones BN, Assaf AR, Jackson RD, Kotchen JM, Wassertheil-smoller S, Wactawski-Wende J, Estrogen plus progestine and the incidence of dementia and mild cognitive impairment in post-menopausal women, The Women Health Initiatives Memory Study : A Randomised Controlled trial, JAMA, 289, 2003, 20.

85. Hachinski V, Munoz D, Cerebrovascular pathology in Alzheimer's disease: cause, effect, or epiphenomenon?, The New York Academy of Sciences, 1997, 1–6.

86. Jagust W, Eberling J, Reed B, Mathis C, Budinger T, Clinical studies of cerebral blood flow in Alzheimer's disease, Cerebrovascular pathology in Alzheimer's Disease, 1997, 254–62.

87. Buée L, Hof P, Delacourte A, Brain microvascular changes in Alzheimer's disease and other dementias, Cerebrovascular pathology in Alzheimer's disease, 1997, 7–24.

88. Dahiyat M, Cumming A, Harrington C, Wischik C, Xuereb J, Corrigan F, Breen G, Shaw D, St Clair D, Association between Alzheimer's disease and the NOS3 gene, Ann Neurol, 46, 1999, 664–67.

89. De la Monte SM, Lu B, Sohn Y, Aberrant expression of nitric oxide synthase III in Alzheimer's disease: relevance to cerebral vasculopathy and neurodegeneration. Neurobiol Aging, 21, 2000, 309–19.

90. Blankevoort CG, van Heuvelen MJ, Boersma F, Luning H, de Jong J, Review of effects of physical activity on strength, balance, mobility and ADL performance in elderly subjects with dementia, Dement Geriatr Cogn Disord, 30, 2010, 392–402.

91. Heyn P, Abreu BC, Ottenbacher KJ, The effects of exercise training on elderly persons with cognitive impairment and dementia: A meta-analysis, Arch Phys Med Rehabil, 85, 2004, 1694–1704.

92. Kalaria RN, Maestre GN, Arizaga R, Friedland RP, Galasko D, Hall K, Luchsinger JA, Ogunniyi A, Perry EK, Potocnik F, Prince M, Stewart R, Wimo A, Zhang ZX, Antuono P, Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors, The Lancet Neurology, 7, 2008, 812–826.

93. Patterson C, Feightner W J, Garcia A, Hsiung GYR, MacKnight C, Sadovnick D, Diagnosis and treatment of dementia Risk assessment and primary prevention of Alzheimer disease, Canadian Medical Association Journal, 178, 2008, 548–556.

94. Colcombe S, Kramer AF, Fitness effects on the cognitive function of older adults: a meta-analytic study, Psychological Science, 14, 2003, 125–130.

95. Anderson BJ, Eckburg PB, Relucio KI, Alterations in the thickness of motor cortical subregions after motor-skill learning and exercise Learning and Memory, 9, 2002,1–9.

96. Liu-Ambrose T, Donaldson MG, Exercise and cognition in older adults: Is there a role for resistance training programmes?, Br J Sports Med, 43, 2009, 25–27

97. Huang T, Larsen KT, Ried-Larsen M, Moller NC, Andersen LB, The effects of physical activity and exercise on brain-derived neurotrophic factor in healthy humans: A review, Scand J Med Sci Sports, 24, 2014, 1–10.

98. Cotman CW, Berchtold NC, Physical activity and the maintenance of cognition: learning from animal models, Alzheimer's Dementia, 3, 2007, 30–37.

99. Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC, Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging, Mayo Clin Proc, 86, 2011, 876–884.

100. Parbery-Clark A, Strait DL, Anderson S, Hittner E, Kraus N, Musical experience and the aging auditory system: implications for cognitive abilities and hearing speech in noise, PLoS One, 6, 2011, e18082

101. Cooper JK, Mungas D, Weiler PG, Relation of cognitive status and abnormal behaviours in alzheimers disease, JAM Geriatr SOC, 38, 1990, 867-870.

102. Teri L, Larson EB, Reifler BV, Behavioural disturbance in dementia of the Alzheimer's type, JAM Geriatric SOC, 36, 1988,1-6.

103. Desai A, Gross GT, Recognition and management of behavioural disturbances in dementia primary care companion, J Clinpsychiatry, 3, 2001,93-109

104. Finkel SI, Silva JC, Cohen G, Miller S, Sartorius N, Behavioral and Psychological Signs and Symptoms of Dementia: A Consensus Statement on Current Knowledge and Implications for Research and Treatment, International Psychogeriatrics, 8, 1996, 497-500.

105. Wancata J, Windhaber J, Krautgartner M, Alexandrowicz R, The consequences of non-cognitive symptoms of dementia in medical hospital departments, Int J Psychiatry Med, 33, 2003, 257-271.

106. Steele C, Rovner B, Chase GA, Folstein M, Psychiatric symptoms and nursing home placement of patients with Alzheimer's disease, AmJ Psychiatry, 147, 1990, 1049- 1051.

107. Yaffe K, Fox P, Newcomer R, Sands L, Lindquist K, Dane K, Covinsky KE, Patient and caregiver characteristics and nursing home placement in patients with dementia, JAMA, 287, 2002, 2090-2097.

108. Stern Y, Tang MX, Albert MS, Brandt J, Jacobs DM, Bell K, Marder K, Sano M, Devanand D, Albert SM, Bylsma F, Tsai WY, Predicting time to nursing home care and death in individuals with Alzheimer disease, JAMA, 277, 1997, 806-812.

109. Gonzales-Salvador T, Lyketsos CG, Baker AS, Hovanec L, Roques C, Brandt J, Steele C. Quality of life of patients with dementia in long-term care. Int J Geriatr Psychiatry, 15, 2000, 181-189.

110. Steele C, Rovner B, Chase GA, Folstein M, Psychiatric symptoms and nursing home placement of patients with Alzheimer's disease, Am J Psychiatry, 147, 1990,1049-1051.

111. Gonzales-Salvador T, Aragano C, Lyketsos CG, Barba AC, The stress and psychological morbidity of the Alzheimer patient caregiver, Int J Geriatr Psychiatry, 14, 1999,701-710.

112. Raglio A, Bellelli G, Traficante D, Gianotti M, Ubezio MC, Villani D, Trabucchi M, Efficacy of Music Therapy in the Treatment of Behavioral and Psychiatric Symptoms of Dementia, Alzheimer Disease & Associated Disorders, 22, 2008,158-162.

113. Finkel SI, Silva JC, Cohen G, Miller S, Sartorius N, Behavioral and Psychological Signs and Symptoms of Dementia: A Consensus Statement on Current Knowledge and Implications for Research and Treatment, International Psychogeriatrics, 8, 1996, 497-500.

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